Clinical trial results:
An open, multicentric phase II trial to evaluate the efficacy and safety of Bendamustine, Lenalidomide (Revlimid®) and Dexamethasone (BRd) as 2nd-line therapy for patients with relapsed or refractory multiple myeloma

Summary

EudraCT number	2010-022253-42
Trial protocol	DE
Global end of trial date	25 December 2015

Results information

Result version number	v1 (current)
This version publication date	01 December 2021
First version publication date	01 December 2021

Trial information

Trial identification

Sponsor protocol code	CTU10.041/BRd

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01701076
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Kantonsspital St. Gallen Dept of Medical Oncology and Haematology Prof. Dr. Christoph Driessen
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 December 2015
Global end of trial reached?	Yes
Global end of trial date	25 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of the combination of bendamustine, lenalidomide and dexamethasone as 2nd-line therapy in patients with refractory/ relapsed multiple myeloma as defined by the combined CR-/VGPR-rate being achieved during the induction treatment phase or within four weeks after administration of the last induction cycle of the BRd regimen.

Protection of trial subjects:

1. Interim analysis was performed after the first 13 patients have been enrolled
1.1 Efficacy: 4 weeks after the 13th patient had completed the induction phase of the trial. If the number of patients with either complete response (CR) or very good partial response (VGPR) at this interim analysis is 3 or lower, the treatment would have been rejected and the study was stopped early. Otherwise, the trial would continue until a total of 43 patients have been accrued.
1.2 Safety: 4 weeks after the 13th patient had completed the induction phase, by examining the following observed adverse events: grade 4 febrile neutropenia and grade 4 thromboembolic events. If > 3/13 patients experienced any of the described grade 4 adverse events, the trial would have been stopped.

2. Dose modifications in case of predefined AEs

3. Predefined prerequisites for each new treatment cycle

4. Mandatory concomitant medication in case of defined toxicities

Background therapy:

Pegfilgrastim (Neulasta®) day 3 in case of severe neutropenia (treatment continued in all cycles of the induction phase, once pegfilgrastim treatment was indicated)
severe neutropenia is defined as
- Development of grade 4 neutropenia (ANC < 0.5 x 109/L) at any time of a treatment cycle
- Early occurrence of an ANC < 0.75 x 109/L before or at day 15 of a treatment cycle
- Any delay of the next treatment cycle due to neutropenia (i.e. due to persistent neutropenia ANC < 1.0 x 109/L on the scheduled day 1 of the following cycle as defined in 13.4)
- Development of febrile neutropenia (defined as grade 3 or 4 neutropenia (ANC < 1.0 x 109/L) and fever >=38.5°C))

Evidence for comparator:

not applicable

Actual start date of recruitment	01 March 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Switzerland: 30
Country: Number of subjects enrolled	Germany: 20
Worldwide total number of subjects	50
EEA total number of subjects	20

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)	18
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited at heamato-oncological clinics or practices in Switzerland and Germany
Recruitment period: February 2012 until July 2014

Pre-assignment

Screening details:

Patients with
- first relapsed or refractory multiple myeloma who have received no more than one prior anti-myeloma treatment line.
- measurable disease (serum M-protein level ≥ 1 g/dl or urine M-protein level ≥ 200 mg/24hours or serum FLC level ≥ 10 mg/dl)
- adequate haematological values
- adequate hepatic and renal function

Period 1

Period 1 title	Induction treatment phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Induction treatment phase cycles 1 - ≤ 6

Arm description:

Induction treatment phase:
Cycle 1 - 6, q 4 weeks, or until progressive disease (PD) or unacceptable toxicity
• Bendamustine: 75mg/m2 i.v., day 1 and 2
• Lenalidomide: 25 mg p.o., day 1-21
• Dexamethasone: 40/20mg p.o. day 1, 8, 15, 22 (40mg for patients ≤75 years and 20 mg for patients >75 years)

Patients fulfilling all eligibility criteria were treated in a first period, in the induction treatment.
A cycle was 28 days in length.

In case of severe neutropenia, patients received Pegfilgrastim 6mg s.c., day 3 in all subsequent cycles.

Arm type	Experimental
Investigational medicinal product name	bendamustine
Investigational medicinal product code	
Other name	Ribomustin®, LEVACT®
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

In the induction treatment phase, patients received Bendamustine 75 mg/m2 i.v. on day 1 and day 2 of every 28 day cycle for a maximum of 6 cycles .
Bendamustine dose was calculated according to the BSA (body surface area). The BSA had to be determined within 3 days prior to each new cycle of the induction treatment phase.
After preparation according to the preparation guidelines of the SmPC and as outlined in the study protocol, bendamustine was administered by intravenous infusion over 30-60 minutes on days 1 and 2 of every cycle.

Investigational medicinal product name	lenalidomide
Investigational medicinal product code	
Other name	Revlimid®
Pharmaceutical forms	Capsule

Routes of administration	Oral use

Dosage and administration details:

Lenalidomide 25 mg was administered daily on d1-21 every 28 days during the induction treatment phase.

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

Dosage and administration details:

For patients ≤ 75 years of age, Dexamethasone was given on day 1, 8, 15, and 22 at a dose of 40 mg p.o. , for patients >75 years of age at a dose of 20mg p.o. of every 28 day cycle

Number of subjects in period 1	Induction treatment phase cycles 1 - ≤ 6
Started	50
Induction treatment 6 cycles received	26
Induction treatment phase <6 cycles	24 [1]
Completed	25
Not completed	25
Consent withdrawn by subject	3
Physician decision	2
Adverse event, non-fatal	14
Response not evaluable	1
Death, due to respiratory insufficiency	1
Progressive disease	3
Planned stem cell transplantation	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Patients could prematurely switch into the maintenance treatment phase without having completed all 6 induction treatment cycles.
Further, not all patients completing the induction treatment have proceeded with the mainenance treatment.

Period 2

Period 2 title	Maintenance treatment phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Maintenance treatment

Arm description:

Maintenance treatment phase:
Cycle 7 – ≥18, q 4 weeks, or until PD or unacceptable toxicity.
• Lenalidomide: 25 mg p.o., day 1-21
• Dexamethasone: 40/20mg p.o., day 1, 8, 15, 22 (40mg for patients ≤ 75 years and 20 mg for patients >75 years)

All patients having completed the induction treatment phase could proceed with the maintenance treatment phase if they were without PD and/or unacceptable toxicity. Patients who had to terminate the preceding induction phase prematurely due to adverse events (AEs) could also proceed if there were no contraindications as specified in the SmPC of Revlimid® and if AEs improved to CTC grade ≤2 and the criteria for a new treatment cycle were met:
- ANC ≥ 1.0 x 109/L, platelet counts ≥ 50 x 109/L
- any other study-drug-related AE resolved to ≤ grade 2
- any allergic reaction/ hypersensitivity or sinus bradycardia/ other cardiac arrhythmia adverse event resolved to

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

Dosage and administration details:

Lenalidomide 25 mg was administered daily on d1-21 every 28 days during the induction treatment phase.

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

Dosage and administration details:

For patients ≤ 75 years of age, Dexamethasone was given on day 1, 8, 15, and 22 at a dose of 40 mg p.o. , for patients >75 years of age at a dose of 20mg p.o. of every 28 day cycle

Number of subjects in period 2	Maintenance treatment
Started	25
Completed	16
Not completed	9
Consent withdrawn by subject	1
Physician decision	1
Delay of study treatment > 3 weeks	1
Adverse event, non-fatal	3
Progressive disease	3

Baseline characteristics

Reporting groups

Reporting group title	Induction treatment phase

Reporting group description: -

Reporting group values	Induction treatment phase	Total	
Number of subjects	50	50	
Age categorical Units: Subjects			
Adults > 18 years	50	50	
Age continuous Units: years			
arithmetic mean	68.5		
full range (min-max)	46 to 83	-	
Gender categorical Units: Subjects			
Female	15	15	
Male	35	35	
Myeloma type Units: Subjects			
IgG	26	26	
IgA	15	15	
Light chain only	9	9	
Previous autologous stem cell transplantation, Units: Subjects			
Received	21	21	
Not received	29	29	
ISS-stage Units: Subjects			
ISS-stage I	21	21	
ISS-stage II	15	15	
ISS stage III	13	13	
ISS stage unknown	1	1	
Cytogenetic risk Units: Subjects			
High risk	15	15	
Standard risk	21	21	
Unknown	14	14	

End points

End points reporting groups

Reporting group title	Induction treatment phase cycles 1 - ≤ 6

Reporting group description:

Induction treatment phase:
Cycle 1 - 6, q 4 weeks, or until progressive disease (PD) or unacceptable toxicity
• Bendamustine: 75mg/m2 i.v., day 1 and 2
• Lenalidomide: 25 mg p.o., day 1-21
• Dexamethasone: 40/20mg p.o. day 1, 8, 15, 22 (40mg for patients ≤75 years and 20 mg for patients >75 years)

Patients fulfilling all eligibility criteria were treated in a first period, in the induction treatment.
A cycle was 28 days in length.

In case of severe neutropenia, patients received Pegfilgrastim 6mg s.c., day 3 in all subsequent cycles.

Reporting group title	Maintenance treatment

Reporting group description:

Maintenance treatment phase:
Cycle 7 – ≥18, q 4 weeks, or until PD or unacceptable toxicity.
• Lenalidomide: 25 mg p.o., day 1-21
• Dexamethasone: 40/20mg p.o., day 1, 8, 15, 22 (40mg for patients ≤ 75 years and 20 mg for patients >75 years)

All patients having completed the induction treatment phase could proceed with the maintenance treatment phase if they were without PD and/or unacceptable toxicity. Patients who had to terminate the preceding induction phase prematurely due to adverse events (AEs) could also proceed if there were no contraindications as specified in the SmPC of Revlimid® and if AEs improved to CTC grade ≤2 and the criteria for a new treatment cycle were met:
- ANC ≥ 1.0 x 109/L, platelet counts ≥ 50 x 109/L
- any other study-drug-related AE resolved to ≤ grade 2
- any allergic reaction/ hypersensitivity or sinus bradycardia/ other cardiac arrhythmia adverse event resolved to

Primary: CR-/VGPR-rate achieved during the induction treatment phase or within four weeks after administration of the last induction cycle of the BRd regimen

End point title	CR-/VGPR-rate achieved during the induction treatment phase or within four weeks after administration of the last induction cycle of the BRd regimen[1]

End point description:

Combined CR (complete remission) and VGPR (very good partial remission rate) as defined by IMWG criteria achieved during the induction treatment phase or within 4 weeks after the last administration of the induction treatment phase.
Only patients who completed at least one cycle of study treatment and who could be assessed for the primary endpoint were considered to be evaluable for the primary endpoint.

Assessments or the primary endpoint were done as applicable according to IMWG criteria every 4 weeks:
- Quantitation of M-protein level in serum and urine (24 hours urine collection) by densitometry of protein electrophoresis. (SPEP and UPEP) or direct (nephelometric) serum-IgA-measurement,
- Quantitation of serum immunoglobulin levels
- Serum and urine immunofixation
- Free light chain concentrations in serum and ratio
- plasma cell percentage in the bone marrow by cytology + immunohistochemistry
- Radiologic assessments (CT/MRI)

End point type	Primary

End point timeframe:

During the induction treatment phase (cycle 1-6) or within four weeks after administration of the last induction cycle of the BRd regimen (Bendamustine + lenalidomide (Revlimid) + dexamethasone)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The following information about primary endpont analysis can be made:
A descriptive analysis was performed.
For sample size calculation, a Simon's two-stge design was applied , with significance level of 5% and 80% power.
P0=20% (if proportion of patients with response ≥VGPR is ≤20% , treatment is considered uninteresting), P1=40% (patients with either ≥ VGPR is ≥ 40% , treatment is considered promising) sample size = 43
Drop-outs were replaced.

End point values	Induction treatment phase cycles 1 - ≤ 6			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Number of patients				
≥VGPR (sCR, CR, VGPR)	23			
sCR	1			
CR	2			
VGPR	20			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rates (sCR, CR, VGPR, PR, MR) achieved during the induction treatment phase or within four weeks after the last administration of six induction treatment cycles of the BRd-regimen

End point title	Objective response rates (sCR, CR, VGPR, PR, MR) achieved during the induction treatment phase or within four weeks after the last administration of six induction treatment cycles of the BRd-regimen

End point description:

Objective response rates sCR (stringent response), CR (complete response) and VGPR (very good partial response), PR partial response), MR (minor response) as defined by IMWG criteria achieved during the induction treatment phase or within four weeks after the last administration of of six induction cycles of the BRd regimen.

End point type	Secondary

End point timeframe:

During the induction treatment phase (cycle 1-6) or within four weeks after administration of the last induction cycle of the BRd regimen (Bendamustine + lenalidomide (Revlimid) + dexamethasone)

End point values	Induction treatment phase cycles 1 - ≤ 6			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: Number of patients				

sCR	1			
CR	2			
VGPR	20			
PR	17			
MR	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Best response (sCR, CR, VGPR, PR, MR) achieved during the whole study duration

End point title	Best response (sCR, CR, VGPR, PR, MR) achieved during the whole study duration

End point description:

Objective response rates sCR (stringent response), CR (complete response) and VGPR (very good partial response), PR partial response), MR (minor response) as defined by IMWG criteria achieved during the whole study treatment.

Assessments were done as applicable according to IMWG criteria every 4 weeks.

End point type	Secondary

End point timeframe:

Within the whole study duration (cycle 1-18 comprising induction and maintenance treatment phase)

End point values	Induction treatment phase cycles 1 - ≤ 6	Maintenance treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	25		
Units: Number of patients				
sCR	2	2		
CR	1	2		
VGPR	4	14		
PR	8	7		
MR	2	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of informed consent until 30 days after end of study treatment (induction/maintenance treatment phase)

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Induction & maintenance treatment phase

Reporting group description: -

Serious adverse events	Induction & maintenance treatment phase		
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 50 (70.00%)		
number of deaths (all causes)	14		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphomatoide granulomatosis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myelodysplastic syndrome			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Plasma cell leukemia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Pulmonary embolism			

subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombosis				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Stroke				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Fatigue				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fever				
subjects affected / exposed	3 / 50 (6.00%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	2 / 50 (4.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Worsening of general condition				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Allergic reaction				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory insufficiency			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Confusion			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Desorientation			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Neutropenia			
subjects affected / exposed	16 / 50 (32.00%)		
occurrences causally related to treatment / all	25 / 26		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			

subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	8 / 50 (16.00%)			
occurrences causally related to treatment / all	8 / 10			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Other_fracture of the femur				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Other_Tractus irritation				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Other_Port Luxation				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Other_Inguinal hernia				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				

Unstable angina pectoris				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Epileptic seizure				
subjects affected / exposed	2 / 50 (4.00%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Presyncope (orthostatic)				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Eye disorders				
Retinal detachment				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhea				
subjects affected / exposed	2 / 50 (4.00%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Emesis				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspepsia				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroparesis				

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	1 / 1		
Colitis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
ALT/AST increased (CTC Grade 4/3)			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences causally related to treatment / all	6 / 8		
deaths causally related to treatment / all	0 / 0		
Infections_not other specified			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Interstitial pneumopathy			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Induction & maintenance treatment phase		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 50 (100.00%)		
Investigations			
Neutropenia	Additional description: CTC grade 3/4		
subjects affected / exposed	30 / 50 (60.00%)		
occurrences (all)	37		
Anemia	Additional description: CTC grade 3/4		
subjects affected / exposed	9 / 50 (18.00%)		
occurrences (all)	10		
Leucopenia	Additional description: CTC grade 3/4		
subjects affected / exposed	10 / 50 (20.00%)		
occurrences (all)	18		
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	12 / 50 (24.00%)		
occurrences (all)	18		
ALT increased	Additional description: CTC grade 3/4		
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Vascular disorders			
Thromboembolism	Additional description: CTC grade 3/4		
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Nervous system disorders			
Fatigue			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Seizure			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	2		
Immune system disorders			
Allergic reaction	Additional description: CTC grade 3/4		
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea	Additional description: CTC grade 3/4		
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	3		
Infections and infestations			
Infections	Additional description: CTC grade 3/4		
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	8		
Urogenital infection	Additional description: CTC grade 3/4		
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperglycemia	Additional description: CTC grade 3/4		
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 June 2012	The safety cohort, as outlined in the preceding protocol version 1.1 (D)_16. 01.2012 of the CTU10.041/BRd-study, was omitted. The safety data of the phase I/II study (RBP-01/08 / OSHO- #077) investigating the safety and tolerability of bendamustine 75mg/m2/d, p.o. on d1+2 and lenalidomide 25mg/d, p.o. on d1-21 have become available and were published at the 17th congress of the European Hematology Association in 2012, Abstract #0848) The data demonstrate the safety and tolerability of the target dose-level of bendamustine 75mg/m2/d, p.o. on d1+2 in combination with lenalidomide 25mg/d, p.o. on d1-21 in patients with pre-treated multiple myeloma. Thus, the safety cohort, was no longer necessary and the appropriate parts of the protocol were deleted (section 1, 3.2, 6, 14.1, 15). Label Change of Ribomustin® in Levact® Bendamustine-hydrochloride had received a marketing authorization in Germany and the following Member States of the EU: Austria, Belgium, Denmark, Finland, France, Ireland, Italy, Luxembourg, Norway, Poland, Spain and the United Kingdom (UK) for the treatment of patients with indolent non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL) and multiple myeloma. Concomitant with this authorization a) the former German trade name Ribomustin® changed into Levact® b) the safety information of the Summary of Product Characteristics (SmPC) changed The study protocol was changed appropriately in section 4.1 and 12.3. To allow patients with relapsed or refractory multiple myeloma without measurable M-protein in the serum or urine but with abnormal elevated serum free light chain concentrations to participate in this clinical trial, the inclusion criterion bullet point #4 in section 7.1 of the study protocol has been extended appropriately. Concomitantly, the efficacy assessments in section 9.2.3 and response criteria to assess the primary and secondary endpoints in section 14.2 and 14.3.1 and appendix 4 and 5 have been changed accordingly. In
25 April 2013	Allowance to enrol patients with prior lenalidomide treatment: Modification of in- and exclusion criteria regarding the previous prohibition of prior treatment with lenalidomide prior to study entry Extension of the inclusion criterion bullet point # 12 in section 7.1 of the protocol regarding enrolment of patients with prior malignancies Possibility of patients to proceed trial treatment in the maintenance treatment phase if study treatment has to be prematurely terminated in the induction treatment phase due to toxicities. Modification of Efficacy and Survival Assessments of patients withdrawn from study treatment

17 December 2013	Due to low patient recruitment at the beginning of the study, the study duration was extended for additionally 24 months. Extension of one inclusion criterion regarding the measurability of the disease Patients with non-measurable MM by electrophoresis could be enrolled, if serum IgA levels were > ULN by direct serum-IgA measurement. Only in that case, direct IgA measurement should be used for response assessment. Addition of further rules of drug modification in section 13.8 Bendamustine and Lenalidomide dose modifications for non-hematologic toxicity during a cycle Due to emerging rash following bendamustine administration during study treatment, binding rules for dose modifications for bendamustine related rash became necessary. Addition of further information regarding response assessment in section 14.3.1 and appendix 5 Due to the addition of a fourth possibility of disease measurement (direct IgA measurement in case of patients with non-measurable disease by electrophoresis but show serum IgA levels> ULN), response assessment had been concomitantly adopted.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported