Clinical trial results:
A randomized Phase II, 2-armed study in transplant ineligible (TI) patients with newly diagnosed multiple myeloma (NDMM) comparing Carfilzomib + Thalidomide + dexamethasone (KTd) versus Carfilzomib + Lenalidomide + dexamethasone (KRd) induction therapy with respect to response rates and investigating a Carfilzomib (K) monotherapy maintenance strategy

Summary

EudraCT number	2016-000475-24
Trial protocol	AT DE
Global end of trial date	28 March 2024

Results information

Result version number	v1 (current)
This version publication date	18 October 2024
First version publication date	18 October 2024

Trial information

Trial identification

Sponsor protocol code	AGMT_MM-2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02891811
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AGMT
Sponsor organisation address	Gentzgasse 60/21, Vienna, Austria, 1180
Public contact	Daniela Wolkersdorfer, AGMT, +43 6626404412, d.wolkersdofer@agmt.at
Scientific contact	Richard Greil, AGMT, +43 6626404412, office@agmt.at

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	24 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 March 2023
Global end of trial reached?	Yes
Global end of trial date	28 March 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To show non-inferiority with respect to response rates between KTd and KRd: Overall response rate (ORR) are assessed according to International Myeloma Working Group (IMWG) criteria to determine the ORR in patients NDMM after receiving max 9 cycles induction therapy with either carfilzomib in combination with thalidomide and dexamethasone or carfilzomib in combination with lenalidomide and dexamethasone

Protection of trial subjects:

Anti-biotic, anti-viral, and anti-thrombosis pretreatment and prophylaxis was mandatory. Guidelines for dose modifications on case of toxicities were given. In general, concomitant medications and therapies necessary for supportive care and safety of the patient were allowed. The administration of any other anticancer agent or other concurrent investigational drug was not permitted. The inclusion of women of childbearing potential (WOCBP) and male subjects with pregnant or non-pregnant WOCBP had to follow specific recommendations for contraception and pregnancy testing. Furthermore, for all participating patients special counselling regarding use of thalidomide or lenalidomide had to be done prior to each treatment cycle.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 March 2017
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	Austria: 121
Country: Number of subjects enrolled	Germany: 3
Worldwide total number of subjects	124
EEA total number of subjects	124

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)	4
From 65 to 84 years	118
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Between 20-Mar-2017 and 16-Dec-2021, 124 patients were enrolled in 16 sites in Austria and 2 sites in Germany. 1 patient withdrew concent shortly after randomization, did not receive any study treatment and is excluded from analysis.

Pre-assignment

Screening details:

Adult patients (≥18 years) with newly diagnosed, symptomatic MM not eligible or not willing to undergo autologous stem cell transplantation following induction and who are < NYHA class III/IV, ECOG PS 0-1, CrCl > 30ml/min, PN ≤ 2 (without pain).

Period 1

Period 1 title	Induction
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	KTd Induction

Arm description:

Induction therapy for a maximum of 9 cycles

Arm type	Experimental
Investigational medicinal product name	Carfilzomib
Investigational medicinal product code	
Other name	Kyprolis
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Cycle 1: 20mg/m2 on day 1+2, 27mg/m2 on day 8, 9, 15 and 16; Cycle 2: 27mg/m2 on day 1,2,8,9,15 and 16; Cycle 3-9: 56mg/m2 on day 1, 8 and 15

Investigational medicinal product name	Thalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

100mg/day, day 1-28 (50mg in patients aged ≥75 years)

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion, Tablet
Routes of administration	Infusion , Injection , Oral use

Dosage and administration details:

40mg/week- day 1,8,15,22 (20mg in patients aged ≥75 years)

Arm title	KRd Induction

Arm description:

Induction therapy for a maximum of 9 cycles

Arm type	Experimental

Investigational medicinal product name	Carfilzomib
Investigational medicinal product code	
Other name	Kyprolis
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Cycle 1: 20mg/m2 on day 1+2, 27mg/m2 on day 8, 9, 15 and 16; Cycle 2: 27mg/m2 on day 1,2,8,9,15 and 16; Cycle 3-9: 56mg/m2 on day 1, 8 and 15

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

25mg/day, day 1-21

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion, Tablet
Routes of administration	Infusion , Injection , Oral use

Dosage and administration details:

40mg/week- day 1,8,15,22 (20mg in patients aged ≥75 years)

Number of subjects in period 1[1]	KTd Induction	KRd Induction
Started	63	60
Completed	46	38
Not completed	17	22
investigator's decision	2	1
severe AE/toxicity	9	15
progressive disease/death	2	3
patient's decision	4	2
dialysis-dependent	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One patient withdrew concent shortly after randomization in KRd arm and did not receive any study treatment. This patient is excluded from analysis.

Period 2

Period 2 title	Maintenance
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	K monotherapy
Arm description: Maintenance treatment with carfilzomib for a maximum period of 12 months.	
Arm type	Experimental
Investigational medicinal product name	Carfilzomib
Investigational medicinal product code	
Other name	Kyprolis
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Infusion
Dosage and administration details: day 1 and day 15 using the last tolerated dose for 12 cylces	
Arm title	Observation
Arm description: Observation for 12 months	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	K monotherapy	Observation
Started	42	42
Completed	28	26
Not completed	14	16
investigator's decision	2	2
ongoing at primary endpoint analysis	1	1
progressive disease/death	7	13
severe AE/toxicity	2	-
patient's decision	2	-

Baseline characteristics

Reporting groups	
Reporting group title	KTd Induction
Reporting group description:	
Induction therapy for a maximum of 9 cycles	
Reporting group title	KRd Induction
Reporting group description:	
Induction therapy for a maximum of 9 cycles	

Reporting group values	KTd Induction	KRd Induction	Total
Number of subjects	63	60	123
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	75	75	
full range (min-max)	58 to 84	55 to 84	-
Gender categorical			
Units: Subjects			
Female	31	24	55
Male	32	36	68

End points

End points reporting groups	
Reporting group title	KTd Induction
Reporting group description:	
Induction therapy for a maximum of 9 cycles	
Reporting group title	KRd Induction
Reporting group description:	
Induction therapy for a maximum of 9 cycles	
Reporting group title	K monotherapy
Reporting group description:	
Maintenance treatment with carfilzomib for a maximum period of 12 months.	
Reporting group title	Observation
Reporting group description:	
Observation for 12 months	

Primary: Response	
End point title	Response
End point description:	
Response in patients treated with KTd or KRd during induction therapy. Patients who received study medication for at least 4 weeks were evaluable for response.	
End point type	Primary
End point timeframe:	
Response assessment was done at day 1 of each cylce (except cycle 1) and at the end of K combination treatment	

End point values	KTd Induction	KRd Induction		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	55		
Units: Subjects				
stringent complete response (sCR)	7	4		
complete response (CR)	20	17		
very good partial response (VGPR)	21	19		
partial response (PR)	8	8		
minimal response (MR)	3	2		
stable disease (SD)	2	4		
progressive disease (PD)	0	1		

Statistical analyses

Statistical analysis title	Overall response rates
Statistical analysis description:	
Response rates were similiar during induction therapy with KTd (91.8%) and KRd (87.3%), meeting the requirements for non-inferiority.	

Comparison groups	KTd Induction v KRd Induction
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Difference
Point estimate	-4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17
upper limit	7.1

Notes:

[1] - Non-inferiority is postulated if the CI of the differences does not cross 11%. CI was calculated using the Miettinen-Nurminen method

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All patients having received at least one dose of the study medication were followed for adverse events for at least 28 days after discontinuing study treatment or completion of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Safety population

Reporting group description:

The safety population includes all enrolled patients who received at least one dose of the study treatment. SARs are assessed as related to carfilzomib.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	86 / 123 (69.92%)		
number of deaths (all causes)	23		
number of deaths resulting from adverse events	6		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 123 (1.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Myelodysplastic syndrome			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bowen's disease			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			

subjects affected / exposed	2 / 123 (1.63%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Embolism			
subjects affected / exposed	2 / 123 (1.63%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Circulatory collapse			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arterial stenosis			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertension			

subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 123 (4.07%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	3 / 123 (2.44%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	3 / 123 (2.44%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	2 / 123 (1.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Oedema			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Drug intolerance			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion site reaction			

subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hernia				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Cystocele				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pulmonary embolism				
subjects affected / exposed	2 / 123 (1.63%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Dyspnoea				
subjects affected / exposed	2 / 123 (1.63%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary congestion				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				

subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device dislocation			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
C-reactive protein increased			
subjects affected / exposed	2 / 123 (1.63%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatic enzyme increased			
subjects affected / exposed	2 / 123 (1.63%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			
subjects affected / exposed	2 / 123 (1.63%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Blood creatine increased			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	3 / 123 (2.44%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Infusion related reaction			
subjects affected / exposed	2 / 123 (1.63%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Thoracic vertebral fracture			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound haemorrhage			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ankle fracture			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar vertebral fracture			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	8 / 123 (6.50%)		
occurrences causally related to treatment / all	7 / 8		
deaths causally related to treatment / all	0 / 0		

Sinus bradycardia				
subjects affected / exposed	2 / 123 (1.63%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	2 / 123 (1.63%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Syncope				
subjects affected / exposed	2 / 123 (1.63%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	2 / 123 (1.63%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Polyneuropathy				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				

subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depressed level of consciousness			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peroneal nerve palsy			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Facial paralysis			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombotic microangiopathy			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Iron deficiency anaemia			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	3 / 123 (2.44%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	3 / 123 (2.44%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Enteritis			
subjects affected / exposed	2 / 123 (1.63%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Haematochezia			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			

Hepatic failure				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Rash				
subjects affected / exposed	6 / 123 (4.88%)			
occurrences causally related to treatment / all	3 / 7			
deaths causally related to treatment / all	0 / 0			
Toxic epidermal necrolysis				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rash maculo-papular				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dermatitis acneiform				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Decubitus ulcer				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Drug reaction with eosinophilia and systemic symptoms				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	4 / 123 (3.25%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			

Urinary retention				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic kidney disease				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	3 / 123 (2.44%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Spinal pain				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neck pain				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Back pain				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bone lesion				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rheumatoid arthritis				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Bone pain				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thoracic spinal stenosis				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gouty arthritis				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc disorder				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				
subjects affected / exposed	15 / 123 (12.20%)			
occurrences causally related to treatment / all	11 / 16			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	4 / 123 (3.25%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	2 / 123 (1.63%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	2 / 123 (1.63%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				

subjects affected / exposed	2 / 123 (1.63%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	2 / 123 (1.63%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	2 / 123 (1.63%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	2 / 123 (1.63%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Viral pericarditis				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Febrile infection				

subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Neuroborreliosis				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis norovirus				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral myocarditis				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Escherichia bacteraemia				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mastoiditis				
subjects affected / exposed	1 / 123 (0.81%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hypocalcaemia				

subjects affected / exposed	2 / 123 (1.63%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cachexia			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hypokalaemia			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	1 / 123 (0.81%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	118 / 123 (95.93%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 123 (9.76%)		
occurrences (all)	20		
Hypotension			
subjects affected / exposed	8 / 123 (6.50%)		
occurrences (all)	8		
Thrombophlebitis			

subjects affected / exposed	6 / 123 (4.88%)		
occurrences (all)	7		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	63 / 123 (51.22%)		
occurrences (all)	110		
Oedema peripheral			
subjects affected / exposed	44 / 123 (35.77%)		
occurrences (all)	71		
Pyrexia			
subjects affected / exposed	19 / 123 (15.45%)		
occurrences (all)	29		
Pain			
subjects affected / exposed	12 / 123 (9.76%)		
occurrences (all)	18		
Chills			
subjects affected / exposed	8 / 123 (6.50%)		
occurrences (all)	9		
Asthenia			
subjects affected / exposed	8 / 123 (6.50%)		
occurrences (all)	9		
Chest pain			
subjects affected / exposed	7 / 123 (5.69%)		
occurrences (all)	7		
Influenza like illness			
subjects affected / exposed	7 / 123 (5.69%)		
occurrences (all)	7		
Oedema			
subjects affected / exposed	6 / 123 (4.88%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	23 / 123 (18.70%)		
occurrences (all)	29		
Cough			

subjects affected / exposed	13 / 123 (10.57%)		
occurrences (all)	15		
Oropharyngeal pain			
subjects affected / exposed	10 / 123 (8.13%)		
occurrences (all)	10		
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	10 / 123 (8.13%)		
occurrences (all)	11		
Insomnia			
subjects affected / exposed	9 / 123 (7.32%)		
occurrences (all)	12		
Investigations			
C-reactive protein increased			
subjects affected / exposed	19 / 123 (15.45%)		
occurrences (all)	22		
Platelet count decreased			
subjects affected / exposed	8 / 123 (6.50%)		
occurrences (all)	27		
Neutrophil count decreased			
subjects affected / exposed	7 / 123 (5.69%)		
occurrences (all)	18		
Nervous system disorders			
Polyneuropathy			
subjects affected / exposed	22 / 123 (17.89%)		
occurrences (all)	27		
Tremor			
subjects affected / exposed	15 / 123 (12.20%)		
occurrences (all)	17		
Paraesthesia			
subjects affected / exposed	11 / 123 (8.94%)		
occurrences (all)	12		
Neuropathy peripheral			
subjects affected / exposed	8 / 123 (6.50%)		
occurrences (all)	9		
Headache			

subjects affected / exposed occurrences (all)	14 / 123 (11.38%) 16		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all)	 20 / 123 (16.26%) 33 17 / 123 (13.82%) 34 11 / 123 (8.94%) 17 6 / 123 (4.88%) 8		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) Tinnitus subjects affected / exposed occurrences (all)	 27 / 123 (21.95%) 35 7 / 123 (5.69%) 9		
Eye disorders Visual impairment subjects affected / exposed occurrences (all) Cataract subjects affected / exposed occurrences (all)	 6 / 123 (4.88%) 7 6 / 123 (4.88%) 6		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea	 37 / 123 (30.08%) 67 32 / 123 (26.02%) 40		

subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all)	27 / 123 (21.95%) 43 14 / 123 (11.38%) 21 6 / 123 (4.88%) 7 6 / 123 (4.88%) 7		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	25 / 123 (20.33%) 39 9 / 123 (7.32%) 11		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Bone pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Myalgia	18 / 123 (14.63%) 22 18 / 123 (14.63%) 25 17 / 123 (13.82%) 27 10 / 123 (8.13%) 15 9 / 123 (7.32%) 12		

subjects affected / exposed occurrences (all)	7 / 123 (5.69%) 10		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Infection subjects affected / exposed occurrences (all)	 19 / 123 (15.45%) 20 14 / 123 (11.38%) 15 11 / 123 (8.94%) 14 8 / 123 (6.50%) 8		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hypocalcaemia subjects affected / exposed occurrences (all)	 17 / 123 (13.82%) 19 9 / 123 (7.32%) 9 7 / 123 (5.69%) 11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 January 2017	Based on data from Biran et al. 2016, presented at ASH 2016, increased cardiotoxicity and thrombotic microangiopathy were seen in elderly patients receiving 70 mg carfilzomib in combination with dexamethasone and lenalidomide. Due to these observations, the dose and scheduling of carfilzomib was adapted for this trial. Also frail patients and those with an ECOG PS status ≥2 were excluded from this study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/38895059

http://www.ncbi.nlm.nih.gov/pubmed/38425185