



Clinical trial results:

Safety of Vorinostat in combination with Bortezomib, Doxorubicin and Dexamethasone (VBDD) in patients with refractory or relapsed multiple myeloma

Summary

EudraCT number	2011-000388-28
Trial protocol	DE
Global end of trial date	01 December 2015

Results information

Result version number	v1 (current)
This version publication date	05 September 2020
First version publication date	05 September 2020

Trial information

Trial identification

Sponsor protocol code	00658;MK-0683-201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01394354
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical Center – University of Freiburg
Sponsor organisation address	Breisacher Str. 153, Freiburg, Germany, 79110
Public contact	Prof. Dr. med. Monika Engelhardt, Abt. Innere Medizin I, Dept. Hematology and Oncology, 0049 76127032460, monika.engelhardt@uniklinik-freiburg.de
Scientific contact	Prof. Dr. med. Monika Engelhardt, Abt. Innere Medizin I, Dept. Hematology and Oncology, 0049 76127032460, monika.engelhardt@uniklinik-freiburg.de

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 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2015
Global end of trial reached?	Yes
Global end of trial date	01 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective of the study is the determination of the maximum tolerated dose (MTD) of Vorinostat (V), given in combination with fixed doses of Doxorubicin (D), Bortezomib (B) and Dexamethasone (D).

Protection of trial subjects:

Possibility to withdraw consent by patient. Assessment of safety and tolerability of VBDD, evaluated in terms of AEs, SAEs, laboratory parameters.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 September 2011
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	Germany: 33
Worldwide total number of subjects	33
EEA total number of subjects	33

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)	19
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Mono-center study at the University Medical Center Freiburg in Germany. Recruitment period: 20 Sept 2011 - 1 Dec 2014.

Pre-assignment

Screening details:

Included and analysed were 33 patients, included from study start on 20th September 2011 (inclusion of the first patient) until closure on 1st December 2015 (last patient out, i.e. one year follow-up period after inclusion of the last patient).

Pre-assignment period milestones

Number of subjects started	33
Number of subjects completed	33

Period 1

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

Arms

Arm title	Combination therapy
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Arm description:

Vorinostat 100 mg/d vs. 200 mg/d vs. 300 mg/d given on days 1-4, 8-11, 15-18 in combination with doxorubicin (9 mg/m² body surface area on d1 and d8) and bortezomib (1.3 mg/m² on d1, d8, and d15) as well as dexamethasone (VBDD) in patients with refractory or relapsed multiple myeloma.

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

Dosage and administration details:

A first cohort of 3 patients was treated at the starting dose level of Vorinostat 100 mg/d, on days 1-4, 8-11, and 15-18 in combination with Bortezomib, Doxorubicin and Dexamethasone (BDD). The dose level of Vorinostat was escalated in each new cohort: if no dose limiting toxicity had been observed in the previous dose level in 3 patients, the second cohort of 3 new patients were treated with Vorinostat 200 mg/d in combination with BDD and the third cohort was given Vorinostat with 300 mg/d in combination with BDD.

Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use, Intravenous use

Dosage and administration details:

Bortezomib was administered with a dose of 1.3 mg/m² on d1, d8 and d15 intravenously (i.v.), or (after amendment) subcutaneously (s.c.). After the amendment in April 2013, Bortezomib administration was switched to s.c. whenever possible for the patient in the phase II, because results of another study had shown in the meantime that s.c. is as effective as i.v. application but had fewer side effects.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Doxorubicin was administered i.v. with a total dose of 18 mg/m² per cycle (9 mg/m², d1 and d8).

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

Dosage and administration details:

Dexamethasone was administered per os (p.o.) with 40 mg (first cycle) and 20 mg (all other subsequent cycles) on d1, d8, d15 and d22.

Number of subjects in period 1	Combination therapy
Started	33
Completed	33

Baseline characteristics

Reporting groups

Reporting group title	Baseline
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Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	33	33	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	19	19	
From 65-84 years	14	14	
85 years and over	0	0	
Years of age	0	0	
Age continuous			
Units: years			
median	62		
full range (min-max)	47 to 77	-	
Gender categorical			
Units: Subjects			
Female	14	14	
Male	19	19	

Subject analysis sets

Subject analysis set title	Full analysis set
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Subject analysis set type	Full analysis
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Subject analysis set description:

Full analysis set included 33 patients.

Reporting group values	Full analysis set		
Number of subjects	33		
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)	19		
From 65-84 years	14		
85 years and over	0		
Years of age	0		
Age continuous			
Units: years			
median	62		
full range (min-max)	47 to 77		
Gender categorical			
Units: Subjects			
Female	14		
Male	19		

End points

End points reporting groups

Reporting group title	Combination therapy
Reporting group description:	
Vorinostat 100 mg/d vs. 200 mg/d vs. 300 mg/d given on days 1-4, 8-11, 15-18 in combination with doxorubicin (9 mg/m ² body surface area on d1 and d8) and bortezomib (1.3 mg/m ² on d1, d8, and d15) as well as dexamethasone (VBDD) in patients with refractory or relapsed multiple myeloma.	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
Full analysis set included 33 patients.	

Primary: Maximum tolerated dose of Vorinostat

End point title	Maximum tolerated dose of Vorinostat ^[1]
End point description:	
Maximum tolerated dose of Vorinostat, given in combination with fixed doses of Doxorubicin, Bortezomib and Dexamethasone was defined as the highest dose of vorinostat at which six patients have been treated and less than two patients experienced dose limiting toxicity within the first cycle of treatment. No DLT occurred in 9 patients who were consecutively included in the phase I part of the study (levels 0, + 1 and +2) (see section 7.3), therefore the MTD for vorinostat could not be determined within this trial with planned vorinostat <loses up to 300 mg/d p.o.. Thus, the recommended dose of vorinostat for Phase II (RDP2) was 300 mg/d p.o.. With this dose the remaining 24 patients were treated throughout the phase II part of the study.	
End point type	Primary
End point timeframe:	
Maximum tolerated dose of Vorinostat is based on safety data from the first 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: Descriptive analyses, as the primary objective of the study was the determination of the maximum tolerated dose of vorinostat.

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: mg/d	300			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival
End point description:	
End point type	Secondary
End point timeframe:	
Time from start of treatment until death or the first observation of disease progression, whichever occurred first.	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: Months				
median (confidence interval 95%)	9.6263 (6.0780 to 13.3717)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival
End point description:	
End point type	Secondary
End point timeframe:	
Time from start of treatment until death from any cause.	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: Months				
median (confidence interval 95%)	33.8 (14.8 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: dose-limiting toxicity

End point title	Safety: dose-limiting toxicity
End point description:	
End point type	Secondary
End point timeframe:	
At the end of the study	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: Number of patients	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response
End point description: Complete response occurred only in one patient so that duration of response could only be determined for this single patient.	
End point type	Secondary
End point timeframe: During study	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	1			
Units: Months				
median (confidence interval 95%)	6.8 (0.1 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geriatric depression scale score

End point title	Geriatric depression scale score
End point description:	
End point type	Secondary
End point timeframe: Change from screening to end of therapy	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: Score difference				
arithmetic mean (confidence interval 95%)	0.3 (-0.9 to 2.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geriatric assessment: Timed "up and go" test

End point title	Geriatric assessment: Timed "up and go" test
End point description:	
End point type	Secondary
End point timeframe:	
Change from screening to end of therapy	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	16			
Units: sec				
arithmetic mean (confidence interval 95%)	0.3 (-0.6 to 1.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geriatric assessment: instrumental activities of daily living (IADL) score

End point title	Geriatric assessment: instrumental activities of daily living (IADL) score
End point description:	
End point type	Secondary
End point timeframe:	
Change from screening to end of therapy	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: Score difference				
arithmetic mean (confidence interval 95%)	0.5 (-0.4 to 1.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geriatric assessment: Mini-Mental Status score

End point title	Geriatric assessment: Mini-Mental Status score
End point description:	
End point type	Secondary
End point timeframe:	
Change from screening to end of therapy	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: Score difference				
arithmetic mean (confidence interval 95%)	0.2 (-1.1 to 1.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geriatric assessment: hematopoietic cell transplantation-comorbidity index (HCT-CI) score

End point title	Geriatric assessment: hematopoietic cell transplantation-comorbidity index (HCT-CI) score
End point description:	
End point type	Secondary
End point timeframe:	
Change from screening to end of therapy	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: Score difference				
arithmetic mean (standard deviation)	0.4 ($\pm$ 0.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geriatric assessment: Freiburg comorbidity index (FCI) score

End point title	Geriatric assessment: Freiburg comorbidity index (FCI) score
End point description:	
End point type	Secondary
End point timeframe:	
Change from screening to end of therapy	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: FCI score difference				
arithmetic mean (confidence interval 95%)	0.1 (-0.3 to 0.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geriatric assessment: Kaplan-Feinsteinindex (KF) score

End point title	Geriatric assessment: Kaplan-Feinsteinindex (KF) score
End point description:	
End point type	Secondary
End point timeframe:	
Change from screening to end of therapy	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: Score difference				
arithmetic mean (confidence interval 95%)	0.1 (-0.2 to 0.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Response rates

End point title	Response rates
End point description:	
End point type	Secondary
End point timeframe:	
Best response observed until end of treatment	

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: Number of patients				
Stringent complete remission	0			
Complete remission	1			
Very good partial response	7			
Partial remission	14			
Stable disease	9			
Progressive disease	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Response rates

End point title	Response rates
End point description:	
End point type	Secondary

End point timeframe:

Study end

End point values	Full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	33			
Units: Number of patients				
Stringent complete remission	0			
Complete remission	3			
Very good partial response	1			
Partial remission	3			
Stable disease	1			
Progressive disease	23			
n.e.	1			
Missing	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Complete study

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18
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Reporting groups

Reporting group title	VBDD
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Reporting group description:

Vorinostat, Bortezomib, Doxorubicin and Dexamethason

Serious adverse events	VBDD		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 33 (27.27%)		
number of deaths (all causes)	15		
number of deaths resulting from adverse events	2		
Injury, poisoning and procedural complications			
Spinal cord injury thoracic			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal pain			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile colitis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster disseminated			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Respiratory tract infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Sepsis			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Septic shock			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	VBDD		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 33 (100.00%)		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Haematoma			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Surgical and medical procedures			
Catheterisation venous			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Glaucoma surgery			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
General disorders and administration site conditions			
Administration site extravasation			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Application site erythema			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Asthenia			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Chest discomfort			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Face oedema			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	9 / 33 (27.27%)		
occurrences (all)	9		
Feeling hot			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Influenza like illness			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Pain			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Puncture site pain			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Systemic inflammatory response			

syndrome			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Sleep disorder			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Blood pressure increased			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
C-reactive protein increased			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	6		
Creatinine renal clearance decreased			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		

Sputum abnormal subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Injury, poisoning and procedural complications Limb injury subjects affected / exposed occurrences (all) Spinal compression fracture subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1 1 / 33 (3.03%) 1		
Cardiac disorders Angina pectoris subjects affected / exposed occurrences (all) Tachycardia subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1 1 / 33 (3.03%) 1		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Polyneuropathy subjects affected / exposed occurrences (all) Radial nerve palsy subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all) Speech disorder subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3 1 / 33 (3.03%) 1 4 / 33 (12.12%) 4 1 / 33 (3.03%) 1 2 / 33 (6.06%) 2 1 / 33 (3.03%) 1		

Syncope subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	10 / 33 (30.30%) 14		
Cytopenia subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 2		
Febrile neutropenia subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Leukopenia subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2		
Neutropenia subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 2		
Thrombocytopenia subjects affected / exposed occurrences (all)	8 / 33 (24.24%) 10		
Ear and labyrinth disorders			
Tinnitus subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Eye disorders			
Dry eye subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Eye haemorrhage subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Eyelid haematoma subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Lacrimation increased			

subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Ocular discomfort			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	9 / 33 (27.27%)		
occurrences (all)	11		
Diarrhoea			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Dysphagia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	6 / 33 (18.18%)		
occurrences (all)	6		
Vomiting			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Rosacea			

subjects affected / exposed occurrences (all) Scar pain subjects affected / exposed occurrences (all) Skin lesion subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1 1 / 33 (3.03%) 1 1 / 33 (3.03%) 1 1 / 33 (3.03%) 1		
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Endocrine disorders Cushing's syndrome subjects affected / exposed occurrences (all) Hypothyroidism subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1 1 / 33 (3.03%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Osteoarthritis subjects affected / exposed occurrences (all) Osteolysis	2 / 33 (6.06%) 2 1 / 33 (3.03%) 1 1 / 33 (3.03%) 1 1 / 33 (3.03%) 1		

subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Pathological fracture			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Bronchitis			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Candida infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Herpes zoster oticus			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	5		
Influenza			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Klebsiella sepsis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	4		

Oesophageal candidiasis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Skin infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Staphylococcal sepsis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
Hyperkalaemia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Hypomagnesaemia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Increased appetite			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2013	Bortezomib application was switched from i.v. to s.c., as s.c. has been shown (according to Moreau et al. 2011) to be equally effective but with fewer side effects. Ultrasound examination was included to diagnose soft tissue plasmacytoma. Adequate bone marrow function was redefined.

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/29674494>