Clinical trial results:
Randomised phase III trial for previously untreated multiple myeloma to evaluate two regimens of bortezomib based induction therapy and lenalidomide consolidation followed by lenalidomide maintenance treatment

Summary

EudraCT number	2010-019173-16
Trial protocol	DE
Global end of trial date	11 March 2017

Results information

Result version number	v1 (current)
This version publication date	27 April 2022
First version publication date	27 April 2022

Trial information

Trial identification

Sponsor protocol code	MM5

Additional study identifiers

ISRCTN number	ISRCTN05622749
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospital Heidelberg
Sponsor organisation address	Im Neuenheimer Feld 672, Heidelberg, Germany, 69120
Public contact	GMMG Studiensekretariat Im Neuenheimer Feld 130.3 69120 Heidelberg, Germany, GMMG Study Office, 0049 6221568198, studiensekretariat.gmmg@med.uni-heidelberg.de
Scientific contact	GMMG Studiensekretariat Im Neuenheimer Feld 130.3 69120 Heidelberg, Germany, GMMG Study Office, 0049 6221568198, studiensekretariat.gmmg@med.uni-heidelberg.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	16 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 March 2017
Global end of trial reached?	Yes
Global end of trial date	11 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1.) Demonstration of non-inferiority of VCD induction therapy compared to PAd induction therapy with respect to response rate (very good partial remission or better; response criteria of the International Myeloma Working Group, IMWG).

2.) Determination of the best of four treatment strategies with respect to progression-free survival (PFS). The four treatment strategies are defined by PAd vs. VCD induction treatment, standard intensification therapy, lenalidomide consolidation and maintenance treatment with lenalidomide for 2 years vs. lenalidomide until CR.

Protection of trial subjects:

regular safety assessments:
- reporting and assessment of serious adverse events (SAE), all CTC grades, during all treatment phases.
- reporting and assessment of adverse events (AE) CTC grade > 3 during induction, consolidation and maintenance. Additionally,
the specific AEs polyneuropathy, thromboembolic events, cardiac events and infections already have to be reported if CTCAE grade 2.
AEs are assessed according to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0).
List of safety parameter according to protocol to assess “adverse events”:
• laboratory findings (hematology, creatinine, blood chemistry incl. ASAT, ALAT, γ-GT, urea, bilirubin, etc., hCG for women of childbearing potential)
• physical examination
• medical history
• ECG and cardiac echo

Implementation of "pregnancy prevention programme"

Background therapy:

All patients received during the induction therapy:
- dexamethasone plus doxorubicin (arm A1/B1) or cyclophosphamide (arm A2/B2) as standard therapy

Alle patients received during intensification:
- cyclophosphamide base mobilization therapy (e.g. CAD) and high dose melphalan plus autologous stem cell transplantation

Evidence for comparator:

standard therapy for newly diagnosed multiple myeloma

Actual start date of recruitment	26 July 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	9 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 604
Worldwide total number of subjects	604
EEA total number of subjects	604

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)	447
From 65 to 84 years	157
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrolment periods:
1.) Inclusion of patients no. 0001– 0504 (for primary analyses):
FPI (first patient in): 26.07.2010
LPI (last patient in): 11.10.2012
Aimed patient number was reached prematurely.
2.) Inclusion of patients no. 0505 – 0604 (to perform additional descriptive and exploratory analyses):
FPI: 12.07.2013
LPI: 14.11.2013

Pre-assignment

Screening details:

The investigations required for checking the eligibility criteria and for enrollment usually are consistent with the routine medical care for myeloma patients at diagnosis and prior to treatment. Routine data obtained up to 3 weeks prior to enrollment could be used for screening.

Period 1

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

Blinding implementation details:

not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A1

Arm description:

Baseline of Arm A1 (PAd induction, lenalidomide maintenance for 2 years)

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

Dosage and administration details:

Bortezomib was given during induction therapy (3 cycles of PAd).
Dosage: 1,3 mg/m2 body surface area in induction cycle 1 – 3 on day 1, 4, 8 and 11, respectively. Dose adjustments due to toxicities were performed as described in the study protocol. The route of administration for bortezomib was changed from intravenous (patients 001 – 314) to subcutaneous (patients 315 – 604) after implementation of protocol version 2.0 due to an expected improvement of safety profile.

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

Dosage and administration details:

Continuous treatment with Lenalidomide. Dosage: 10 mg/d within the first 3 months of maintenance treatment. Subsequently the lenalidomide dose was increased to 15mg/d if the treatment was well tolerated. Lenalidomide maintenance was continued for 2 years or until disease progression.

Arm title	Arm B1

Arm description:

Baseline of arm B1 (PAd induction, lenalidomide maintenance if no CR)

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

Dosage and administration details:

Bortezomib was given during induction therapy (3 cycles of PAd).
Dosage: 1,3 mg/m2 body surface area in induction cycle 1 – 3 on day 1, 4, 8 and 11, respectively. Dose adjustments due to toxicities were performed as described in the study protocol. The route of administration for bortezomib was changed from intravenous (patients 001 – 314) to subcutaneous (patients 315 – 604) after implementation of protocol version 2.0 due to an expected improvement of safety profile.

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

Dosage and administration details:

In case patients did not achieve a complete response (CR) according to the IMWG criteria 2 after consolidation, maintenance treatment with lenalidomide was given. Maintenance treatment was stopped after achievement of a CR (Lenalidomide is given until confirmation of CR). Dosage: 10 mg/d (continuously) within the first 3 months of maintenance treatment. Subsequently the Lenalidomide dose was increased to 15mg/d if the treatment was well tolerated. In case no CR was achieved, Lenalidomide was given for 2 years or until disease progression.

Arm title	Arm A2

Arm description:

Baseline of arm A2 (VCD induction, lenalidomide maintenance for 2 years)

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

Dosage and administration details:

Bortezomib was given during induction therapy (3 cycles of VCD).
Dosage: 1,3 mg/m2 body surface area in induction cycle 1 – 3 on day 1, 4, 8 and 11, respectively. Dose adjustments due to toxicities were performed as described in the study protocol. The route of administration for bortezomib was changed from intravenous (patients 001 – 314) to subcutaneous (patients 315 – 604) after implementation of protocol version 2.0 due to an expected improvement of safety profile.

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

Dosage and administration details:

Continuous treatment with Lenalidomide. Dosage: 10 mg/d within the first 3 months of maintenance treatment. Subsequently the lenalidomide dose was increased to 15mg/d if the treatment was well tolerated. Lenalidomide maintenance was continued for 2 years or until disease progression.

Arm title	Arm B2

Arm description:

Baseline of arm B2 (VCD induction, lenalidomide maintenance if no CR)

Arm type	Experimental

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

Dosage and administration details:

Bortezomib was given during induction therapy (3 cycles of VCD).
Dosage: 1,3 mg/m2 body surface area in induction cycle 1 – 3 on day 1, 4, 8 and 11, respectively. Dose adjustments due to toxicities were performed as described in the study protocol. The route of administration for bortezomib was changed from intravenous (patients 001 – 314) to subcutaneous (patients 315 – 604) after implementation of protocol version 2.0 due to an expected improvement of safety profile.

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

Dosage and administration details:

In case patients did not achieve a complete response (CR) according to the IMWG criteria 2 after consolidation, maintenance treatment with lenalidomide was given. Maintenance treatment was stopped after achievement of a CR (Lenalidomide is given until confirmation of CR). Dosage: 10 mg/d (continuously) within the first 3 months of maintenance treatment. Subsequently the Lenalidomide dose was increased to 15mg/d if the treatment was well tolerated. In case no CR was achieved, Lenalidomide was given for 2 years or until disease progression.

Number of subjects in period 1	Arm A1	Arm B1	Arm A2
Started	150	150	151
Completed	149	148	150
Not completed	1	2	1
Consent withdrawn by subject	-	-	1
violation of inclusion criteria	1	-	-
Non compliance	-	-	-
Myocardial infarction previous to therapy	-	1	-
Death prior to therapy	-	1	-

Number of subjects in period 1	Arm B2
Started	153
Completed	149
Not completed	4
Consent withdrawn by subject	1
violation of inclusion criteria	2
Non compliance	1
Myocardial infarction previous to therapy	-
Death prior to therapy	-

Period 2

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

Blinding implementation details:

not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	PAd (arms A1+B1)

Arm description:

All patients randomized to study arms A1 and B1 received PAd for induction treatment, primary cohort.

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

Dosage and administration details:

Bortezomib was given during induction therapy (3 cycles of PAd).
Dosage: 1,3 mg/m2 body surface area in induction cycle 1 – 3 on day 1, 4, 8 and 11, respectively. Dose adjustments due to toxicities were performed as described in the study protocol. The route of administration for bortezomib was changed from intravenous (patients 001 – 314) to subcutaneous (patients 315 – 604) after implementation of protocol version 2.0 due to an expected improvement of safety profile.

Arm title	VCD (arms A2+B2)

Arm description:

All patients randomized to study arms A2 and B2 received VCD for induction treatment, primary cohort.

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

Dosage and administration details:

Bortezomib was given during induction therapy (3 cycles of VCD).
Dosage: 1,3 mg/m2 body surface area in induction cycle 1 – 3 on day 1, 4, 8 and 11, respectively. Dose adjustments due to toxicities were performed as described in the study protocol. The route of administration for bortezomib was changed from intravenous (patients 001 – 314) to subcutaneous (patients 315 – 604) after implementation of protocol version 2.0 due to an expected improvement of safety profile.

Number of subjects in period 2	PAd (arms A1+B1)	VCD (arms A2+B2)
Started	296	300
Completed	265	280
Not completed	31	20
Adverse event, serious fatal	5	2
Consent withdrawn by subject	2	-
Physician decision	1	2
Adverse event, non-fatal	2	2
Non compliance	4	2
High risk situation	5	9
Progressive disease	11	1
Lost to follow-up	-	1
Protocol deviation	1	-
patient's condition	-	1

Period 3	
Period 3 title	Intensification (ASCT) + Consolidation
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Standard Intensification + consolidation post PAd (A1+B1)

Arm description:

Standard mobilization + ASCT + Lenalidomide consolidation after PAd induction.

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

Dosage and administration details:

Standard stem cell mobilisation, standard high dose melphalan (200mg/m²) and autologous stem cell transplantation.
Consolidation with Lenalidomide. Dosage: 25 mg/d; day 1-21, start of cycle 2 at day 29.

Arm title	Standard Intensification + consolidation post VCD (Arm A2+B2

Arm description:

Standard mobilization + ASCT + Lenalidomide consolidation after VCD induction

Arm type	Experimental

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

Dosage and administration details:

Standard stem cell mobilisation, standard high dose melphalan (200mg/m²) and autologous stem cell transplantation.
Consolidation with Lenalidomide. Dosage: 25 mg/d; day 1-21, start of cycle 2 at day 29.

Number of subjects in period 3	Standard Intensification + consolidation post PAd (A1+B1)	Standard Intensification + consolidation post VCD (Arm A2+B2
Started	265	280
Completed	204	227
Not completed	61	53
Adverse event, serious fatal	8	8
Mobilization not effective	2	-
Allogeneic transplantation	1	1
observation, completion after 2 years	8	4
patient's condition	2	-
Consent withdrawn by subject	6	7
Adverse event, non-fatal	3	7
Non compliance	4	7
High risk situation	4	-
Progressive disease	21	16
Lost to follow-up	-	1
Lack of efficacy	2	1
Protocol deviation	-	1

Period 4

Period 4 title	Maintenance
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	Maintenance Arm A1

Arm description:

Lenalidomide maintenance for 2 years after PAd induction, standard intensification (ASCT) and lenalidomide consolidation

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

Dosage and administration details:

Continuous treatment with Lenalidomide. Dosage: 10 mg/d within the first 3 months of maintenance treatment. Subsequently the lenalidomide dose was increased to 15mg/d if the treatment was well tolerated. Lenalidomide maintenance was continued for 2 years or until disease progression.

Arm title	Maintenance Arm B1

Arm description:

Lenalidomide maintenance if no CR; after PAd induction, standard intensification (ASCT) and lenalidomide consolidation

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

Dosage and administration details:

In case patients did not achieve a complete response (CR) according to the IMWG criteria 2 after consolidation, maintenance treatment with lenalidomide was given. Maintenance treatment was stopped after achievement of a CR (Lenalidomide is given until confirmation of CR). Dosage: 10 mg/d (continuously) within the first 3 months of maintenance treatment. Subsequently the Lenalidomide dose was increased to 15mg/d if the treatment was well tolerated. In case no CR was achieved, Lenalidomide was given for 2 years or until disease progression.

Arm title	Maintenance Arm A2

Arm description:

Lenalidomide maintenance for 2 years after VCD induction, standard intensification (ASCT) and lenalidomide consolidation

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

Dosage and administration details:

Continuous treatment with Lenalidomide. Dosage: 10 mg/d within the first 3 months of maintenance treatment. Subsequently the lenalidomide dose was increased to 15mg/d if the treatment was well tolerated. Lenalidomide maintenance was continued for 2 years or until disease progression.

Arm title	Maintenance Arm B2

Arm description:

Lenalidomide maintenance if no CR after VCD induction, standard intensification (ASCT) and lenalidomide consolidation

Arm type	Experimental

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

Dosage and administration details:

In case patients did not achieve a complete response (CR) according to the IMWG criteria 2 after consolidation, maintenance treatment with lenalidomide was given. Maintenance treatment was stopped after achievement of a CR (Lenalidomide is given until confirmation of CR). Dosage: 10 mg/d (continuously) within the first 3 months of maintenance treatment. Subsequently the Lenalidomide dose was increased to 15mg/d if the treatment was well tolerated. In case no CR was achieved, Lenalidomide was given for 2 years or until disease progression.

Number of subjects in period 4	Maintenance Arm A1	Maintenance Arm B1	Maintenance Arm A2
Started	109	95	116
Completed	78	69	76
Not completed	31	26	40
Adverse event, serious fatal	-	-	3
Physician decision	1	1	-
Consent withdrawn by subject	-	-	3
Adverse event, non-fatal	3	-	1
Non compliance	-	2	1
Patient's decision	-	-	1
Progressive disease	27	23	29
Lost to follow-up	-	-	1
High risk situation	-	-	1
Protocol deviation	-	-	-

Number of subjects in period 4	Maintenance Arm B2
Started	111
Completed	68
Not completed	43
Adverse event, serious fatal	1
Physician decision	-
Consent withdrawn by subject	-
Adverse event, non-fatal	2
Non compliance	-
Patient's decision	-
Progressive disease	39
Lost to follow-up	-
High risk situation	-
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm A1
Reporting group description:	
Baseline of Arm A1 (PAd induction, lenalidomide maintenance for 2 years)	
Reporting group title	Arm B1
Reporting group description:	
Baseline of arm B1 (PAd induction, lenalidomide maintenance if no CR)	
Reporting group title	Arm A2
Reporting group description:	
Baseline of arm A2 (VCD induction, lenalidomide maintenance for 2 years)	
Reporting group title	Arm B2
Reporting group description:	
Baseline of arm B2 (VCD induction, lenalidomide maintenance if no CR)	

Reporting group values	Arm A1	Arm B1	Arm A2
Number of subjects	150	150	151
Age categorical Units: Subjects			
Adults - 18-70 years	150	150	151
Gender categorical Units: Subjects			
Female	81	88	87
Male	69	62	64

Reporting group values	Arm B2	Total	
Number of subjects	153	604	
Age categorical Units: Subjects			
Adults - 18-70 years	153	604	
Gender categorical Units: Subjects			
Female	97	353	
Male	56	251	

Subject analysis sets	
Subject analysis set title	ITT - expanded cohort
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intent-to-treat (ITT) population is defined as all patients randomized with written informed consent, excluding patients with violation of major eligibility criteria. Patients in the ITT population are analysed according to treatment randomized.
The expanded cohort consists of n=604 enrolled patients (increased patient number for additional exploratory analyses)

Subject analysis set title	Safety - expanded cohort
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population consists of all patients randomized which received at least one dose of trial medication, out of the expanded cohort of n=604 enrolled patients.
Patients are analysed as treated.

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

Subject analysis set description:

The intent-to-treat (ITT) population is defined as all patients randomized with written informed consent, excluding patients with violation of major eligibility criteria. Patients in the ITT population are analysed according to treatment randomized.
The primary cohort consists of n=504 enrolled patients (inital cohort, for primary analyses)

Subject analysis set title	Safety - primary cohort
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population (primary cohort) consists of all patients randomized which received at least one dose of trial medication - out of the primarily enrolled n=504 patients (initial cohort, for primary analyses).
Patients are analysed as treated.

Reporting group values	ITT - expanded cohort	Safety - expanded cohort	ITT - primary cohort
Number of subjects	601	598	502
Age categorical Units: Subjects			
Adults - 18-70 years	601	598	502
Gender categorical Units: Subjects			
Female			
Male			

Reporting group values	Safety - primary cohort		
Number of subjects	498		
Age categorical Units: Subjects			
Adults - 18-70 years	498		
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Arm A1
Reporting group description:	
Baseline of Arm A1 (PAd induction, lenalidomide maintenance for 2 years)	
Reporting group title	Arm B1
Reporting group description:	
Baseline of arm B1 (PAd induction, lenalidomide maintenance if no CR)	
Reporting group title	Arm A2
Reporting group description:	
Baseline of arm A2 (VCD induction, lenalidomide maintenance for 2 years)	
Reporting group title	Arm B2
Reporting group description:	
Baseline of arm B2 (VCD induction, lenalidomide maintenance if no CR)	
Reporting group title	PAd (arms A1+B1)
Reporting group description:	
All patients randomized to study arms A1 and B1 received PAd for induction treatment, primary cohort.	
Reporting group title	VCD (arms A2+B2)
Reporting group description:	
All patients randomized to study arms A2 and B2 received VCD for induction treatment, primary cohort.	
Reporting group title	Standard Intensification + consolidation post PAd (A1+B1)
Reporting group description:	
Standard mobilization + ASCT + Lenalidomide consolidation after PAd induction.	
Reporting group title	Standard Intensification + consolidation post VCD (Arm A2+B2
Reporting group description:	
Standard mobilization + ASCT + Lenalidomide consolidation after VCD induction	
Reporting group title	Maintenance Arm A1
Reporting group description:	
Lenalidomide maintenance for 2 years after PAd induction, standard intensification (ASCT) and lenalidomide consolidation	
Reporting group title	Maintenance Arm B1
Reporting group description:	
Lenalidomide maintenance if no CR; after PAd induction, standard intensification (ASCT) and lenalidomide consolidation	
Reporting group title	Maintenance Arm A2
Reporting group description:	
Lenalidomide maintenance for 2 years after VCD induction, standard intensification (ASCT) and lenalidomide consolidation	

Reporting group title	Maintenance Arm B2
Reporting group description:	
Lenalidomide maintenance if no CR after VCD induction, standard intensification (ASCT) and lenalidomide consolidation	

Subject analysis set title	ITT - expanded cohort
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The intent-to-treat (ITT) population is defined as all patients randomized with written informed consent, excluding patients with violation of major eligibility criteria. Patients in the ITT population are analysed according to treatment randomized. The expanded cohort consists of n=604 enrolled patients (increased patient number for additional exploratory analyses)	

Subject analysis set title	Safety - expanded cohort
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population consists of all patients randomized which received at least one dose of trial medication, out of the expanded cohort of n=604 enrolled patients.
Patients are analysed as treated.

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

Subject analysis set description:

The intent-to-treat (ITT) population is defined as all patients randomized with written informed consent, excluding patients with violation of major eligibility criteria. Patients in the ITT population are analysed according to treatment randomized.
The primary cohort consists of n=504 enrolled patients (inital cohort, for primary analyses)

Subject analysis set title	Safety - primary cohort
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population (primary cohort) consists of all patients randomized which received at least one dose of trial medication - out of the primarily enrolled n=504 patients (initial cohort, for primary analyses).
Patients are analysed as treated.

Primary: Progression free survival (primary cohort)

End point title	Progression free survival (primary cohort)

End point description:

time from randomisation to progression or death from any cause whichever occurs first

End point type	Primary

End point timeframe:

response assessment visits (after induction, after mobilization, after ASCT, after consolidation, every 3 months during maintenance)

End point values	Arm A1	Arm B1	Arm A2	Arm B2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	125	126	126	125
Units: months				
median (confidence interval 95%)	43.2 (37.3 to 51.8)	35.9 (26.4 to 47.7)	40.9 (32.8 to 56.2)	35.7 (30.5 to 41.6)

Statistical analyses

Statistical analysis title	PFS in all four treatment arms

Statistical analysis description:

The second primary endpoint of the trial is progression-free survival in all four treatment arms. The second primary analysis will be based on the ITT population as this is a superiority objective. Treatment arms are compared in a closed testing procedure as introduced by Marcus, Peritz and Gabriel (Biometrika, 1976).

Comparison groups	Arm A1 v Arm B1 v Arm A2 v Arm B2

Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.6
Method	Logrank

Notes:

[1] - closed testing procedure

Primary: VGPR+ rate after induction therapy (primary cohort)

End point title	VGPR+ rate after induction therapy (primary cohort)

End point description:

The first primary endpoint aimed at demonstrating non-inferiority of bortezomib/cyclophosphamide/dexamethasone (VCD) compared to bortezomib/doxorubicin/dexamethasone (PAd) induction therapy with respect to very good partial response rates or better (≥VGPR).

End point type	Primary

End point timeframe:

Response assessment after end of 3 cycles induction treatment

End point values	PAd (arms A1+B1)	VCD (arms A2+B2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	251	251		
Units: Number of responders				
Responders (VGPR+)	86	93		
Non-responder	165	158		

Statistical analyses

Statistical analysis title	Response (VGPR+) to treatment

Statistical analysis description:

The proportions of responders after induction treatment are compared between induction regimens at the non-inferiority margin of 10% difference. Patients without response assessment after induction therapy are defined as non-responders for the ITT analysis. The two-sided confidence interval using Newcombe's Hybrid score interval is calculated. This is the primary analysis as described in the protocol.

Comparison groups	PAd (arms A1+B1) v VCD (arms A2+B2)
Number of subjects included in analysis	502
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	= 0.0013
Method	Newcombe's Hybrid score interval

Notes:

[2] - If the lower limit of the confidence interval is above the non-inferiority margin, non-inferiority is established. In order to demonstrate non-inferiority of VCD, for both ITT and PP population NI needs to be confirmed. In addition, the one-sided null hypothesis of non-inferiority is tested with the method of Farrington and Manning matching sample size calculation methodology. The two-sided significance level for this final analysis is set to 2.4%, the one-sided level accordingly to 1.2%.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE reporting: from start of study treatment, during induction and subsequent 30days.
During intensification: only SAE reporting.
Re-start of reporting: during consolidation/maintenance, up to 30d after last study visit or start of subsequent therapy.

Adverse event reporting additional description:

All AEs CTCAE grade 3, 4 and 5 had to be reported during induction, consolidation and maintenance.
For specific AEs (polyneuropathy, thromboembolic events, infections, cardiac disorders) also CTC grade 2 events had to be reported.
All SAEs have to be reporting independent from CTCAE grade.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Safety population - expanded cohort

Reporting group description:

The safety population consists of all patients randomized which received at least one dose of trial medication. Patients are analysed as treated.
This is the safety population for the expanded cohort (after n=604 patients randomized)

Reporting group title	Safety population - primary cohort

Reporting group description:

The safety population consists of all patients randomized which received at least one dose of trial medication. Patients are analysed as treated.
This is the safety population for the primary cohort (after n=504 patients randomized)

Serious adverse events	Safety population - expanded cohort	Safety population - primary cohort	
Total subjects affected by serious adverse events			
subjects affected / exposed	305 / 598 (51.00%)	253 / 498 (50.80%)	
number of deaths (all causes)	177	160	
number of deaths resulting from adverse events	22	19	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified			
subjects affected / exposed	28 / 598 (4.68%)	23 / 498 (4.62%)	
occurrences causally related to treatment / all	24 / 33	21 / 28	
deaths causally related to treatment / all	4 / 7	4 / 7	
Vascular disorders			
Vascular disorders			

subjects affected / exposed	17 / 598 (2.84%)	16 / 498 (3.21%)	
occurrences causally related to treatment / all	15 / 22	15 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
subjects affected / exposed	12 / 598 (2.01%)	11 / 498 (2.21%)	
occurrences causally related to treatment / all	0 / 13	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	52 / 598 (8.70%)	40 / 498 (8.03%)	
occurrences causally related to treatment / all	24 / 72	23 / 52	
deaths causally related to treatment / all	1 / 2	1 / 2	
Immune system disorders			
Immune system disorders			
subjects affected / exposed	1 / 598 (0.17%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Social circumstances			
subjects affected / exposed	1 / 598 (0.17%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Reproductive system and breast disorders			
subjects affected / exposed	1 / 598 (0.17%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	27 / 598 (4.52%)	18 / 498 (3.61%)	
occurrences causally related to treatment / all	16 / 44	12 / 31	
deaths causally related to treatment / all	1 / 2	1 / 2	

Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	4 / 598 (0.67%)	3 / 498 (0.60%)	
occurrences causally related to treatment / all	2 / 6	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Product issues			
subjects affected / exposed	1 / 598 (0.17%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	27 / 598 (4.52%)	24 / 498 (4.82%)	
occurrences causally related to treatment / all	0 / 39	0 / 36	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	14 / 598 (2.34%)	9 / 498 (1.81%)	
occurrences causally related to treatment / all	2 / 19	1 / 14	
deaths causally related to treatment / all	0 / 3	0 / 2	
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	32 / 598 (5.35%)	28 / 498 (5.62%)	
occurrences causally related to treatment / all	22 / 47	21 / 41	
deaths causally related to treatment / all	0 / 1	0 / 1	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	28 / 598 (4.68%)	26 / 498 (5.22%)	
occurrences causally related to treatment / all	23 / 48	22 / 45	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Ear and labyrinth disorders			
subjects affected / exposed	3 / 598 (0.50%)	3 / 498 (0.60%)	
occurrences causally related to treatment / all	4 / 7	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eye disorders			
Eye disorders			
subjects affected / exposed	4 / 598 (0.67%)	3 / 498 (0.60%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	50 / 598 (8.36%)	44 / 498 (8.84%)	
occurrences causally related to treatment / all	53 / 109	49 / 99	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	3 / 598 (0.50%)	3 / 498 (0.60%)	
occurrences causally related to treatment / all	2 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	7 / 598 (1.17%)	4 / 498 (0.80%)	
occurrences causally related to treatment / all	4 / 9	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	20 / 598 (3.34%)	17 / 498 (3.41%)	
occurrences causally related to treatment / all	9 / 28	9 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	31 / 598 (5.18%)	26 / 498 (5.22%)	
occurrences causally related to treatment / all	8 / 37	7 / 30	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and infestations			
subjects affected / exposed	150 / 598 (25.08%)	119 / 498 (23.90%)	
occurrences causally related to treatment / all	139 / 267	121 / 205	
deaths causally related to treatment / all	1 / 7	1 / 4	

Investigations			
subjects affected / exposed	10 / 598 (1.67%)	9 / 498 (1.81%)	
occurrences causally related to treatment / all	5 / 15	5 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	11 / 598 (1.84%)	9 / 498 (1.81%)	
occurrences causally related to treatment / all	5 / 20	5 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Safety population - expanded cohort	Safety population - primary cohort	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	446 / 598 (74.58%)	370 / 498 (74.30%)	
Investigations			
Investigations			
subjects affected / exposed	113 / 598 (18.90%)	93 / 498 (18.67%)	
occurrences (all)	275	231	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	30 / 598 (5.02%)	26 / 498 (5.22%)	
occurrences (all)	37	32	
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	103 / 598 (17.22%)	91 / 498 (18.27%)	
occurrences (all)	128	112	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	253 / 598 (42.31%)	214 / 498 (42.97%)	
occurrences (all)	798	684	
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	49 / 598 (8.19%)	40 / 498 (8.03%)	
occurrences (all)	60	49	
Gastrointestinal disorders			

Gastrointestinal disorders			
subjects affected / exposed	32 / 598 (5.35%)	30 / 498 (6.02%)	
occurrences (all)	39	37	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	25 / 598 (4.18%)	22 / 498 (4.42%)	
occurrences (all)	29	25	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	25 / 598 (4.18%)	24 / 498 (4.82%)	
occurrences (all)	32	31	
Infections and infestations			
Infections and infestations			
alternative assessment type: Systematic			
subjects affected / exposed	214 / 598 (35.79%)	170 / 498 (34.14%)	
occurrences (all)	461	369	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	59 / 598 (9.87%)	57 / 498 (11.45%)	
occurrences (all)	89	87	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 November 2011	The route of administration for bortezomib was changed from intravenous to subcutaneous for all patients newly randomized due to an expected improvement of safety profile.
06 June 2013	(a) Enrollment of additional 100 patients for additional descriptive and explorative analyses (i.e. to test the expected improvement in the safety profile of subcutaneous administration compared to intravenous administration of bortezomib in a comparable number of patients). (b) Change of bortezomib from study drug to commercial drug.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

not applicable

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32034285

http://www.ncbi.nlm.nih.gov/pubmed/25787915

http://www.ncbi.nlm.nih.gov/pubmed/27540135