Clinical trial results:
Lenalidomide (Revlimid®), Adriamycin and Dexamethasone (RAD) as an Induction Therapy in Newly Diagnosed Multiple Myeloma Followed by a Risk-Defined Transplant Strategy and Lenalidomide Maintenance – A Multicenter Phase II Trial by Deutsche Studiengruppe Multiples Myelom

Summary

EudraCT number	2008-000007-28
Trial protocol	DE
Global end of trial date	20 April 2016

Results information

Result version number	v1 (current)
This version publication date	10 July 2022
First version publication date	10 July 2022

Trial information

Trial identification

Sponsor protocol code	DSMMXII

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00925821
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Wuerzburg University Hospital, Dept. of Hematology and Oncology, Center for Internal Medicine (ZIM)
Sponsor organisation address	Oberduerrbacher Str. 6, Wuerzburg, Germany, 97080
Public contact	Wuerzburg University Hospital Dept. of Hematology and Oncology Center for Internal Medicine (ZIM), Wuerzburg University Hospital Dept. of Hematology and Oncology Center for Internal Medicine (ZIM), +49 93120135156,
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 April 2016
Global end of trial reached?	Yes
Global end of trial date	20 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine efficacy of the novel induction regimen (combination of lenalidomide, adriamycin, and dexamethasone; RAD) followed by a risk-defined transplant strategy and subsequent lenalidomide maintenance in patients with symptomatic multiple myeloma

Protection of trial subjects:

Safety monitoring (adverse events, serious adverse events, adverse drug reactions) and continuous assessment of laboratory values (hematology and biochemistry assessments).
Subject insurance according to §40 Article 1 No. 8 and Article 3 German Drug Law had been obtained.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 August 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 190
Worldwide total number of subjects	190
EEA total number of subjects	190

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)	183
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient (FPFV) was enrolled on 18th August 2009. Last-patient-last visit (LPLV) took place on 20th April 2016. 215 patients were recruited by 17 clincial sites in Germany. 25 patients did not enter the treatment phase, i.e. 190 received treatment. Data are available for these 190 patients.

Pre-assignment

Screening details:

All subjects were screened for eligibility. Screning had to take place within 28 days prior to initiation of therapy.

Period 1

Period 1 title	Screening phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All patients enrolled

Arm description:

All screened patients, including n=25 patients not treated.

Arm type	Screened

No investigational medicinal product assigned in this arm

Number of subjects in period 1	All patients enrolled
Started	190
Completed	190

Period 2

Period 2 title	RAD phase
Is this the baseline period?	Yes[1]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	RAD chemotherapy
Arm description:	
Induction therapy with four 28-day cycles of RAD (lenalidomide, adriamycin, dexamethasone).	
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:	
25 mg / day, day 1-21	
Investigational medicinal product name	Adriamycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
9 mg/m2 for four consecutive days	
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
40 mg po, day 1-4 & day 17-20.	

Investigational medicinal product name	Pegfilgrastim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
6 mg day 6 (+2), single dose	

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Records of all subjects who signed an ICF, i.e. all subjects screened, were kept at the investigational sites. Data were documented in the CRF from the start of the RAD phase only. Complete BL data are therefore available for analysis the FAS/Safety set only.

Number of subjects in period 2	RAD chemotherapy
Started	190
Completed	157
Not completed	33
Consent withdrawn by subject, Lost to follow-up	1
Consent withdrawn by subject	5
Adverse event, non-fatal	11
Other	4
Progression	11

Lost to follow-up	1

Period 3

Period 3 title	Transplantation phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	autograft-allograft arm

Arm description:

An allogeneic stem cell graft was offered to subjects displaying features that have previously been associated with an adverse prognosis for whom a fully HLAidentical sibling or unrelated donor is available.

Arm type	Experimental
Investigational medicinal product name	Cyclophosphamide/etoposide stem cell mobilization
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Cyclophosphamide 2500 mg/m2 iv, day 1 (3 h infusion)
Etoposide 200 mg/m2 iv, days 1-3 (1 h infusion)

Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

100 mg/m2/day, day -3 and -2

Investigational medicinal product name	Treosulfan/fludarabine conditioning
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Treosulfan 14 g/m2/d, iv, day -6 to -4
Fludarabine 30 mg/m2/d, iv, day -6 to -4

Arm title	autograft-autograft arm

Arm description:

All patients not displaying risk parameters were assigned to be of “very favorable” risk. They were not offered an allogeneic graft, but received a second cycle of high-dose melphalan and autologous PBPC transplantation together with those of the high-risk patients without a donor.

Arm type	Experimental
Investigational medicinal product name	Cyclophosphamide/etoposide stem cell mobilization
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

Cyclophosphamide 2500 mg/m2 iv, day 1 (3 h infusion)
Etoposide 200 mg/m2 iv, days 1-3 (1 h infusion)

Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Infusion

Dosage and administration details:

100 mg/m2/day, day -3 and -2

Arm title	No second SCT

Arm description:

Patients who did not receive a second stem cell transplant (SCT)

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 3	autograft-allograft arm	autograft-autograft arm	No second SCT
Started	49	84	24
Completed	22	77	0
Not completed	27	7	24
Consent withdrawn by subject	1	-	3
Adverse event, Progression, Death	1	-	-
Adverse event, non-fatal	2	1	1
Other	13	3	6
Death	2	1	1
Progression	2	-	9
AE, Further criteria for next phase not fulfilled	1	-	-
Further criteria for next phase not fulfilled	5	1	2
Protocol deviation	-	1	2

Period 4

Period 4 title	Maintenance phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	autograft-allograft arm

Arm description:

An allogeneic stem cell graft was offered to subjects displaying features that have previously been associated with an adverse prognosis for whom a fully HLAidentical sibling or unrelated donor is available.
Lenalidomide maintenance therapy for a maximum duration of 12 months was instituted in all patients completing both transplantations.

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 patients with an allogeneic transplant, lenalidomide maintenance was given at a dose of 5 mg once daily continuously (reduced to 5 mg on day 1- day 21 of a 28-day cycle from Amendment 5 onwards). Lenalidomide maintenance therapy was given for a maximum of 12 months or until progression.

Arm title	autograft-autograft arm

Arm description:

All patients not displaying risk parameters were assigned to be of "very favorable" risk. They were not offered an allogeneic graft, but received a second cycle of high-dose melphalan and autologous PBPC transplantation together with those of the high-risk patients without a donor.
Lenalidomide maintenance therapy for a maximum duration of 12 months is instituted in all patients completing both transplantations.

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:

Patients with a tandem autoSCT received lenalidomide maintenance therapy at a dose of 10 mg continuously once daily. Lenalidomide maintenance therapy was given for a maximum of 12 months or until progression.

Number of subjects in period 4	autograft-allograft arm	autograft-autograft arm
Started	22	77
Completed	8	54
Not completed	14	23
Adverse event, serious fatal	1	-
Adverse event, Other	-	2

Consent withdrawn by subject	-	2
Adverse event, non-fatal	2	10
Death	1	2
Other	7	2
Progression	3	4
Adverse event, Death	-	1

Baseline characteristics

Reporting groups	
Reporting group title	RAD chemotherapy
Reporting group description:	
Induction therapy with four 28-day cycles of RAD (lenalidomide, adriamycin, dexamethasone).	

Reporting group values	RAD chemotherapy	Total	
Number of subjects	190	190	
Age categorical Units: Subjects			
Adults (18-64 years)	189	189	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous Units: years			
median	55.0		
full range (min-max)	30.0 to 66.0	-	
Gender categorical Units: Subjects			
Female	64	64	
Male	126	126	

Subject analysis sets	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who have received at least one dose of RAD induction chemotherapy were included in the safety analysis. The safety set was used for all baseline and safety parameters.	

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT analysis included all patients of the safety set as full analysis set. The full analysis set was used for all efficacy parameters.	

Subject analysis set title	FAS - Auto-allo SCT
Subject analysis set type	Full analysis
Subject analysis set description:	
An allogeneic stem cell graft was offered to subjects displaying features that have previously been associated with an adverse prognosis for whom a fully HLAidentical sibling or unrelated donor is available.	

Subject analysis set title	FAS - Auto-auto SCT
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients not displaying risk parameters were assigned to be of “very favorable” risk. They were not offered an allogeneic graft, but received a second cycle of high-dose melphalan and autologous PBPC transplantation together with those of the high-risk patients without a donor.	

Subject analysis set title	FAS - no second SCT
Subject analysis set type	Full analysis

Subject analysis set description:

Patients who did not receive a second stem cell transplant (SCT)

Subject analysis set title	FAS for statistical analysis of primary endpoint.
Subject analysis set type	Full analysis

Subject analysis set description:

For formal reasons, a second FAS needed to be defined since EudraCT does not support the statistical analysis of single-arm studies, see FAQ 82.

Reporting group values	Safety Set	Full Analysis Set (FAS)	FAS - Auto-allo SCT
Number of subjects	190	190	49
Age categorical Units: Subjects			
Adults (18-64 years)	189		
From 65-84 years	1		
85 years and over	0		
Age continuous Units: years			
median	54.2		
full range (min-max)			
Gender categorical Units: Subjects			
Female	64		
Male	126		

Reporting group values	FAS - Auto-auto SCT	FAS - no second SCT	FAS for statistical analysis of primary endpoint.
Number of subjects	84	57	190
Age categorical Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
median			
full range (min-max)			
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	All patients enrolled
Reporting group description:	
All screened patients, including n=25 patients not treated.	

Reporting group title	RAD chemotherapy
Reporting group description:	
Induction therapy with four 28-day cycles of RAD (lenalidomide, adriamycin, dexamethasone).	

Reporting group title	autograft-allograft arm
Reporting group description:	
An allogeneic stem cell graft was offered to subjects displaying features that have previously been associated with an adverse prognosis for whom a fully HLAidentical sibling or unrelated donor is available.	

Reporting group title	autograft-autograft arm
Reporting group description:	
All patients not displaying risk parameters were assigned to be of “very favorable” risk. They were not offered an allogeneic graft, but received a second cycle of high-dose melphalan and autologous PBPC transplantation together with those of the high-risk patients without a donor.	

Reporting group title	No second SCT
Reporting group description:	
Patients who did not receive a second stem cell transplant (SCT)	

Reporting group title	autograft-allograft arm
Reporting group description:	
An allogeneic stem cell graft was offered to subjects displaying features that have previously been associated with an adverse prognosis for whom a fully HLAidentical sibling or unrelated donor is available. Lenalidomide maintenance therapy for a maximum duration of 12 months was instituted in all patients completing both transplantations.	

Reporting group title	autograft-autograft arm
Reporting group description:	
All patients not displaying risk parameters were assigned to be of “very favorable” risk. They were not offered an allogeneic graft, but received a second cycle of high-dose melphalan and autologous PBPC transplantation together with those of the high-risk patients without a donor. Lenalidomide maintenance therapy for a maximum duration of 12 months is instituted in all patients completing both transplantations.	

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who have received at least one dose of RAD induction chemotherapy were included in the safety analysis. The safety set was used for all baseline and safety parameters.	

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT analysis included all patients of the safety set as full analysis set. The full analysis set was used for all efficacy parameters.	

Subject analysis set title	FAS - Auto-allo SCT
Subject analysis set type	Full analysis
Subject analysis set description:	
An allogeneic stem cell graft was offered to subjects displaying features that have previously been associated with an adverse prognosis for whom a fully HLAidentical sibling or unrelated donor is available.	

Subject analysis set title	FAS - Auto-auto SCT
Subject analysis set type	Full analysis

Subject analysis set description:

All patients not displaying risk parameters were assigned to be of "very favorable" risk. They were not offered an allogeneic graft, but received a second cycle of high-dose melphalan and autologous PBPC transplantation together with those of the high-risk patients without a donor.

Subject analysis set title	FAS - no second SCT
Subject analysis set type	Full analysis

Subject analysis set description:

Patients who did not receive a second stem cell transplant (SCT)

Subject analysis set title	FAS for statistical analysis of primary endpoint.
Subject analysis set type	Full analysis

Subject analysis set description:

For formal reasons, a second FAS needed to be defined since EudraCT does not support the statistical analysis of single-arm studies, see FAQ 82.

Primary: Response rate (sCR, CR, or VGPR)

End point title	Response rate (sCR, CR, or VGPR)

End point description:

Response rate (sCR, CR, or VGPR) at the start of scheduled lenalidomide maintenance.
For patients with NE or missing, e.g. due to termination before the 3rd restaging, the data of the last assessment before restaging 3 were imputed.

The reposnse rate without data imputation, i.e. when NE or missing are analysed as non-responder, is 89/190, 46.8% (90%-CI 40.7, 53.1).

End point type	Primary

End point timeframe:

3rd restaging after transplantation phase, at the start of maintenance therapy.

End point values	Full Analysis Set (FAS)	FAS for statistical analysis of primary endpoint.		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	190	190		
Units: Response rate (%)				
number (confidence interval 90%)	62.6 (56.5 to 68.5)	62.6 (56.5 to 68.5)		

Statistical analyses

Statistical analysis title	Primary endpoint analysis

Statistical analysis description:

The primary objective of the study was to demonstrate with a power of 90% and a one-sided type I error rate of α=0.05 that the true response rate was at least 47.5%.

Comparison groups	Full Analysis Set (FAS) v FAS for statistical analysis of primary endpoint.

Number of subjects included in analysis	380
Analysis specification	Pre-specified
Analysis type	superiority[1]
Parameter estimate	Confidence interval
Point estimate	46.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	40.7
upper limit	53.1

Notes:

[1] - The treatment strategy was defined as promising if the lower boundary of the two-sided 90% confidence interval (CI) was equal or above 47.5%.

Secondary: Other efficacy: objective response (sCR, CR, VGPR, or PR)

End point title	Other efficacy: objective response (sCR, CR, VGPR, or PR)

End point description:

The objective response rate (ORR) was defined as the proportion of patients with response sCR, CR, VGPR or PR at the respective restaging .

End point type	Secondary

End point timeframe:

At the first restaging after RAD induction treatment; at the third restaging (before the start of scheduled maintenance therapy).

End point values	autograft-allograft arm	autograft-autograft arm	No second SCT	RAD chemotherapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	49	84	24[2]	190
Units: ORR (%)				
number (confidence interval 90%)	65.3 (52.6 to 76.5)	94.1 (87.9 to 97.6)	0.0 (0 to 0)	74.2 (68.5 to 79.4)

Notes:

[2] - Over all, n=57 non-responders, including NE and missing; n=24 patients received CE mobilisation.

End point values	Full Analysis Set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	190			
Units: ORR (%)				
number (confidence interval 90%)	58.4 (52.2 to 64.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Other efficacy: progression-free survival (PFS)

End point title	Other efficacy: progression-free survival (PFS)

End point description:

PFS was defined as the time from day 1 of the first RAD cycle to the date of first progression or death of any cause, whichever occurred first. Patients without event were censored with the last date known to be progression-free.

End point type	Secondary

End point timeframe:

From day 1 of the first RAD cycle to the date of first progression or death of any cause, whichever occurred first.

End point values	Full Analysis Set (FAS)	FAS - Auto-allo SCT	FAS - Auto-auto SCT	FAS - no second SCT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	190	49	84	57
Units: PFS (months)				
median (confidence interval 90%)	47.0 (38.9 to 54.6)	46.0 (28.4 to 58.1)	9999 (55.5 to 9999)	10.9 (6.5 to 18.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Other efficacy: overall survival (OS)

End point title	Other efficacy: overall survival (OS)

End point description:

Overall survival was defined as the time from first day of administration of the study drugs to the date of death of any cause. All patients without event were censored with the last date known to be alive.

End point type	Secondary

End point timeframe:

From first day of administration of the study drugs to the date of death of any cause.

End point values	Full Analysis Set (FAS)	FAS - Auto-allo SCT	FAS - Auto-auto SCT	FAS - no second SCT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	190	49	84	57
Units: OS (months)				
median (confidence interval 90%)	83.9 (76.6 to 9999)	0000 (0000 to 9999)	83.9 (76.6 to 9999)	50.8 (40.5 to 9999)

Statistical analyses

No statistical analyses for this end point

Secondary: Other efficacy: time to next anti-myeloma therapy (TTNT)

End point title	Other efficacy: time to next anti-myeloma therapy (TTNT)

End point description:

Time to next anti-myeloma therapy was defined as the time from last treatment during study treatment to start of subsequent anti-myeloma therapy. All patients without event were censored with the last date known to be alive.

End point type	Secondary

End point timeframe:

From last treatment during study treatment to start of subsequent anti-myeloma therapy.

End point values	Full Analysis Set (FAS)	FAS - Auto-allo SCT	FAS - Auto-auto SCT	FAS - no second SCT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	190	49	84	57
Units: TTNT (months)				
median (confidence interval 90%)	9999 (35.5 to 9999)	9999 (24.5 to 9999)	9999 (0000 to 9999)	4.1 (2.3 to 22.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events

End point title	Adverse events

End point description:

Incidence of adverse events taking into account type, severity, and relationship to study Treatment.

End point type	Secondary

End point timeframe:

AEs were recorded continuously from the first day of administration of study medication during RAD induction therapy until 28 days after the last administration of the study drugs.

End point values	Safety Set			
Subject group type	Subject analysis set			
Number of subjects analysed	190			
Units: Patients				
TEAEs total	190			
TEAEs related to RAD/lenalidomide	189			
TEAEs NCI-CTCAE grade 3-5	175			
TEAEs grade 3-5 related to RAD/lenalidomide	126			
TEAEs NCI-CTCAE grade 5	8			
TEAEs grade 5 related to RAD/lenalidomide	3			
TESAEs total	122			

TESAEs related to RAD/lenalidomide	83			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event reporting started with screening and ended with the final safety assessment which took place about 28 days after last study drug administration.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Safety set

Reporting group description:

All patients who have received at least one dose of RAD induction chemotherapy were included in the safety analysis.

Serious adverse events	Safety set		
Total subjects affected by serious adverse events			
subjects affected / exposed	122 / 190 (64.21%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Lymphoproliferative disorder			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Venous thrombosis limb			

subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vena cava thrombosis				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombosis				
subjects affected / exposed	2 / 190 (1.05%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Subclavian vein thrombosis				
subjects affected / exposed	6 / 190 (3.16%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	0 / 0			
Jugular vein thrombosis				
subjects affected / exposed	2 / 190 (1.05%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Embolism				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	3 / 190 (1.58%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Inguinal hernia repair				

subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystectomy				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Pyrexia				
subjects affected / exposed	19 / 190 (10.00%)			
occurrences causally related to treatment / all	17 / 25			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mucosal inflammation				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infusion site extravasation				
subjects affected / exposed	3 / 190 (1.58%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Granuloma				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				

subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Chest pain				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Hypersensitivity				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Graft versus host disease				
subjects affected / exposed	3 / 190 (1.58%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	1 / 1			
Acute graft versus host disease in skin				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Acute graft versus host disease in liver				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Acute graft versus host disease in intestine				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	2 / 190 (1.05%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Oropharyngeal pain			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung disorder			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	2 / 190 (1.05%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Cough				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Acute respiratory distress syndrome				
subjects affected / exposed	2 / 190 (1.05%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 2			
Psychiatric disorders				
Depression				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute psychosis				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Weight decreased				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcus test positive				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Simplex virus test positive				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Pregnancy test positive				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac output decreased				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
C-reactive protein increased				
subjects affected / exposed	2 / 190 (1.05%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Blood creatinine increased				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Spinal fracture				
subjects affected / exposed	2 / 190 (1.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural complication				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lumbar vertebral fracture				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Fracture			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myopericarditis			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	2 / 190 (1.05%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	3 / 190 (1.58%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Paresis			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Haemorrhage intracranial				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Epilepsy				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Blood and lymphatic system disorders				
Thrombocytopenia				
subjects affected / exposed	2 / 190 (1.05%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	2 / 190 (1.05%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	2 / 190 (1.05%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Haemolysis				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	10 / 190 (5.26%)			
occurrences causally related to treatment / all	6 / 11			
deaths causally related to treatment / all	0 / 0			
Febrile bone marrow aplasia				

subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	5 / 190 (2.63%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	2 / 190 (1.05%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	5 / 190 (2.63%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			

subjects affected / exposed	2 / 190 (1.05%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic fibrosis			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 190 (1.58%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Purpura			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Dermatitis allergic			
subjects affected / exposed	2 / 190 (1.05%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure acute			
subjects affected / exposed	3 / 190 (1.58%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Renal failure				
subjects affected / exposed	4 / 190 (2.11%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Rhabdomyolysis				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal pain				
subjects affected / exposed	2 / 190 (1.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc protrusion				
subjects affected / exposed	2 / 190 (1.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bone pain				
subjects affected / exposed	2 / 190 (1.05%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Back pain				
subjects affected / exposed	3 / 190 (1.58%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Varicella				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Urinary tract infection			
subjects affected / exposed	3 / 190 (1.58%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	2 / 190 (1.05%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Tracheobronchitis			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal sepsis			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	5 / 190 (2.63%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	1 / 2		
Respiratory tract infection			
subjects affected / exposed	2 / 190 (1.05%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Rectal abscess			

subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pseudomembranous colitis				
subjects affected / exposed	2 / 190 (1.05%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia primary atypical				
subjects affected / exposed	5 / 190 (2.63%)			
occurrences causally related to treatment / all	3 / 5			
deaths causally related to treatment / all	0 / 0			
Pneumonia fungal				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	14 / 190 (7.37%)			
occurrences causally related to treatment / all	6 / 16			
deaths causally related to treatment / all	0 / 1			
Pertussis				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Parotitis				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenic infection				
subjects affected / exposed	2 / 190 (1.05%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Nasopharyngitis				

subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Meningitis				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	2 / 190 (1.05%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	7 / 190 (3.68%)			
occurrences causally related to treatment / all	7 / 7			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	5 / 190 (2.63%)			
occurrences causally related to treatment / all	4 / 5			
deaths causally related to treatment / all	0 / 0			
Hepatitis B				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
H1N1 influenza				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal infection				
subjects affected / exposed	2 / 190 (1.05%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis norovirus				

subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Fungal infection				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile infection				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	5 / 190 (2.63%)			
occurrences causally related to treatment / all	4 / 6			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus infection				
subjects affected / exposed	4 / 190 (2.11%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridial infection				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic sinusitis				
subjects affected / exposed	1 / 190 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Catheter site infection				

subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Adenovirus infection			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Metabolism and nutrition disorders			
Fluid retention			
subjects affected / exposed	1 / 190 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	188 / 190 (98.95%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	16 / 190 (8.42%)		
occurrences (all)	21		
Hypertension			
subjects affected / exposed	27 / 190 (14.21%)		
occurrences (all)	40		
Flushing			
subjects affected / exposed	22 / 190 (11.58%)		
occurrences (all)	31		
General disorders and administration site conditions			

Pyrexia				
subjects affected / exposed	100 / 190 (52.63%)			
occurrences (all)	200			
Pain				
subjects affected / exposed	12 / 190 (6.32%)			
occurrences (all)	17			
Oedema peripheral				
subjects affected / exposed	84 / 190 (44.21%)			
occurrences (all)	186			
Oedema				
subjects affected / exposed	30 / 190 (15.79%)			
occurrences (all)	52			
Mucosal inflammation				
subjects affected / exposed	68 / 190 (35.79%)			
occurrences (all)	123			
Influenza like illness				
subjects affected / exposed	20 / 190 (10.53%)			
occurrences (all)	29			
Feeling cold				
subjects affected / exposed	15 / 190 (7.89%)			
occurrences (all)	18			
Fatigue				
subjects affected / exposed	123 / 190 (64.74%)			
occurrences (all)	345			
Face oedema				
subjects affected / exposed	12 / 190 (6.32%)			
occurrences (all)	14			
Chills				
subjects affected / exposed	27 / 190 (14.21%)			
occurrences (all)	40			
Chest pain				
subjects affected / exposed	22 / 190 (11.58%)			
occurrences (all)	23			
Catheter site pain				
subjects affected / exposed	11 / 190 (5.79%)			
occurrences (all)	14			

Catheter site erythema			
subjects affected / exposed	18 / 190 (9.47%)		
occurrences (all)	23		
Asthenia			
subjects affected / exposed	25 / 190 (13.16%)		
occurrences (all)	32		
Respiratory, thoracic and mediastinal disorders			
Productive cough			
subjects affected / exposed	12 / 190 (6.32%)		
occurrences (all)	15		
Oropharyngeal pain			
subjects affected / exposed	45 / 190 (23.68%)		
occurrences (all)	61		
Hiccups			
subjects affected / exposed	20 / 190 (10.53%)		
occurrences (all)	35		
Epistaxis			
subjects affected / exposed	26 / 190 (13.68%)		
occurrences (all)	32		
Dyspnoea exertional			
subjects affected / exposed	21 / 190 (11.05%)		
occurrences (all)	28		
Dyspnoea			
subjects affected / exposed	30 / 190 (15.79%)		
occurrences (all)	41		
Dysphonia			
subjects affected / exposed	14 / 190 (7.37%)		
occurrences (all)	14		
Cough			
subjects affected / exposed	68 / 190 (35.79%)		
occurrences (all)	120		
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	23 / 190 (12.11%)		
occurrences (all)	36		
Restlessness			

subjects affected / exposed	20 / 190 (10.53%)		
occurrences (all)	26		
Depression			
subjects affected / exposed	14 / 190 (7.37%)		
occurrences (all)	16		
Investigations			
Weight increased			
subjects affected / exposed	36 / 190 (18.95%)		
occurrences (all)	117		
Weight decreased			
subjects affected / exposed	32 / 190 (16.84%)		
occurrences (all)	39		
Gamma-glutamyltransferase increased			
subjects affected / exposed	32 / 190 (16.84%)		
occurrences (all)	53		
C-reactive protein increased			
subjects affected / exposed	42 / 190 (22.11%)		
occurrences (all)	94		
Body temperature increased			
subjects affected / exposed	18 / 190 (9.47%)		
occurrences (all)	21		
Blood pressure increased			
subjects affected / exposed	29 / 190 (15.26%)		
occurrences (all)	56		
Alanine aminotransferase increased			
subjects affected / exposed	21 / 190 (11.05%)		
occurrences (all)	46		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	13 / 190 (6.84%)		
occurrences (all)	15		
Nervous system disorders			
Tremor			
subjects affected / exposed	29 / 190 (15.26%)		
occurrences (all)	44		
Somnolence			

subjects affected / exposed	16 / 190 (8.42%)		
occurrences (all)	18		
Polyneuropathy			
subjects affected / exposed	25 / 190 (13.16%)		
occurrences (all)	30		
Paraesthesia			
subjects affected / exposed	33 / 190 (17.37%)		
occurrences (all)	42		
Hypoaesthesia			
subjects affected / exposed	19 / 190 (10.00%)		
occurrences (all)	24		
Headache			
subjects affected / exposed	81 / 190 (42.63%)		
occurrences (all)	200		
Dysgeusia			
subjects affected / exposed	46 / 190 (24.21%)		
occurrences (all)	59		
Dizziness			
subjects affected / exposed	66 / 190 (34.74%)		
occurrences (all)	107		
Ageusia			
subjects affected / exposed	10 / 190 (5.26%)		
occurrences (all)	11		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	61 / 190 (32.11%)		
occurrences (all)	197		
Neutropenia			
subjects affected / exposed	57 / 190 (30.00%)		
occurrences (all)	147		
Lymphopenia			
subjects affected / exposed	11 / 190 (5.79%)		
occurrences (all)	34		
Leukopenia			
subjects affected / exposed	79 / 190 (41.58%)		
occurrences (all)	278		

Febrile neutropenia subjects affected / exposed occurrences (all)	34 / 190 (17.89%) 45		
Anaemia subjects affected / exposed occurrences (all)	84 / 190 (44.21%) 248		
Eye disorders Visual impairment subjects affected / exposed occurrences (all)	15 / 190 (7.89%) 17		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	78 / 190 (41.05%) 192		
Tongue coated subjects affected / exposed occurrences (all)	10 / 190 (5.26%) 14		
Stomatitis subjects affected / exposed occurrences (all)	23 / 190 (12.11%) 36		
Oedema mouth subjects affected / exposed occurrences (all)	13 / 190 (6.84%) 17		
Nausea subjects affected / exposed occurrences (all)	124 / 190 (65.26%) 377		
Gastrointestinal pain subjects affected / exposed occurrences (all)	24 / 190 (12.63%) 31		
Dysphagia subjects affected / exposed occurrences (all)	25 / 190 (13.16%) 31		
Dyspepsia subjects affected / exposed occurrences (all)	48 / 190 (25.26%) 61		
Dry mouth			

subjects affected / exposed	12 / 190 (6.32%)		
occurrences (all)	16		
Diarrhoea			
subjects affected / exposed	129 / 190 (67.89%)		
occurrences (all)	307		
Constipation			
subjects affected / exposed	96 / 190 (50.53%)		
occurrences (all)	189		
Abdominal pain upper			
subjects affected / exposed	31 / 190 (16.32%)		
occurrences (all)	49		
Abdominal pain			
subjects affected / exposed	28 / 190 (14.74%)		
occurrences (all)	32		
Abdominal distension			
subjects affected / exposed	28 / 190 (14.74%)		
occurrences (all)	37		
Abdominal discomfort			
subjects affected / exposed	37 / 190 (19.47%)		
occurrences (all)	45		
Skin and subcutaneous tissue disorders			
Rash pruritic			
subjects affected / exposed	20 / 190 (10.53%)		
occurrences (all)	24		
Rash			
subjects affected / exposed	73 / 190 (38.42%)		
occurrences (all)	113		
Pruritus			
subjects affected / exposed	50 / 190 (26.32%)		
occurrences (all)	63		
Petechiae			
subjects affected / exposed	21 / 190 (11.05%)		
occurrences (all)	23		
Night sweats			
subjects affected / exposed	56 / 190 (29.47%)		
occurrences (all)	86		

Hyperhidrosis subjects affected / exposed occurrences (all)	36 / 190 (18.95%) 50		
Erythema subjects affected / exposed occurrences (all)	56 / 190 (29.47%) 88		
Dry skin subjects affected / exposed occurrences (all)	42 / 190 (22.11%) 48		
Alopecia subjects affected / exposed occurrences (all)	29 / 190 (15.26%) 31		
Renal and urinary disorders Renal pain subjects affected / exposed occurrences (all)	10 / 190 (5.26%) 10		
Nocturia subjects affected / exposed occurrences (all)	13 / 190 (6.84%) 23		
Dysuria subjects affected / exposed occurrences (all)	21 / 190 (11.05%) 26		
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	36 / 190 (18.95%) 57		
Myalgia subjects affected / exposed occurrences (all)	19 / 190 (10.00%) 20		
Musculoskeletal pain subjects affected / exposed occurrences (all)	27 / 190 (14.21%) 35		
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	12 / 190 (6.32%) 13		
Muscle spasms			

subjects affected / exposed	53 / 190 (27.89%)		
occurrences (all)	90		
Bone pain			
subjects affected / exposed	77 / 190 (40.53%)		
occurrences (all)	137		
Back pain			
subjects affected / exposed	79 / 190 (41.58%)		
occurrences (all)	117		
Arthralgia			
subjects affected / exposed	34 / 190 (17.89%)		
occurrences (all)	58		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	17 / 190 (8.95%)		
occurrences (all)	20		
Upper respiratory tract infection			
subjects affected / exposed	23 / 190 (12.11%)		
occurrences (all)	41		
Staphylococcal infection			
subjects affected / exposed	12 / 190 (6.32%)		
occurrences (all)	12		
Sinusitis			
subjects affected / exposed	12 / 190 (6.32%)		
occurrences (all)	15		
Respiratory tract infection			
subjects affected / exposed	22 / 190 (11.58%)		
occurrences (all)	32		
Oral herpes			
subjects affected / exposed	20 / 190 (10.53%)		
occurrences (all)	24		
Oral candidiasis			
subjects affected / exposed	17 / 190 (8.95%)		
occurrences (all)	24		
Nasopharyngitis			
subjects affected / exposed	57 / 190 (30.00%)		
occurrences (all)	105		

Infection			
subjects affected / exposed	32 / 190 (16.84%)		
occurrences (all)	42		
Device related infection			
subjects affected / exposed	36 / 190 (18.95%)		
occurrences (all)	47		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	36 / 190 (18.95%)		
occurrences (all)	53		
Hypocalcaemia			
subjects affected / exposed	18 / 190 (9.47%)		
occurrences (all)	25		
Hyperglycaemia			
subjects affected / exposed	31 / 190 (16.32%)		
occurrences (all)	76		
Decreased appetite			
subjects affected / exposed	80 / 190 (42.11%)		
occurrences (all)	152		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 July 2009	Clarification / modification of AE/SAE reporting requirements. Modification of lenalidomide reduction schedule in maintenance therapy. Modification of additional inclusion criteria for lenalidomide maintenance phase. Reduction of fludarabine dosage in the conditioning regimen. Time points of ATG and calcium folinate administration adapted according to common clinical practice. Mycophenolate mofetil may replace MTX/calcium folinate according to local protocols of participating centers. Additional restaging between the 1st and 2nd cycle of stem cell transplantation. Additional determination of uric acid. Clarification of the required donor HLA-identity for allogeneic SCT: In case no HLAidentical donor (10 out of 10 gene loci) is available, one antigen disparity (class I) and/or one allele disparity (class II) between patient and donor is acceptable. Lenalidomide maintenance treatment starts 8 to 20 weeks after an allogeneic SCT. Permanent discontinuation of lenalidomide maintenance treatment, if patients develop acute GvHD ≥ grade III. Administrative changes.
19 October 2010	Myocardial infarction, myocarditis, perimyocarditis added as exclusion criteria. Clarification of respective inclusion criterion: If DLCO cannot be determined, pO2 [art.] as a substitute has to be ≥70 mm Hg. No other experimental drugs are allowed during the entire study in addition to being not permitted within 28 days before baseline. Adaption of the time frame for the administration of pegfilgrastim during RAD cycles. Modification of the administration of ciclosporin A during conditioning for allogeneic SCT according to common clinical practice. Maximum permitted delay of three weeks for start of next RAD cycles, if conditions for initiation of a new cycle are not fulfilled. Lenalidomide maintenance therapy must start two weeks after the restaging assessments prior to lenalidomide maintenance therapy. Update of required dose modifications for lenalidomide in relation to creatinine clearance in accordance with updated SmPC for lenalidomide. Separate dose reductions for neutropenia and thrombocytopenia during the RAD cycles. Both interim analyses will be exploratory only.
19 January 2011	Permitted interruption of lenalidomide maintenance therapy limited to max. 1 month. Monthly assessments of response, urine protein electrophoresis, immunofixation (serum and 24-h-urine specimen), serum immunoglobulins, and serum free light chain assay during lenalidomide maintenance instead of assessments every three months.

03 May 2011	Continuous daily administration of 10 mg lenalidomide maintenance therapy only in patients who received tandem autoSCT. Dose reduction for patients who received auto-allo transplantation to 5 mg daily on day 1-21 of a 28-day cycle after a reduced starting dose of 5 mg lenalidomide every other day on day 1-21 of cycle 1. Start of maintenance therapy in patients after auto-alloSCT 10-22 weeks after end of alloSCT instead after 8-20 weeks. Modified additional inclusion and exclusion criteria for lenalidomide maintenance: ▪ Inclusion of patients with neutrophil count ≥ 1.5 x 109 /L permitted ▪ Exclusion of patients with acute GvHD ≥ grade II or extensive chronic GvHD ▪ Restriction of allowed steroid medication to ≤ 1mg/kg BW methylprednisolone or equivalent, only ciclosporin and MMF permitted as immunosuppressants ▪ At least three-week interval from last taper of ciclosporin and MMF required GvHD needs to be reported as SAE when it occurred after the start of lenalidomide maintenance therapy. Long-term follow up for two years after last administration of lenalidomide maintenance (including explicit follow up with regard to second primary malignancies).
15 July 2011	Sample size increased from 146 to 190 patients due to drop-out rate of 23 % nonevaluable patients in the first interim analysis. Extension of the recruitment period to 2.5 years.
07 November 2011	Due to availability of 2.5 mg lenalidomide capsules, the application schedule of lenalidomide maintenance in cycle 1 of lenalidomide maintenance (starting dose) after alloSCT was modified to 2.5 mg daily on day 1-21 of this cycle.
03 June 2013	Modification of the study protocol according to the updated Pregnancy Prevention Program for lenalidomide. Among others modifications, females of childbearing potential requirement must use two contraceptives measures simultaneously.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported