Clinical trial results:
A randomized phase III trial on the effect of elotuzumab in VRD induction /consolidation and lenalidomide maintenance in patients with newly diagnosed myeloma

Summary

EudraCT number	2014-003079-40
Trial protocol	DE
Global end of trial date	24 June 2021

Results information

Result version number	v1 (current)
This version publication date	16 January 2023
First version publication date	16 January 2023

Trial information

Trial identification

Sponsor protocol code	GMMG-HD6

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02495922
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, GMMG Study Office, 0049 6221568015, studiensekretariat.gmmg@med.uni-heidelberg.de
Scientific contact	GMMG Studiensekretariat, GMMG Study Office, 0049 6221568015, 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	02 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 June 2021
Global end of trial reached?	Yes
Global end of trial date	24 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is the determination of the best of four treatment strategies regarding progression-free survival (PFS). The four treatment strategies are
1. (arm A1): VRD (Bortezomib (Velcade) / Lenalidomide (Revlimid) / Dexamethasone) induction, standard intensification, VRD consolidation and lenalidomide maintenance
2. (arm A2): VRD induction, standard intensification, VRD + elotuzumab consolidation and lenalidomide maintenance + elotuzumab
3. (arm B1): VRD + elotuzumab induction, standard intensification, VRD consolidation and lenalidomide maintenance
4. (arm B2): VRD + elotuzumab induction, standard intensification, VRD + elotuzumab consolidation and lenalidomide maintenance + elotuzumab

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:
- VRD (Bortezomib, lenalidomide, dexamethasone)

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

All patients received during the maintenance therapy:
- lenalidomide

Evidence for comparator:

standard therapy for newly diagnosed multiple myeloma

Actual start date of recruitment	29 June 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 564
Worldwide total number of subjects	564
EEA total number of subjects	564

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)	427
From 65 to 84 years	137
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrolment periods:
1.) Inclusion of patients no. 0001– 0516
FPI (first patient in): 29.06.2015
LPI (last patient in): 04.05.2017
Aimed patient number was reached prematurely. After an amendment additional patients were enrolled.
2.) Inclusion of patients no. 0517 – 0564:
FPI (first patient in): 30.06.2017
LPI (last patient in): 11.09.2017

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:

VRD (Bortezomib (Velcade) / Lenalidomide (Revlimid) / Dexamethasone) induction, intensification, VRD consolidation and lenalidomide maintenance

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:

Lenalidomide was given in induction, consolidation and maintenance.
Induction:
25mg/d for d1-d14 in 4 cycles of 21 days.
Consolidation:
25mg/d for d1-d14 in 2 cycles of 21 days.
Maintenance:
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 A2

Arm description:

VRD induction, intensification, VRD + elotuzumab consolidation and lenalidomide maintenance + elotuzumab

Arm type	Experimental

Investigational medicinal product name	Elotuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Consolidation:
Elotuzumab 10mg/kg on d1, d8 and d15 in 2 cycles (21d)
Maintenance:
Elotuzumab 10mg/kg
for first 6 months: d1 and d15 of each cycle (28d cycles)
subsequently: d1 of each cycle

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

Dosage and administration details:

Lenalidomide was given in induction, consolidation and maintenance.
Induction:
25mg/d for d1-d14 in 4 cycles of 21 days.
Consolidation:
25mg/d for d1-d14 in 2 cycles of 21 days.
Maintenance:
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:

VRD + elotuzumab induction, intensification, VRD consolidation and lenalidomide maintenance

Arm type	Experimental
Investigational medicinal product name	Elotuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Induction
Elotuzumab 10mg/kg
- d1, d8 and d15 in cycle 1 and 2 (duration of each cycle: 21d)
- d1, d11 in cycle 3 and 4 (duration of each cycle: 21d)

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

Dosage and administration details:

Lenalidomide was given in induction, consolidation and maintenance.
Induction:
25mg/d for d1-d14 in 4 cycles of 21 days.
Consolidation:
25mg/d for d1-d14 in 2 cycles of 21 days.
Maintenance:
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:

VRD + elotuzumab induction, intensification, VRD + elotuzumab consolidation and lenalidomide maintenance + elotuzumab

Arm type	Experimental
Investigational medicinal product name	Elotuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Induction
Elotuzumab 10mg/kg
- d1, d8 and d15 in cycle 1 and 2 (duration of each cycle: 21d)
- d1, d11 in cycle 3 and 4 (duration of each cycle: 21d)
Consolidation:
Elotuzumab 10mg/kg on d1, d8 and d15 in 2 cycles (21d)
Maintenance:
Elotuzumab 10mg/kg
for first 6 months: d1 and d15 of each cycle (28d cycles)
subsequently: d1 of each cycle

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

Dosage and administration details:

Lenalidomide was given in induction, consolidation and maintenance.
Induction:
25mg/d for d1-d14 in 4 cycles of 21 days.
Consolidation:
25mg/d for d1-d14 in 2 cycles of 21 days.
Maintenance:
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.

Number of subjects in period 1	Arm A1	Arm A2	Arm B1
Started	140	142	139
Completed	139	141	137
Not completed	1	1	2
violation of inclusion/exclusion criteria	1	1	2

Number of subjects in period 1	Arm B2
Started	143

Completed	142
Not completed	1
violation of inclusion/exclusion criteria	1

Period 2

Period 2 title	Treatment period
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	Arm A1

Arm description:

VRD (Bortezomib (Velcade) / Lenalidomide (Revlimid) / Dexamethasone) induction, intensification, VRD consolidation and lenalidomide maintenance

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:

Lenalidomide was given in induction, consolidation and maintenance.
Induction:
25mg/d for d1-d14 in 4 cycles of 21 days.
Consolidation:
25mg/d for d1-d14 in 2 cycles of 21 days.
Maintenance:
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 A2

Arm description:

VRD induction, intensification, VRD + elotuzumab consolidation and lenalidomide maintenance + elotuzumab

Arm type	Experimental
Investigational medicinal product name	Elotuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Consolidation:
Elotuzumab 10mg/kg on d1, d8 and d15 in 2 cycles (21d)

Maintenance:
Elotuzumab 10mg/kg
for first 6 months: d1 and d15 of each cycle (28d cycles)
subsequently: d1 of each cycle

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

Dosage and administration details:

Lenalidomide was given in induction, consolidation and maintenance.
Induction:
25mg/d for d1-d14 in 4 cycles of 21 days.
Consolidation:
25mg/d for d1-d14 in 2 cycles of 21 days.
Maintenance:
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:

VRD + elotuzumab induction, intensification, VRD consolidation and lenalidomide maintenance

Arm type	Experimental
Investigational medicinal product name	Elotuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Induction
Elotuzumab 10mg/kg
- d1, d8 and d15 in cycle 1 and 2 (duration of each cycle: 21d)
- d1, d11 in cycle 3 and 4 (duration of each cycle: 21d)

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

Dosage and administration details:

Lenalidomide was given in induction, consolidation and maintenance.
Induction:
25mg/d for d1-d14 in 4 cycles of 21 days.
Consolidation:
25mg/d for d1-d14 in 2 cycles of 21 days.
Maintenance:
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:

VRD + elotuzumab induction, intensification, VRD + elotuzumab consolidation and lenalidomide maintenance + elotuzumab

Arm type	Experimental

Investigational medicinal product name	Elotuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Induction
Elotuzumab 10mg/kg
- d1, d8 and d15 in cycle 1 and 2 (duration of each cycle: 21d)
- d1, d11 in cycle 3 and 4 (duration of each cycle: 21d)
Consolidation:
Elotuzumab 10mg/kg on d1, d8 and d15 in 2 cycles (21d)
Maintenance:
Elotuzumab 10mg/kg
for first 6 months: d1 and d15 of each cycle (28d cycles)
subsequently: d1 of each cycle

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

Dosage and administration details:

Lenalidomide was given in induction, consolidation and maintenance.
Induction:
25mg/d for d1-d14 in 4 cycles of 21 days.
Consolidation:
25mg/d for d1-d14 in 2 cycles of 21 days.
Maintenance:
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.

Number of subjects in period 2	Arm A1	Arm A2	Arm B1
Started	139	141	137
Completed	68	80	68
Not completed	71	61	69
Adverse event, serious fatal	4	4	6
Consent withdrawn by subject	5	8	2
Physician decision	5	4	6
Adverse event, non-fatal	20	16	24
Subject non-compliance	3	1	1
other	7	3	6
Progressive disease	26	23	22
Lost to follow-up	1	-	1
High risk situation and change of therapy	-	2	-
Protocol deviation	-	-	1

Number of subjects in period 2	Arm B2

Started	142
Completed	76
Not completed	66
Adverse event, serious fatal	5
Consent withdrawn by subject	7
Physician decision	3
Adverse event, non-fatal	16
Subject non-compliance	2
other	5
Progressive disease	26
Lost to follow-up	2
High risk situation and change of therapy	-
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm A1
Reporting group description:	
VRD (Bortezomib (Velcade) / Lenalidomide (Revlimid) / Dexamethasone) induction, intensification, VRD consolidation and lenalidomide maintenance	
Reporting group title	Arm A2
Reporting group description:	
VRD induction, intensification, VRD + elotuzumab consolidation and lenalidomide maintenance + elotuzumab	
Reporting group title	Arm B1
Reporting group description:	
VRD + elotuzumab induction, intensification, VRD consolidation and lenalidomide maintenance	
Reporting group title	Arm B2
Reporting group description:	
VRD + elotuzumab induction, intensification, VRD + elotuzumab consolidation and lenalidomide maintenance + elotuzumab	

Reporting group values	Arm A1	Arm A2	Arm B1
Number of subjects	140	142	139
Age categorical Units: Subjects			
Adults 18-64 years	107	111	105
Adults 65-70 years	33	31	34
Gender categorical Units: Subjects			
Female	59	66	54
Male	81	76	85

Reporting group values	Arm B2	Total	
Number of subjects	143	564	
Age categorical Units: Subjects			
Adults 18-64 years	104	427	
Adults 65-70 years	39	137	
Gender categorical Units: Subjects			
Female	65	244	
Male	78	320	

Subject analysis sets	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients randomized. Not included in the ITT population are patients who withdraw informed consent before start of treatment or about whom it becomes known, that major in/exclusion criteria were violated which would have excluded them from study treatment when known at start of treatment.	

Reporting group values	ITT population		
Number of subjects	559		
Age categorical Units: Subjects			
Adults 18-64 years	136		
Adults 65-70 years	423		
Gender categorical Units: Subjects			
Female	243		
Male	316		

End points

End points reporting groups

Reporting group title	Arm A1
Reporting group description:	
VRD (Bortezomib (Velcade) / Lenalidomide (Revlimid) / Dexamethasone) induction, intensification, VRD consolidation and lenalidomide maintenance	
Reporting group title	Arm A2
Reporting group description:	
VRD induction, intensification, VRD + elotuzumab consolidation and lenalidomide maintenance + elotuzumab	
Reporting group title	Arm B1
Reporting group description:	
VRD + elotuzumab induction, intensification, VRD consolidation and lenalidomide maintenance	
Reporting group title	Arm B2
Reporting group description:	
VRD + elotuzumab induction, intensification, VRD + elotuzumab consolidation and lenalidomide maintenance + elotuzumab	
Reporting group title	Arm A1
Reporting group description:	
VRD (Bortezomib (Velcade) / Lenalidomide (Revlimid) / Dexamethasone) induction, intensification, VRD consolidation and lenalidomide maintenance	
Reporting group title	Arm A2
Reporting group description:	
VRD induction, intensification, VRD + elotuzumab consolidation and lenalidomide maintenance + elotuzumab	
Reporting group title	Arm B1
Reporting group description:	
VRD + elotuzumab induction, intensification, VRD consolidation and lenalidomide maintenance	
Reporting group title	Arm B2
Reporting group description:	
VRD + elotuzumab induction, intensification, VRD + elotuzumab consolidation and lenalidomide maintenance + elotuzumab	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients randomized. Not included in the ITT population are patients who withdraw informed consent before start of treatment or about whom it becomes known, that major in/exclusion criteria were violated which would have excluded them from study treatment when known at start of treatment.	

Primary: Progression free survival

End point title	Progression free survival
End point description:	
Progression-free survival (PFS) is defined as time from randomization to progression or death from any cause, whichever occurs first. PFS is censored at the date of the last response assessment. Patients without any response assessment after randomization are censored at the date of randomization. High-risk patients leaving the study and receiving an allogeneic transplantation are censored at the date of transplantation. If the interval between two response assessments exceeds 5.5 months during protocol treatment (until end of study) or 8 months during follow-up right before the diagnosis of PD, PFS is censored at the last date	

of response before this interval.

End point type	Primary

End point timeframe:

Response assessment visits (after induction, after mobilization, after ASCT, every 3month during maintenance)

End point values	Arm A1	Arm A2	Arm B1	Arm B2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	139	141	137	142
Units: survival probability				
number (confidence interval 95%)				
3 year PFS rate	68.8 (60.9 to 76.8)	68.5 (60.7 to 76.4)	66.2 (58.2 to 74.3)	67.2 (59.2 to 75.2)

Statistical analyses

Statistical analysis title	progression free survival

Statistical analysis description:

The primary analysis of PFS is based on the ITT population.
The four treatment arms were compared in a closed testing procedure as introduced by Marcus, Peritz and Gabriel (1976).
Kaplan-Meier estimates are provided giving the 3 year survival probability including 95% confidence interval.

Comparison groups	Arm A1 v Arm A2 v Arm B1 v Arm B2
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE reporting: from start of study treatment, during induction and subsequent 40days.
During intensification: only SAE reporting.
Re-start of reporting: during consolidation/maintenance, up to 40d after last study visit or start of subsequent therapy.

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Safety population

Reporting group description: -

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	351 / 555 (63.24%)		
number of deaths (all causes)	78		
number of deaths resulting from adverse events	24		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms			
subjects affected / exposed	32 / 555 (5.77%)		
occurrences causally related to treatment / all	24 / 36		
deaths causally related to treatment / all	2 / 5		
Vascular disorders			
Vascular disorders			
subjects affected / exposed	16 / 555 (2.88%)		
occurrences causally related to treatment / all	8 / 18		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	3 / 555 (0.54%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	59 / 555 (10.63%)		
occurrences causally related to treatment / all	24 / 73		
deaths causally related to treatment / all	0 / 4		
Immune system disorders			
Immune system disorders			
subjects affected / exposed	5 / 555 (0.90%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	33 / 555 (5.95%)		
occurrences causally related to treatment / all	16 / 37		
deaths causally related to treatment / all	1 / 4		
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	6 / 555 (1.08%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		
Product issues			
Product issues			
subjects affected / exposed	2 / 555 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Investigations			
Investigations			
subjects affected / exposed	13 / 555 (2.34%)		
occurrences causally related to treatment / all	3 / 15		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			

subjects affected / exposed	27 / 555 (4.86%)		
occurrences causally related to treatment / all	1 / 30		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	26 / 555 (4.68%)		
occurrences causally related to treatment / all	16 / 30		
deaths causally related to treatment / all	1 / 2		
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	47 / 555 (8.47%)		
occurrences causally related to treatment / all	21 / 57		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
alternative assessment type: Non-systematic			
subjects affected / exposed	17 / 555 (3.06%)		
occurrences causally related to treatment / all	7 / 19		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Ear and labyrinth disorders			
subjects affected / exposed	1 / 555 (0.18%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Eye disorders			
subjects affected / exposed	5 / 555 (0.90%)		
occurrences causally related to treatment / all	3 / 6		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	49 / 555 (8.83%)		
occurrences causally related to treatment / all	12 / 63		
deaths causally related to treatment / all	1 / 1		
Hepatobiliary disorders			

Hepatobiliary disorders			
subjects affected / exposed	9 / 555 (1.62%)		
occurrences causally related to treatment / all	4 / 9		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	7 / 555 (1.26%)		
occurrences causally related to treatment / all	3 / 7		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	27 / 555 (4.86%)		
occurrences causally related to treatment / all	15 / 32		
deaths causally related to treatment / all	2 / 2		
Endocrine disorders			
Endocrine disorders			
subjects affected / exposed	1 / 555 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	27 / 555 (4.86%)		
occurrences causally related to treatment / all	3 / 29		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infections and infestations			
subjects affected / exposed	188 / 555 (33.87%)		
occurrences causally related to treatment / all	129 / 300		
deaths causally related to treatment / all	6 / 14		
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	27 / 555 (4.86%)		
occurrences causally related to treatment / all	11 / 32		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events subjects affected / exposed	468 / 555 (84.32%)		
Nervous system disorders			
Polyneuropathy			
subjects affected / exposed	130 / 555 (23.42%)		
occurrences (all)	151		
Peripheral sensory neuropathy			
subjects affected / exposed	61 / 555 (10.99%)		
occurrences (all)	76		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	77 / 555 (13.87%)		
occurrences (all)	184		
Thrombocytopenia			
subjects affected / exposed	54 / 555 (9.73%)		
occurrences (all)	82		
Neutrophil count decrease			
subjects affected / exposed	52 / 555 (9.37%)		
occurrences (all)	128		
Lymphocyte count decreased			
subjects affected / exposed	42 / 555 (7.57%)		
occurrences (all)	94		
Platelet count decrease			
subjects affected / exposed	41 / 555 (7.39%)		
occurrences (all)	58		
Leukopenia			
subjects affected / exposed	35 / 555 (6.31%)		
occurrences (all)	45		
Lymphopenia			

subjects affected / exposed	33 / 555 (5.95%)		
occurrences (all)	66		
Anaemia			
subjects affected / exposed	28 / 555 (5.05%)		
occurrences (all)	51		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	30 / 555 (5.41%)		
occurrences (all)	38		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	30 / 555 (5.41%)		
occurrences (all)	39		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	92 / 555 (16.58%)		
occurrences (all)	153		
Bronchitis			
subjects affected / exposed	64 / 555 (11.53%)		
occurrences (all)	83		
Nasopharyngitis			
subjects affected / exposed	43 / 555 (7.75%)		
occurrences (all)	83		
Respiratory tract infection			
subjects affected / exposed	35 / 555 (6.31%)		
occurrences (all)	47		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 2016	(a) Changes in the scientific program (inclusion of additional objectives and requirement of additional blood and bone marrow samples) (b) Implementation of the updated Pregnancy Prevention Program (c) Clarification of definitions for "end of study"
03 May 2017	(a) Change in sample size and trial duration: sample size was increased to n=564 patients. (b) Marketing Authorization of Lenalidomide for maintenance therapy (c) Correction of detailed definition of primary endpoint (d) Clarifications regarding laboratory investigations and Follow up documentation

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/31138244