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

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
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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

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 previos 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 sid 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

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
Subject analysis set type	Full analysis

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/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.

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 occured 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 occured 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 (± 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

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18

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

Syncope			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 33 (30.30%)		
occurrences (all)	14		
Cytopenia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
Febrile neutropenia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Neutropenia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
Thrombocytopenia			
subjects affected / exposed	8 / 33 (24.24%)		
occurrences (all)	10		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Eye haemorrhage			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Eyelid haematoma			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	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	1 / 33 (3.03%)		
occurrences (all)	1		
Scar pain			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Skin lesion			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Endocrine disorders			
Cushing's syndrome			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hypothyroidism			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Muscle spasms			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Osteoarthritis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Osteolysis			

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