Clinical trial results:
An Open-Label Phase II Study of the Safety and Efficacy of Doxorubicin and Cyclophosphamide in Combination with Bortezomib, Lenalidomide, and Dexamethasone for Treatment of Patients with Newly Diagnosed Multiple Myeloma

Summary

EudraCT number	2011-002751-34
Trial protocol	DK
Global end of trial date	28 September 2017

Results information

Result version number	v1 (current)
This version publication date	07 April 2019
First version publication date	07 April 2019

Trial information

Trial identification

Sponsor protocol code	8050

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Vejle Hospital
Sponsor organisation address	Kabbeltoft 25, 7100 Vejle, Vejie, Denmark,
Public contact	Lena Bjerre, Vejle Hospital, 45 79406316, lena.bjerre.haarbo@slb.regionsyddanmark.dk
Scientific contact	Lena Bjerre, Vejle Hospital, 45 79406316, lena.bjerre.haarbo@slb.regionsyddanmark.dk

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	30 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 August 2015
Global end of trial reached?	Yes
Global end of trial date	28 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of the combination therapy of doxorubicin, cyclophosphamide, bortezomib, dexamethasone and lenalidomide in newly diagnosed multiple myeloma patients

Protection of trial subjects:

The study was conducted in accordance with ethical principles founded in the Declaration of Helsinki.
The EC reviewed all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study was conducted at site where EC approval had been obtained.
Patients had the right to withdraw from the study at any time for any reason, without prejudice to their medical care.
The patient's confidentiality was maintained and would not be made publicly available to the extent permitted by the applicable laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 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	Denmark: 35
Worldwide total number of subjects	35
EEA total number of subjects	35

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)	20
From 65 to 84 years	15

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 1 single site in 1 country. The date of first patient enrollment was 17 Nov 2011 and the date of last patient enrollment was 13 May 2014. A total of 35 subjects were enrolled in the study.

Pre-assignment

Screening details:

Patients enrolled in the study to evaluate the efficacy and safety of ACVDL in adult patients with newly diagnosed multiple myeloma

Period 1

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

Arms

Arm title	ACVDL

Arm description:

Combination therapy of Doxorubicin, Cyclophosphamide, Bortezomib, Dexamethasone and Lenalidomide (ACVDL) for 8 cycles with the exception of patients who attained a CR/PR after 4 cycles of the therapy and were eligible to stem cell mobilization and transplantation, and then 5 cycles bortezomib consolidation therapy for patients who did not attain mCR.

Arm type	Experimental
Investigational medicinal product name	ACVDL
Investigational medicinal product code	
Other name	Doxorubicin, Cyclophosphamide, Bortezomib, Dexamethasone, Lenalidomide
Pharmaceutical forms	Capsule, Concentrate and solvent for solution for infusion, Tablet
Routes of administration	Intravenous use, Oral use, Subcutaneous use

Dosage and administration details:

8 cycles of ACVDL therapy was administered for patients with the exception of those who attained a CR/PR after 4 cycles of the therapy and were eligible to stem cell mobilization and transplantation. After the end of ACVDL therapy, 5 cycles of bortezomib consolidation therapy were administered for patients who did not attain mCR.
Each 21-day cycle of ACVDL therapy consisted of the following treatment regime:
-Doxorubicin (50mg/m^2/IV) and cyclophosphamide (750mg/m^2/IV) will be given on Day 1.
-Bortezomib will be given at 1.3 mg/m^2/IV as a 3-5 second IV push on Days 2 and 9 followed by a 10-day rest period.
-Lenalidomide will be given as a single daily oral dose of 15 mg on Days 1-14 followed by a 7-day rest period.
-Dexamethasone will be given as a single daily oral dose of 20mg/day on Days 2, 3, 9 and 10.
Each 35-day cycle of bortezomib consolidation therapy is as follows:
Bortezomib will be given at 1.6mg/m^2 subcutaneously on Day 1, 8, 15 and 22

Number of subjects in period 1	ACVDL
Started	35
Completed	14
Not completed	21
Consent withdrawn by subject	4
Disease progression	3
Adverse event, non-fatal	3
Achieving mCR	4
Intercurrent illness	1
Trombocytopenia	1
Lack of efficacy	4
Death of wife	1

Baseline characteristics

Reporting groups

Reporting group title	ACVDL

Reporting group description:

Combination therapy of Doxorubicin, Cyclophosphamide, Bortezomib, Dexamethasone and Lenalidomide (ACVDL) for 8 cycles with the exception of patients who attained a CR/PR after 4 cycles of the therapy and were eligible to stem cell mobilization and transplantation, and then 5 cycles bortezomib consolidation therapy for patients who did not attain mCR.

Reporting group values	ACVDL	Total	
Number of subjects	35	35	
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			
arithmetic mean	64.4		
standard deviation	± 8.04	-	
Gender categorical Units: Subjects			
Female	14	14	
Male	21	21	

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

It included subjects who completed one cycle of therapy. Subjects with protocol violations or those who withdrew from the study prematurely would also be included. However, subjects who violated the entry criteria that were clinically relevant to the outcome would be excluded.

Subject analysis set title	PP
Subject analysis set type	Per protocol

Subject analysis set description:

It included subjects fulfilling the following criteria:
a) Tumor remission measures available at the End of ACVDL and 4 weeks after completion of consolidation therapy (if applicable)
b) The absence of any major protocol violations including the violation of entry criteria

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

It included subjects who received the first dose of the study therapy.

Reporting group values	ITT	PP	Safety
Number of subjects	35	33	35
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	64.4	63.9	64.4
standard deviation	± 8.04	± 7.93	± 8.04
Gender categorical Units: Subjects			
Female	14	14	14
Male	21	19	21

End points

End points reporting groups

Reporting group title	ACVDL

Reporting group description:

Combination therapy of Doxorubicin, Cyclophosphamide, Bortezomib, Dexamethasone and Lenalidomide (ACVDL) for 8 cycles with the exception of patients who attained a CR/PR after 4 cycles of the therapy and were eligible to stem cell mobilization and transplantation, and then 5 cycles bortezomib consolidation therapy for patients who did not attain mCR.

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

It included subjects who completed one cycle of therapy. Subjects with protocol violations or those who withdrew from the study prematurely would also be included. However, subjects who violated the entry criteria that were clinically relevant to the outcome would be excluded.

Subject analysis set title	PP
Subject analysis set type	Per protocol

Subject analysis set description:

It included subjects fulfilling the following criteria:
a) Tumor remission measures available at the End of ACVDL and 4 weeks after completion of consolidation therapy (if applicable)
b) The absence of any major protocol violations including the violation of entry criteria

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

It included subjects who received the first dose of the study therapy.

Primary: Response rate (mCR/sCR/CR/VGPR)

End point title	Response rate (mCR/sCR/CR/VGPR)[1]

End point description:

The response rate was reported as percentage of subjects achieving Molecular Complete Response (mCR), Stringent Complete Response (sCR), Complete Response (CR) or Very Good Partial Response (VGPR) at 4-weeks after completion of 8 cycles of ACVDL or 3 months after 4 cycles of ACVDL followed by high-dose melphalan and after consolidation therapy. Analysis was performed on ITT and PP set.

End point type	Primary

End point timeframe:

Baseline, Interim Assessment, End of ACVDL (4-weeks after completion of 8 cycles of ACVDL or 3 months after 4 cycles of ACVDL followed by high-dose melphalan) and End of Consolidation Therapy

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: The primary endpoint was estimation of parameter and therefore no statistical analyses were specified.

End point values	ITT	PP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35	33		
Units: Percentage of subjects				
number (confidence interval 95%)	54.3 (36.7 to 71.2)	57.6 (39.2 to 74.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete response rate (mCR/sCR/CR)

End point title	Complete response rate (mCR/sCR/CR)

End point description:

The complete response rate was reported as percentage of subjects achieving Molecular Complete Response (mCR), Stringent Complete Response (sCR) or Complete Response (CR) at 4-weeks after completion of 8 cycles of ACVDL or 3 months after 4 cycles of ACVDL followed by high-dose melphalan and after consolidation therapy. Analysis was performed on ITT set.

End point type	Secondary

End point timeframe:

Baseline, Interim Assessment, End of ACVDL (4-weeks after completion of 8 cycles of ACVDL or 3 months after 4 cycles of ACVDL followed by high-dose melphalan) and End of Consolidation Therapy

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: Percentage of subjects				
number (confidence interval 95%)	37.1 (21.5 to 55.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Very good partial response rate (VGPR)

End point title	Very good partial response rate (VGPR)

End point description:

Very good partial response rate was reported as percentage of subjects achieving Very Good Partial Response (VGPR) at 4-weeks after completion of 8 cycles of ACVDL or 3 months after 4 cycles of ACVDL followed by high-dose melphalan and after consolidation therapy. Analysis was performed on ITT set.

End point type	Secondary

End point timeframe:

Baseline, Interim Assessment, End of ACVDL (4-weeks after completion of 8 cycles of ACVDL or 3 months after 4 cycles of ACVDL followed by high-dose melphalan) and End of Consolidation Therapy

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: Percentage of subjects				
number (confidence interval 95%)	28.6 (14.6 to 46.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression (TTP)

End point title	Time to progression (TTP)

End point description:

Time to progression was defined as the time interval from date of first dose of the ACVDL therapy until the date of the first documentation of disease progression. Death due to cause other than progression was censored. Patient without an event was censored at date last known progression-free. Analysis was performed on ITT set using Kaplan-Meier method.

End point type	Secondary

End point timeframe:

Baseline, Interim Assessment, End of ACVDL, End of Consolidation Therapy, every 12 weeks up to the 4-year, or any other reason for study discontinuation

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: months				
median (confidence interval 95%)	26.8 (19.8 to 30.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Progression free survival was defined as the time interval from date of first dose of the ACVDL therapy until the date of the first documentation of disease progression or death due to any cause, whichever occurred first. Patient without an event was censored at date last known progression-free. Analysis was performed on ITT set using Kaplan-Meier method.

End point type	Secondary

End point timeframe:

Baseline, Interim Assessment, End of ACVDL, End of Consolidation Therapy, every 12 weeks up to the 4-year, or any other reason for study discontinuation

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: months				
median (confidence interval 95%)	23.9 (19.8 to 29.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Dose intensity for ACVDL cycle 1-4 (Non-SCT Patients)

End point title	Dose intensity for ACVDL cycle 1-4 (Non-SCT Patients)

End point description:

The mean dose intensity measured for the first 4 cycles of ACVDL for Non-SCT Patients

End point type	Secondary

End point timeframe:

Baseline, End of 4 cycles of ACVDL Therapy

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: mg/day				
arithmetic mean (standard deviation)				
Lenalidomide	6.93 (± 1.644)			
Dexamethasone	2.44 (± 0.958)			
Bortezomib	0.15 (± 0.046)			
Doxorubicin	2.99 (± 1.633)			
Cyclophosphamide	53.90 (± 14.678)			

Statistical analyses

No statistical analyses for this end point

Secondary: Dose intensity for ACVDL cycle 1-8 (Non-SCT Patients)

End point title	Dose intensity for ACVDL cycle 1-8 (Non-SCT Patients)

End point description:

The mean dose intensity measured for the cycles 1-8 of ACVDL Therapy for Non-SCT Patients

End point type	Secondary

End point timeframe:

Baseline, End of 8 cycles of ACVDL Therapy

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: mg/day				
arithmetic mean (standard deviation)				
Lenalidomide	6.80 (± 1.768)			
Dexamethasone	2.33 (± 0.883)			
Bortezomib	0.15 (± 0.041)			
Doxorubicin	2.91 (± 1.569)			
Cyclophosphamide	52.13 (± 13.990)			

Statistical analyses

No statistical analyses for this end point

Secondary: Dose intensity for consolidation therapy cycle 1-5

End point title	Dose intensity for consolidation therapy cycle 1-5

End point description:

The mean dose intensity measured for Cycles 1-5 of Consolidation Therapy

End point type	Secondary

End point timeframe:

Start of Consolidation Therapy Cycle 1, End of Consolidation Therapy Cycle 5

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: mg/day				
arithmetic mean (standard deviation)				
Bortezomib	0.32 (± 0.049)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start of the first dose of any medication of the ACVDL therapy to 4 weeks after the last dose of ACVDL or 3 months post stem cell transplantation, or 4 weeks after the combination therapy.

Adverse event reporting additional description:

ACVDL- or combination therapy- related SAEs were reported during the 4-year follow-up period.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	ACVDL

Reporting group description:

Combination therapy of Doxorubicin, Cyclophosphamide, Bortezomib, Dexamethasone and Lenalidomide (ACVDL) for 8 cycles with the exception of patients who attained a CR/PR after 4 cycles of the therapy and were eligible to stem cell mobilization and transplantation, and then 5 cycles bortezomib consolidation therapy for patients who did not attain mCR.

Serious adverse events	ACVDL		
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 35 (82.86%)		
number of deaths (all causes)	14		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Treatment related secondary malignancy			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Phlebitis			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thromboembolic event - lung			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Fever			
subjects affected / exposed	13 / 35 (37.14%)		
occurrences causally related to treatment / all	21 / 27		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleuritic pain			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Chest pain - cardiac			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Left ventricular systolic dysfunction			

subjects affected / exposed	2 / 35 (5.71%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	6 / 35 (17.14%)		
occurrences causally related to treatment / all	8 / 8		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhea			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower gastrointestinal hemorrhage			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal pain			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lung infection			
subjects affected / exposed	12 / 35 (34.29%)		
occurrences causally related to treatment / all	15 / 15		
deaths causally related to treatment / all	0 / 0		
Upper respiratory infection			

subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract				
subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infection with unknown origin				
subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumocystis carinii				
subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Progressive multifocal leucoencepha				
subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis - Listeria				
subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Suspected tooth abscess				
subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				

subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycemia			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	ACVDL		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 35 (100.00%)		
Vascular disorders			
Hematoma			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	6		
Hypertension			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Hypotension			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Phlebitis			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	5		
Thromboembolic event			
subjects affected / exposed	5 / 35 (14.29%)		
occurrences (all)	5		
General disorders and administration site conditions			
Edema limbs			
subjects affected / exposed	15 / 35 (42.86%)		
occurrences (all)	17		
Fatigue			

subjects affected / exposed occurrences (all) Fever subjects affected / exposed occurrences (all) Flu like symptoms subjects affected / exposed occurrences (all) Injection site reaction subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4 20 / 35 (57.14%) 44 8 / 35 (22.86%) 9 4 / 35 (11.43%) 5 2 / 35 (5.71%) 2		
Respiratory, thoracic and mediastinal disorders Dyspnea subjects affected / exposed occurrences (all)	 3 / 35 (8.57%) 4		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 4 / 35 (11.43%) 4		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Neutrophil count decreased subjects affected / exposed occurrences (all) Platelet count decreased subjects affected / exposed occurrences (all) CD4 count decreased subjects affected / exposed occurrences (all)	 2 / 35 (5.71%) 2 24 / 35 (68.57%) 85 11 / 35 (31.43%) 29 17 / 35 (48.57%) 17		
Cardiac disorders			

Atrial fibrillation subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2		
Sinus tachycardia subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2		
Left ventricular systolic dysfunction subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2		
Nervous system disorders Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	12 / 35 (34.29%) 14		
Syncope subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3		
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4		
Febrile neutropenia subjects affected / exposed occurrences (all)	7 / 35 (20.00%) 9		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	5 / 35 (14.29%) 5		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	11 / 35 (31.43%) 12		
Diarrhea subjects affected / exposed occurrences (all)	17 / 35 (48.57%) 23		
Dyspepsia subjects affected / exposed occurrences (all)	5 / 35 (14.29%) 7		

Nausea			
subjects affected / exposed	11 / 35 (31.43%)		
occurrences (all)	17		
Vomiting			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Rash maculo-papular			
subjects affected / exposed	8 / 35 (22.86%)		
occurrences (all)	8		
Urticaria			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	4		
Dermatitis			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Eruption			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Erythema			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		

Back pain			
subjects affected / exposed	8 / 35 (22.86%)		
occurrences (all)	8		
Bone pain			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Chest wall pain			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	6 / 35 (17.14%)		
occurrences (all)	6		
Pain in extremity			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	5		
Cramps			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Infections and infestations			
Lung infection			
subjects affected / exposed	13 / 35 (37.14%)		
occurrences (all)	18		
Mucosal infection			
subjects affected / exposed	6 / 35 (17.14%)		
occurrences (all)	8		
Upper respiratory infection			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	6		
Urinary tract			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	4		
Erysipelas			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Herpes simplex			

subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Herpes zoster			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Oral infection			
subjects affected / exposed	6 / 35 (17.14%)		
occurrences (all)	11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 July 2012	Addition of 5-cycles consolidation therapy with bortezomib for patients not attaining molecular complete response (mCR) at 4 weeks after the last dose of the combination therapy of doxorubicin, cyclophosphamide, bortezomib, dexamethasone and lenalidomide (ACVDL) or 3 months after stem cell transplantation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported