Clinical trial results:
Phase 1b/2, Multicenter, Open-label Study of Carfilzomib, Carboplatin, and Etoposide in Subjects With Previously Untreated Extensive-stage Small-cell Lung Cancer

Summary

EudraCT number	2013-002597-44
Trial protocol	GB DE FR HU
Global end of trial date	04 May 2017

Results information

Result version number	v1 (current)
This version publication date	18 May 2018
First version publication date	18 May 2018

Trial information

Trial identification

Sponsor protocol code	20130399

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01987232
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	01 August 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 May 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to determine the maximum tolerated dose (MTD) of carfilzomib given on days 2, 3, 9, and 10 in combination with standard dose carboplatin on day 1 and etoposide on days 1, 2, and 3 every 3 weeks as treatment for previously untreated extensive-stage small-cell lung cancer (ES-SCLC).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
The investigator submitted the protocol and informed consent form (ICF) to the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) for review and approval prior to study initiation.
All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 November 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 21
Country: Number of subjects enrolled	Russian Federation: 11
Worldwide total number of subjects	32
EEA total number of subjects	0

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)	25
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 17 centers in the United States, Russia, and Canada.

Pre-assignment

Screening details:

In the phase 1b portion of the study participants were assigned sequentially to escalating doses of carfilzomib given in combination with standard dose carboplatin and etoposide to establish the maximum tolerated dose (MTD). The phase 2 portion of the study was not enrolled.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Carfilzomib 20/20 mg/m²

Arm description:

Participants received carfilzomib 20 mg/m² on days 2, 3, 9, and 10 of each 21-day cycle, carboplatin at a target area under the curve (AUC) of 5 on day 1 of each cycle, and etoposide 100 mg/m² on days 1, 2, and 3 of each 21-day cycle for up to 6 cycles. Participants with stable disease or better continued to receive carfilzomib alone until progressive disease (PD), unacceptable toxicity, withdrawal of consent, study closure, or death, whichever occurred earliest.

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

Dosage and administration details:

Administered by intravenous infusion.

Arm title	Carfilzomib 20/27 mg/m²

Arm description:

Participants received carfilzomib 20 mg/m² on cycle 1 days 2 and 3, then 27 mg/m² on days 9 and 10 and thereafter for each subsequent 21-day cycle, carboplatin at a target AUC of 5 on day 1 of each cycle, and etoposide 100 mg/m² on days 1, 2, and 3 of each cycle for up to 6 cycles. Participants with stable disease or better continued to receive carfilzomib alone until PD, unacceptable toxicity, withdrawal of consent, study closure, or death, whichever occurred earliest.

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

Dosage and administration details:

Administered by intravenous infusion.

Arm title	Carfilzomib 20/36 mg/m²

Arm description:

Participants received carfilzomib 20 mg/m² on cycle 1 days 2 and 3, then 36 mg/m² on days 9 and 10 and thereafter for each subsequent 21-day cycle, carboplatin at a target AUC of 5 on day 1 of each cycle, and etoposide 100 mg/m² on days 1, 2, and 3 of each cycle for up to 6 cycles. Participants with

stable disease or better continued to receive carfilzomib alone until PD, unacceptable toxicity, withdrawal of consent, study closure, or death, whichever occurred earliest.

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

Dosage and administration details:

Administered by intravenous infusion.

Arm title	Carfilzomib 20/45 mg/m²

Arm description:

Participants received carfilzomib 20 mg/m² on cycle 1 days 2 and 3, then 45 mg/m² on days 9 and 10 and thereafter for each subsequent 21-day cycle, carboplatin at a target AUC of 5 on day 1 of each cycle, and etoposide 100 mg/m² on days 1, 2, and 3 of each cycle for up to 6 cycles. Participants with stable disease or better continued to receive carfilzomib alone until PD, unacceptable toxicity, withdrawal of consent, study closure, or death, whichever occurred earliest.

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

Dosage and administration details:

Administered by intravenous infusion.

Arm title	Carfilzomib 20/56 mg/m²

Arm description:

Participants received carfilzomib 20 mg/m² on cycle 1 days 2 and 3, then 56 mg/m² on days 9 and 10 and thereafter for each subsequent 21-day cycle, carboplatin at a target AUC of 5 on day 1 of each cycle, and etoposide 100 mg/m² on days 1, 2, and 3 of each cycle for up to 6 cycles. Participants with stable disease or better continued to receive carfilzomib alone until PD, unacceptable toxicity, withdrawal of consent, study closure, or death, whichever occurred earliest.

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

Dosage and administration details:

Administered by intravenous infusion.

Number of subjects in period 1	Carfilzomib 20/20 mg/m²	Carfilzomib 20/27 mg/m²	Carfilzomib 20/36 mg/m²
Started	5	3	3
Completed	5	3	3

Number of subjects in period 1	Carfilzomib 20/45 mg/m²	Carfilzomib 20/56 mg/m²
Started	15	6

Completed	15	6

Baseline characteristics

Reporting groups	
Reporting group title	Carfilzomib 20/20 mg/m²
Reporting group description:	
Participants received carfilzomib 20 mg/m² on days 2, 3, 9, and 10 of each 21-day cycle, carboplatin at a target area under the curve (AUC) of 5 on day 1 of each cycle, and etoposide 100 mg/m² on days 1, 2, and 3 of each 21-day cycle for up to 6 cycles. Participants with stable disease or better continued to receive carfilzomib alone until progressive disease (PD), unacceptable toxicity, withdrawal of consent, study closure, or death, whichever occurred earliest.	
Reporting group title	Carfilzomib 20/27 mg/m²
Reporting group description:	
Participants received carfilzomib 20 mg/m² on cycle 1 days 2 and 3, then 27 mg/m² on days 9 and 10 and thereafter for each subsequent 21-day cycle, carboplatin at a target AUC of 5 on day 1 of each cycle, and etoposide 100 mg/m² on days 1, 2, and 3 of each cycle for up to 6 cycles. Participants with stable disease or better continued to receive carfilzomib alone until PD, unacceptable toxicity, withdrawal of consent, study closure, or death, whichever occurred earliest.	
Reporting group title	Carfilzomib 20/36 mg/m²
Reporting group description:	
Participants received carfilzomib 20 mg/m² on cycle 1 days 2 and 3, then 36 mg/m² on days 9 and 10 and thereafter for each subsequent 21-day cycle, carboplatin at a target AUC of 5 on day 1 of each cycle, and etoposide 100 mg/m² on days 1, 2, and 3 of each cycle for up to 6 cycles. Participants with stable disease or better continued to receive carfilzomib alone until PD, unacceptable toxicity, withdrawal of consent, study closure, or death, whichever occurred earliest.	
Reporting group title	Carfilzomib 20/45 mg/m²
Reporting group description:	
Participants received carfilzomib 20 mg/m² on cycle 1 days 2 and 3, then 45 mg/m² on days 9 and 10 and thereafter for each subsequent 21-day cycle, carboplatin at a target AUC of 5 on day 1 of each cycle, and etoposide 100 mg/m² on days 1, 2, and 3 of each cycle for up to 6 cycles. Participants with stable disease or better continued to receive carfilzomib alone until PD, unacceptable toxicity, withdrawal of consent, study closure, or death, whichever occurred earliest.	
Reporting group title	Carfilzomib 20/56 mg/m²
Reporting group description:	
Participants received carfilzomib 20 mg/m² on cycle 1 days 2 and 3, then 56 mg/m² on days 9 and 10 and thereafter for each subsequent 21-day cycle, carboplatin at a target AUC of 5 on day 1 of each cycle, and etoposide 100 mg/m² on days 1, 2, and 3 of each cycle for up to 6 cycles. Participants with stable disease or better continued to receive carfilzomib alone until PD, unacceptable toxicity, withdrawal of consent, study closure, or death, whichever occurred earliest.	

Reporting group values	Carfilzomib 20/20 mg/m²	Carfilzomib 20/27 mg/m²	Carfilzomib 20/36 mg/m²
Number of subjects	5	3	3
Age Categorical Units: Subjects			
Adults (18-64 years)	2	2	2
From 65-84 years	3	1	1
Age Continuous Units: years			
arithmetic mean	69.2	62.3	59.0
standard deviation	± 13.8	± 8.5	± 7.5
Gender Categorical Units: Subjects			
Female	3	2	1
Male	2	1	2

Race Units: Subjects			
White	5	3	3
Other	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	5	3	3
Not Reported	0	0	0
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)	4	0	1
1 (Restrictive but ambulatory)	1	3	2

Reporting group values	Carfilzomib 20/45 mg/m²	Carfilzomib 20/56 mg/m²	Total
Number of subjects	15	6	32
Age Categorical Units: Subjects			
Adults (18-64 years)	14	5	25
From 65-84 years	1	1	7
Age Continuous Units: years			
arithmetic mean	56.9	58.8	
standard deviation	± 9.4	± 7.9	-
Gender Categorical Units: Subjects			
Female	5	1	12
Male	10	5	20
Race Units: Subjects			
White	14	6	31
Other	1	0	1
Ethnicity Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	14	5	30
Not Reported	0	1	1
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)	3	2	10
1 (Restrictive but ambulatory)	12	4	22

End points

End points reporting groups

Reporting group title	Carfilzomib 20/20 mg/m²

Reporting group description:

Participants received carfilzomib 20 mg/m² on days 2, 3, 9, and 10 of each 21-day cycle, carboplatin at a target area under the curve (AUC) of 5 on day 1 of each cycle, and etoposide 100 mg/m² on days 1, 2, and 3 of each 21-day cycle for up to 6 cycles. Participants with stable disease or better continued to receive carfilzomib alone until progressive disease (PD), unacceptable toxicity, withdrawal of consent, study closure, or death, whichever occurred earliest.

Reporting group title	Carfilzomib 20/27 mg/m²

Reporting group description:

Participants received carfilzomib 20 mg/m² on cycle 1 days 2 and 3, then 27 mg/m² on days 9 and 10 and thereafter for each subsequent 21-day cycle, carboplatin at a target AUC of 5 on day 1 of each cycle, and etoposide 100 mg/m² on days 1, 2, and 3 of each cycle for up to 6 cycles. Participants with stable disease or better continued to receive carfilzomib alone until PD, unacceptable toxicity, withdrawal of consent, study closure, or death, whichever occurred earliest.

Reporting group title	Carfilzomib 20/36 mg/m²

Reporting group description:

Participants received carfilzomib 20 mg/m² on cycle 1 days 2 and 3, then 36 mg/m² on days 9 and 10 and thereafter for each subsequent 21-day cycle, carboplatin at a target AUC of 5 on day 1 of each cycle, and etoposide 100 mg/m² on days 1, 2, and 3 of each cycle for up to 6 cycles. Participants with stable disease or better continued to receive carfilzomib alone until PD, unacceptable toxicity, withdrawal of consent, study closure, or death, whichever occurred earliest.

Reporting group title	Carfilzomib 20/45 mg/m²

Reporting group description:

Participants received carfilzomib 20 mg/m² on cycle 1 days 2 and 3, then 45 mg/m² on days 9 and 10 and thereafter for each subsequent 21-day cycle, carboplatin at a target AUC of 5 on day 1 of each cycle, and etoposide 100 mg/m² on days 1, 2, and 3 of each cycle for up to 6 cycles. Participants with stable disease or better continued to receive carfilzomib alone until PD, unacceptable toxicity, withdrawal of consent, study closure, or death, whichever occurred earliest.

Reporting group title	Carfilzomib 20/56 mg/m²

Reporting group description:

Participants received carfilzomib 20 mg/m² on cycle 1 days 2 and 3, then 56 mg/m² on days 9 and 10 and thereafter for each subsequent 21-day cycle, carboplatin at a target AUC of 5 on day 1 of each cycle, and etoposide 100 mg/m² on days 1, 2, and 3 of each cycle for up to 6 cycles. Participants with stable disease or better continued to receive carfilzomib alone until PD, unacceptable toxicity, withdrawal of consent, study closure, or death, whichever occurred earliest.

Subject analysis set title	All Participants
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received carfilzomib on days 2, 3, 9, and 10 of each 21-day cycle, carboplatin at a target AUC of 5 on day 1 of each cycle, and etoposide 100 mg/m² on days 1, 2, and 3 of each 21-day cycle for up to 6 cycles. Participants with stable disease or better continued to receive carfilzomib alone until PD, unacceptable toxicity, withdrawal of consent, study closure, or death, whichever occurred earliest.

Primary: Number of Participants With Dose-limiting Toxicities

End point title	Number of Participants With Dose-limiting Toxicities[1]

End point description:

The maximum tolerated dose (MTD) was defined as the highest dose level at which < 33% of participants experienced a dose-limiting toxicity (DLT) during the first 21-day cycle. Dose-limiting toxicities were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03. A DLT was defined as:
• A grade 3 or greater non-hematologic toxicity that was assessed as related to carfilzomib by the investigator except in the case of neuropathy. A grade 2 or higher neuropathy with pain was considered a DLT.
• Grade 4 neutropenia: absolute neutrophil count (ANC) < 500 mm³, lasting ≥ 7 days despite granulocyte colony stimulating factor support, or any febrile (temperature > 38.3°C) neutropenia (ANC < 1000 mm³).

• Thrombocytopenia of any grade associated with clinically significant bleeding or platelet/blood transfusion
• Grade 4 fatigue lasting ≥ 7 days
• Grade 3 nausea, vomiting or diarrhea lasting ≥ 7 days.

End point type	Primary

End point timeframe:

First 21-day Cycle

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were conducted in this study.

End point values	Carfilzomib 20/20 mg/m²	Carfilzomib 20/27 mg/m²	Carfilzomib 20/36 mg/m²	Carfilzomib 20/45 mg/m²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	3	15
Units: participants	0	0	0	0

End point values	Carfilzomib 20/56 mg/m²			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: participants	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events (AEs)

End point title	Number of Participants With Adverse Events (AEs)

End point description:

The severity of each adverse event was assessed using the NCI-CTCAE Version 4.03 according to the following:
Grade 1 - Mild: Asymptomatic or mild symptoms; intervention not indicated
Grade 2 – Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3 – Severe: Medically significant but not life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4 – Life-threatening
Grade 5 – Fatal.
A serious AE is an AE that met one 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
• A congenital anomaly/birth defect
• Important medical events that required medical or surgical intervention to prevent one of the outcomes above.

End point type	Secondary

End point timeframe:

From first day of any study treatment (i.e., carfilzomib, carboplatin, or etoposide) up to 30 days after the last day of study treatment. The median overall duration of treatment was 16 weeks.

End point values	Carfilzomib 20/20 mg/m²	Carfilzomib 20/27 mg/m²	Carfilzomib 20/36 mg/m²	Carfilzomib 20/45 mg/m²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	3	15
Units: participants				
Any adverse event	5	3	3	15
Adverse events ≥ grade 3	3	3	2	13
Serious adverse events	1	1	1	7
AEs leading to disocontinuation of study drug	1	0	0	3
Fatal adverse events	0	0	0	0

End point values	Carfilzomib 20/56 mg/m²			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: participants				
Any adverse event	5			
Adverse events ≥ grade 3	4			
Serious adverse events	2			
AEs leading to disocontinuation of study drug	1			
Fatal adverse events	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Phase 2

End point title	Overall Survival (OS) - Phase 2

End point description:

Overall Survival (OS) is defined as the time from randomization to the date of death. Overall survival was a specified secondary endpoint for the phase 2 portion of the study; since phase 2 was not conducted, OS was not analyzed.

End point type	Secondary

End point timeframe:

30 months

End point values	Carfilzomib 20/20 mg/m²	Carfilzomib 20/27 mg/m²	Carfilzomib 20/36 mg/m²	Carfilzomib 20/45 mg/m²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[2]	0[3]	0[4]	0[5]
Units: months				
median (full range (min-max))	(to)	(to)	(to)	(to)

Notes:

[2] - OS was only analyzed in subjects enrolled in phase 2

[3] - OS was only analyzed in subjects enrolled in phase 2

[4] - OS was only analyzed in subjects enrolled in phase 2

[5] - OS was only analyzed in subjects enrolled in phase 2

End point values	Carfilzomib 20/56 mg/m²			
Subject group type	Reporting group			
Number of subjects analysed	0[6]			
Units: months				
median (full range (min-max))	(to)			

Notes:

[6] - OS was only analyzed in subjects enrolled in phase 2

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration - Phase 2

End point title	Maximum Plasma Concentration - Phase 2

End point description:

Pharmacokinetic (PK) analyses were specified as secondary endpoints for the phase 2 portion of the study; since phase 2 was not conducted, PK analyses were not performed.

End point type	Secondary

End point timeframe:

Cycle 1 Day 2

End point values	Carfilzomib 20/20 mg/m²	Carfilzomib 20/27 mg/m²	Carfilzomib 20/36 mg/m²	Carfilzomib 20/45 mg/m²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[7]	0[8]	0[9]	0[10]
Units: ng/mL				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[7] - PK endpoints were only analyzed in subjects enrolled in phase 2

[8] - PK endpoints were only analyzed in subjects enrolled in phase 2

[9] - PK endpoints were only analyzed in subjects enrolled in phase 2

[10] - PK endpoints were only analyzed in subjects enrolled in phase 2

End point values	Carfilzomib 20/56 mg/m²			
Subject group type	Reporting group			
Number of subjects analysed	0[11]			

Units: ng/mL				
arithmetic mean (standard deviation)	()			

Notes:

[11] - PK endpoints were only analyzed in subjects enrolled in phase 2

Statistical analyses

No statistical analyses for this end point

Secondary: Time of Maximum Plasma Concentration - Phase 2

End point title	Time of Maximum Plasma Concentration - Phase 2

End point description:

Pharmacokinetic (PK) analyses were specified as secondary endpoints for the phase 2 portion of the study; since phase 2 was not conducted, PK analyses were not performed.

End point type	Secondary

End point timeframe:

Cycle 1 Day 2

End point values	Carfilzomib 20/20 mg/m²	Carfilzomib 20/27 mg/m²	Carfilzomib 20/36 mg/m²	Carfilzomib 20/45 mg/m²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[12]	0[13]	0[14]	0[15]
Units: hours				
median (full range (min-max))	(to)	(to)	(to)	(to)

Notes:

[12] - PK endpoints were only analyzed in subjects enrolled in phase 2

[13] - PK endpoints were only analyzed in subjects enrolled in phase 2

[14] - PK endpoints were only analyzed in subjects enrolled in phase 2

[15] - PK endpoints were only analyzed in subjects enrolled in phase 2

End point values	Carfilzomib 20/56 mg/m²			
Subject group type	Reporting group			
Number of subjects analysed	0[16]			
Units: hours				
median (full range (min-max))	(to)			

Notes:

[16] - PK endpoints were only analyzed in subjects enrolled in phase 2

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under Plasma Concentration-Time Curve - Phase 2

End point title	Area Under Plasma Concentration-Time Curve - Phase 2

End point description:

Pharmacokinetic (PK) analyses were specified as secondary endpoints for the phase 2 portion of the study; since phase 2 was not conducted, PK analyses were not performed.

End point type	Secondary

End point timeframe:

Cycle 1 Day 2

End point values	Carfilzomib 20/20 mg/m²	Carfilzomib 20/27 mg/m²	Carfilzomib 20/36 mg/m²	Carfilzomib 20/45 mg/m²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[17]	0[18]	0[19]	0[20]
Units: ng/mL*h				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[17] - PK endpoints were only analyzed in subjects enrolled in phase 2

[18] - PK endpoints were only analyzed in subjects enrolled in phase 2

[19] - PK endpoints were only analyzed in subjects enrolled in phase 2

[20] - PK endpoints were only analyzed in subjects enrolled in phase 2

End point values	Carfilzomib 20/56 mg/m²			
Subject group type	Reporting group			
Number of subjects analysed	0[21]			
Units: ng/mL*h				
arithmetic mean (standard deviation)	()			

Notes:

[21] - PK endpoints were only analyzed in subjects enrolled in phase 2

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival

End point title	Progression-free Survival

End point description:

Progression-free survival (PFS) was specified as a primary endpoint for the phase 2 portion of the study. Since phase 2 did not proceed PFS was analyzed in phase 1b participants on an exploratory basis. PFS was defined as the time from the start of treatment to documented disease progression or death due to any cause, whichever occurred first. Disease progression was determined by the investigator according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, defined as at least a 20% increase in the size of target lesions (absolute increase ≥ 5 mm), unequivocal progression of existing non-target lesions, or any new lesions.
Median PFS was calculated using Kaplan-Meier methods. Participants with no baseline disease assessments, who started a new anticancer therapy before documentation of PD or death, with death or PD immediately after more than 1 consecutively missed disease assessment visit or alive without documentation of PD before the data cutoff date were censored.

End point type	Secondary

End point timeframe:

From first dose of study drug until the end of treatment; median duration of treatment was 16 weeks.

End point values	Carfilzomib 20/20 mg/m²	Carfilzomib 20/27 mg/m²	Carfilzomib 20/36 mg/m²	Carfilzomib 20/45 mg/m²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	3	15
Units: months				
median (confidence interval 95%)	4.0 (2.8 to 6.7)	6.4 (6.2 to 6.8)	7.0 (4.0 to 7.0)	2.9 (2.5 to 5.4)

End point values	Carfilzomib 20/56 mg/m²	All Participants		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	6	32		
Units: months				
median (confidence interval 95%)	3.8 (1.1 to 6.3)	4.4 (2.8 to 5.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate

End point title	Overall Response Rate

End point description:

Overall response rate (ORR) was specified as a secondary endpoint for the phase 2 portion of the study. Since phase 2 did not proceed ORR was analyzed in phase 1b participants on an exploratory basis. ORR was defined as the percentage of participants for whom the best overall confirmed response was either complete response (CR) or partial response (PR) assessed by the investigator according to RECIST v1.1 criteria.
CR: Disappearance of all target and non-target lesions, no new lesions and normalization of tumor marker levels. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters, or, the disappearance of all target lesions and persistence of one or more non-target lesion(s) and/or maintenance of tumor marker levels above normal limits.

End point type	Secondary

End point timeframe:

From first dose of study drug until the end of treatment; median duration of treatment was 16 weeks.

End point values	Carfilzomib 20/20 mg/m²	Carfilzomib 20/27 mg/m²	Carfilzomib 20/36 mg/m²	Carfilzomib 20/45 mg/m²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	3	3	15
Units: percentage of participants				
number (confidence interval 95%)	60.0 (14.7 to 94.7)	100.0 (29.2 to 100.0)	66.7 (9.4 to 99.2)	33.3 (11.8 to 61.6)

End point values	Carfilzomib	All Participants		

	20/56 mg/m²			
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	6	32		
Units: percentage of participants				
number (confidence interval 95%)	33.3 (4.3 to 77.7)	46.9 (29.1 to 65.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response (DOR) was calculated for participants who achieved a confirmed CR or PR. defined as the time from first evidence of confirmed PR/CR to disease progression or death due to any cause. Median DOR was calculated using Kaplan-Meier methods. Participants with no baseline disease assessments, who started a new anticancer therapy before documentation of PD or death, with death or PD immediately after more than 1 consecutively missed disease assessment visit or alive without documentation of PD before the data cutoff date were censored.
DOR was originally specified as a secondary endpoint for the phase 2 portion of the study. Since phase 2 did not proceed, DOR was analyzed in phase 1b participants on an exploratory basis. "99999" indicates data that could not be estimated due to the low number of events.

End point type	Secondary

End point timeframe:

From first dose of study drug until the end of treatment; median duration of treatment was 16 weeks.

End point values	Carfilzomib 20/20 mg/m²	Carfilzomib 20/27 mg/m²	Carfilzomib 20/36 mg/m²	Carfilzomib 20/45 mg/m²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	2	5
Units: months				
median (confidence interval 95%)	4.9 (2.8 to 5.4)	5.0 (4.7 to 5.6)	99999 (2.8 to 99999)	4.3 (1.6 to 999999)

End point values	Carfilzomib 20/56 mg/m²	All Participants		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	2	15		
Units: months				
median (confidence interval 95%)	4.5 (4.2 to 4.8)	4.8 (2.8 to 5.4)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first day of any study treatment (i.e., carfilzomib, carboplatin, or etoposide), and within 30 days of the last day of study treatment. The median overall duration of treatment was 16 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Carfilzomib 20/20 mg/m²

Reporting group description:

Participants received carfilzomib 20 mg/m² on days 2, 3, 9, and 10 of each 21-day cycle, carboplatin at a target AUC of 5 on day 1 of each cycle, and etoposide 100 mg/m² on days 1, 2, and 3 of each 21-day cycle for up to 6 cycles. Participants with stable disease or better continued to receive carfilzomib alone until PD, unacceptable toxicity, withdrawal of consent, study closure, or death, whichever occurred earliest.

Reporting group title	Carfilzomib 20/27 mg/m²

Reporting group description:

Participants received carfilzomib 20 mg/m² on cycle 1 days 2 and 3, then 27 mg/m² on days 9 and 10 and thereafter for each subsequent 21-day cycle, carboplatin at a target AUC of 5 on day 1 of each cycle, and etoposide 100 mg/m² on days 1, 2, and 3 of each cycle for up to 6 cycles. Participants with stable disease or better continued to receive carfilzomib alone until progressive disease (PD), unacceptable toxicity, withdrawal of consent, study closure, or death, whichever occurred earliest.

Reporting group title	Carfilzomib 20/36 mg/m²

Reporting group description:

Participants received carfilzomib 20 mg/m² on cycle 1 days 2 and 3, then 36 mg/m² on days 9 and 10 and thereafter for each subsequent 21-day cycle, carboplatin at a target AUC of 5 on day 1 of each cycle, and etoposide 100 mg/m² on days 1, 2, and 3 of each cycle for up to 6 cycles. Participants with stable disease or better continued to receive carfilzomib alone until PD, unacceptable toxicity, withdrawal of consent, study closure, or death, whichever occurred earliest.

Reporting group title	Carfilzomib 20/45 mg/m²

Reporting group description:

Participants received carfilzomib 20 mg/m² on cycle 1 days 2 and 3, then 45 mg/m² on days 9 and 10 and thereafter for each subsequent 21-day cycle, carboplatin at a target AUC of 5 on day 1 of each cycle, and etoposide 100 mg/m² on days 1, 2, and 3 of each cycle for up to 6 cycles. Participants with stable disease or better continued to receive carfilzomib alone until PD, unacceptable toxicity, withdrawal of consent, study closure, or death, whichever occurred earliest.

Reporting group title	Carfilzomib 20/56 mg/m²

Reporting group description:

Participants received carfilzomib 20 mg/m² on cycle 1 days 2 and 3, then 56 mg/m² on days 9 and 10 and thereafter for each subsequent 21-day cycle, carboplatin at a target AUC of 5 on day 1 of each cycle, and etoposide 100 mg/m² on days 1, 2, and 3 of each cycle for up to 6 cycles. Participants with stable disease or better continued to receive carfilzomib alone until PD, unacceptable toxicity, withdrawal of consent, study closure, or death, whichever occurred earliest.

Serious adverse events	Carfilzomib 20/20 mg/m²	Carfilzomib 20/27 mg/m²	Carfilzomib 20/36 mg/m²
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
number of deaths (all causes)	2	0	0
number of deaths resulting from adverse events			

Vascular disorders			
Peripheral artery thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection site abscess			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypoalbuminaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Carfilzomib 20/45 mg/m²	Carfilzomib 20/56 mg/m²	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 15 (46.67%)	2 / 6 (33.33%)	
number of deaths (all causes)	2	3	
number of deaths resulting from adverse events			
Vascular disorders			
Peripheral artery thrombosis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary oedema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site abscess			

subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (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	1 / 15 (6.67%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Carfilzomib 20/20 mg/m²	Carfilzomib 20/27 mg/m²	Carfilzomib 20/36 mg/m²
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	3 / 3 (100.00%)	3 / 3 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Flushing			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypertension			

subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Hypotension			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	2	0	1
Jugular vein thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Orthostatic hypotension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Phlebitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Catheter site pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 5 (20.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	3	1	3
Mucosal inflammation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	1 / 5 (20.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	1	1	1
Dry throat			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Haemoptysis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hypoxia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 5 (20.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Pleural effusion			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Pulmonary embolism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Pulmonary oedema			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	1 / 5 (20.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Insomnia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	4
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Blood glucose increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Blood phosphorus increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Blood potassium decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Blood urea increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood uric acid increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Creatinine renal clearance decreased			
subjects affected / exposed	2 / 5 (40.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	5	0	2
Ejection fraction decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haemoglobin decreased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	2

Neutrophil count decreased			
subjects affected / exposed	1 / 5 (20.00%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	1	12	0
Platelet count decreased			
subjects affected / exposed	0 / 5 (0.00%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	0	15	0
Weight decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	3
Weight increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
White blood cell count decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Head injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Incision site erythema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Incision site swelling			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infusion related reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Laceration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Wound			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Ageusia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Cerebrovascular accident			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Decreased vibratory sense			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	2 / 3 (66.67%)
occurrences (all)	0	1	2
Dysgeusia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	2
Headache			
subjects affected / exposed	0 / 5 (0.00%)	2 / 3 (66.67%)	2 / 3 (66.67%)
occurrences (all)	0	4	3
Hypoaesthesia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Hyporeflexia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Neuropathy peripheral			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Tremor			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Vocal cord paralysis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 5 (40.00%)	3 / 3 (100.00%)	2 / 3 (66.67%)
occurrences (all)	3	20	3
Leukocytosis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Leukopenia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Neutropenia			
subjects affected / exposed	1 / 5 (20.00%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	3	2	0
Thrombocytopenia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 3 (66.67%)	1 / 3 (33.33%)
occurrences (all)	0	5	1
Ear and labyrinth disorders			
Ear congestion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ear discomfort			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hypoacusis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Vertigo			

subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Abdominal distension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	3 / 5 (60.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	3	0	0
Diarrhoea			
subjects affected / exposed	1 / 5 (20.00%)	2 / 3 (66.67%)	1 / 3 (33.33%)
occurrences (all)	2	3	2
Flatulence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Haematochezia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	3 / 5 (60.00%)	3 / 3 (100.00%)	3 / 3 (100.00%)
occurrences (all)	4	4	6
Oesophagitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Toothache			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0

Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	2	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	2 / 3 (66.67%)
occurrences (all)	1	0	2
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Rash macular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Skin discolouration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin irritation			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Swelling face			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Micturition disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Bone pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Costochondritis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Groin pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	2 / 3 (66.67%)
occurrences (all)	0	0	3
Musculoskeletal chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Clostridium difficile colitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Influenza			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injection site infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lung infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Mucosal infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Oral candidiasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Oral herpes			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal candidiasis			

subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 5 (40.00%)	0 / 3 (0.00%)	2 / 3 (66.67%)
occurrences (all)	5	0	3
Dehydration			
subjects affected / exposed	1 / 5 (20.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	1	7	0
Diabetes mellitus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Gout			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hyperkalaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypoglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1

Hypomagnesaemia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Hyponatraemia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 3 (66.67%)	1 / 3 (33.33%)
occurrences (all)	0	2	2
Metabolic acidosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Carfilzomib 20/45 mg/m²	Carfilzomib 20/56 mg/m²	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)	5 / 6 (83.33%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Flushing			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Hypotension			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Jugular vein thrombosis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Orthostatic hypotension			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	

Phlebitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 15 (13.33%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Catheter site pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Chills			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	4 / 15 (26.67%)	2 / 6 (33.33%)	
occurrences (all)	7	4	
Mucosal inflammation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Oedema peripheral			
subjects affected / exposed	2 / 15 (13.33%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	2 / 15 (13.33%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			

Breast pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Cough			
subjects affected / exposed	1 / 15 (6.67%)	1 / 6 (16.67%)	
occurrences (all)	1	2	
Dry throat			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Dyspnoea			
subjects affected / exposed	2 / 15 (13.33%)	1 / 6 (16.67%)	
occurrences (all)	3	2	
Haemoptysis			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Hypoxia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Nasal congestion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pleural effusion			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Pulmonary embolism			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Pulmonary oedema			

subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Rhinorrhoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Confusional state			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Depression			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Insomnia			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	3	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Blood creatinine increased			
subjects affected / exposed	1 / 15 (6.67%)	2 / 6 (33.33%)	
occurrences (all)	3	3	
Blood glucose increased			

subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Blood phosphorus increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Blood potassium decreased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Blood urea increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Blood uric acid increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Creatinine renal clearance decreased			
subjects affected / exposed	1 / 15 (6.67%)	2 / 6 (33.33%)	
occurrences (all)	2	4	
Ejection fraction decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Haemoglobin decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Neutrophil count decreased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	4	
Platelet count decreased			
subjects affected / exposed	2 / 15 (13.33%)	2 / 6 (33.33%)	
occurrences (all)	3	2	
Weight decreased			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Weight increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
White blood cell count decreased			

subjects affected / exposed	1 / 15 (6.67%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Head injury			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Incision site erythema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Incision site swelling			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Infusion related reaction			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Laceration			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Wound			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Cerebrovascular accident			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Decreased vibratory sense			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Dizziness			

subjects affected / exposed	3 / 15 (20.00%)	1 / 6 (16.67%)	
occurrences (all)	7	1	
Dysgeusia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Headache			
subjects affected / exposed	3 / 15 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Hypoaesthesia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hyporeflexia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Neuropathy peripheral			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Paraesthesia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Vocal cord paralysis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 15 (53.33%)	3 / 6 (50.00%)	
occurrences (all)	16	4	
Leukocytosis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	

Leukopenia			
subjects affected / exposed	3 / 15 (20.00%)	1 / 6 (16.67%)	
occurrences (all)	5	1	
Neutropenia			
subjects affected / exposed	10 / 15 (66.67%)	3 / 6 (50.00%)	
occurrences (all)	19	6	
Thrombocytopenia			
subjects affected / exposed	7 / 15 (46.67%)	4 / 6 (66.67%)	
occurrences (all)	15	8	
Ear and labyrinth disorders			
Ear congestion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Ear discomfort			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Ear pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hypoacusis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Vertigo			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Abdominal distension			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Constipation			

subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Diarrhoea			
subjects affected / exposed	5 / 15 (33.33%)	0 / 6 (0.00%)	
occurrences (all)	6	0	
Flatulence			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Haematochezia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	5 / 15 (33.33%)	1 / 6 (16.67%)	
occurrences (all)	9	2	
Oesophagitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Stomatitis			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Toothache			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	3 / 15 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	5	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	5 / 15 (33.33%)	1 / 6 (16.67%)	
occurrences (all)	5	1	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Pruritus			

subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Rash macular			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Skin discolouration			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Skin irritation			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Swelling face			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Micturition disorder			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 15 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Bone pain			
subjects affected / exposed	1 / 15 (6.67%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Costochondritis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Groin pain			

subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Muscular weakness			
subjects affected / exposed	3 / 15 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Influenza			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Injection site infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Lung infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	

Mucosal infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Oral candidiasis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Oral herpes			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Pneumonia			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Respiratory tract infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Skin infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 15 (13.33%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Dehydration			

subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Diabetes mellitus			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Gout			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Hyperkalaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Hypocalcaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hypoglycaemia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hypomagnesaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
Hyponatraemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	7	
Metabolic acidosis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 June 2013	- To revise the DLT definition to include febrile neutropenia as a DLT, regardless of G-CSF support - To revise the DLT definition so that thrombocytopenia of any grade associated with clinically significant bleeding or platelet/blood transfusion Is considered a DLT - To increase the number of doses given at 20 mg/m2 doses (given on cycle 1 day 2 and cycle 1 day 3), prior to stepped-up dosing, as specified by cohort - To improve the clarity regarding the requirement of stepped-up dosing for subjects who crossover from the control arm to receive carfilzomib monotherapy

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported