Clinical trial results:
Lenalidomide in conjunction with methotrexate, leucovorin, cytarabine and rituximab for the treatment of relapsed or refractory CD20-positive aggressive lymphomas: an open-label, multicenter phase I/II trial

Summary

EudraCT number	2012-001891-13
Trial protocol	DE
Global end of trial date	20 February 2020

Results information

Result version number	v1 (current)
This version publication date	06 June 2022
First version publication date	06 June 2022

Trial information

Trial identification

Sponsor protocol code	LeMLAR

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01788189
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospital Essen
Sponsor organisation address	Hufelandstrasse 55, Essen, Germany, 45147
Public contact	Prof. Dr. Ulrich Dührsen, University Hospital Essen, 0049 2102847374, ulrich.duehrsen@uk-essen.de
Scientific contact	Prof. Dr. Ulrich Dührsen, University Hospital Essen, 0049 2102847374, ulrich.duehrsen@uk-essen.de

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 February 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 February 2020
Global end of trial reached?	Yes
Global end of trial date	20 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase 1:
Evaluation of the feasibility, safety and dose-limiting toxicity of the LeMLAR regimen
Phase 2:
Evaluation of the efficacy of the LeMLAR regimen at the maximum tolerated dose

Protection of trial subjects:

Documentation of adverse events according to CTCAE version 3.0

Background therapy: -

Evidence for comparator:

Phase 2:
The objective response rate of patients with relapsed or refractory diffuse large B-cell lymphoma to lenalidomide alone had been reported to be 20% (J Clin Oncol 26: 4952-4957, 2008). The phase II part of the LeMLAR trial tested the hypothesis that the objective response rate will be increased to ≥40% by combining lenalidomide with MLAR at the maximum tolerated dose ($p<0.05$, power=0.4).

Actual start date of recruitment	18 December 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	Germany: 34
Worldwide total number of subjects	34
EEA total number of subjects	34

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)	16
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients ≥18 years with relapsed or refractory CD20-positive aggressive B cell lymphoma (excluding mantle cell lymphoma and central nervous system involvement) lacking other treatment options were eligible. Exclusion criteria included inadequate organ function and uncontrolled infection.
First patient in: 25/01/2013
Last patient in: 23/05/2018

Pre-assignment

Screening details:

Details specified in the inclusion and exclusion criteria (publication of the LeMLAR trial, Blood Cancer J 11: 95, 2021).

Period 1

Period 1 title	Phase 1 and 2 (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

No blinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	1. Dose level 3-1

Arm description:

Lenalidomide 25 mg, methotrexate and cytarabine dose level 1

Arm type	Phase 1 Level 3-1
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg, day 1-21 of each 28-day cycle, maximum 6 cycles

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

30 mg/m2, day 1, 8 and 15 of each 28-day cycle, maximum 6 cycles

Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

45 mg four times per day, day 2, 9 and 16 of each 28-day cycle, maximum 6 cycles

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Injection
Routes of administration	Intravenous use
Dosage and administration details: 75 mg/m2, day 1, 8 and 15 of each 28-day cycle, maximum 6 cycles	
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 375 mg/m2, day 1 of each 28-day cycle, maximum 6 cycles	
Arm title	2. Dose level 3-2
Arm description: Lenalidomide 25 mg, methotrexate and cytarabine dose level 2	
Arm type	Phase 1 Level 3-2
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 25 mg, day 1-21 of each 28-day cycle, maximum 6 cycles	
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use
Dosage and administration details: 60 mg/m2, day 1, 8 and 15 of each 28-day cycle, maximum 6 cycles	
Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 45 mg four times per day, day 2, 9 and 16 of each 28-day cycle, maximum 6 cycles	
Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use
Dosage and administration details: 150 mg/m2, day 1, 8 and 15 of each 28-day cycle, maximum 6 cycles	
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 375 mg/m2, day 1 of each 28-day cycle, maximum 6 cycles	
Arm title	3. Dose level 2-2

Arm description:	
Lenalidomide 20 mg, methotrexate and cytarabine dose level 2	
Arm type	Phase 1 Level 2-2
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
20 mg, day 1-21 of each 28-day cycle, maximum 6 cycles	
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use
Dosage and administration details:	
60 mg/m2, day 1, 8 and 15 of each 28-day cycle, maximum 6 cycles	
Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
45 mg four times per day, day 2, 9 and 16 of each 28-day cycle, maximum 6 cycles	
Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use
Dosage and administration details:	
150 mg/m2, day 1, 8 and 15 of each 28-day cycle, maximum 6 cycles	
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
375 mg/m2, day 1 of each 28-day cycle, maximum 6 cycles	
Arm title	4. Dose level 2-3
Arm description:	
Lenalidomide 20 mg, methotrexate and cytarabine dose level 3	
Arm type	Phase 1 Level 2-3
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
20 mg, day 1-21 of each 28-day cycle, maximum 6 cycles	

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:
90 mg/m2, day 1, 8 and 15 of each 28-day cycle, maximum 6 cycles

Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
45 mg four times per day, day 2, 9 and 16 of each 28-day cycle, maximum 6 cycles

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:
225 mg/m2, day 1, 8 and 15 of each 28-day cycle, maximum 6 cycles

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:
375 mg/m2, day 1 of each 28-day cycle, maximum 6 cycles

Arm title	Phase 2 at MTD level (2-2)

Arm description:
Treatment at MTD level and comparison with published results for lenalidomide monotherapy

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

Dosage and administration details:
20 mg, day 1-21 of each 28-day cycle, maximum 6 cycles

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:
60 mg/m2, day 1, 8 and 15 of each 28-day cycle, maximum 6 cycles

Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details: 45 mg four times per day, day 2, 9 and 16 of each 28-day cycle, maximum 6 cycles	
Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use
Dosage and administration details: 150 mg/m2, day 1, 8 and 15 of each 28-day cycle, maximum 6 cycles	
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 375 mg/m2, day 1 of each 28-day cycle, maximum 6 cycles	

Number of subjects in period 1	1. Dose level 3-1	2. Dose level 3-2	3. Dose level 2-2
Started	4	4	8
Completed	4	4	8

Number of subjects in period 1	4. Dose level 2-3	Phase 2 at MTD level (2-2)
Started	6	12
Completed	6	12

Baseline characteristics

Reporting groups	
Reporting group title	1. Dose level 3-1
Reporting group description:	
Lenalidomide 25 mg, methotrexate and cytarabine dose level 1	
Reporting group title	2. Dose level 3-2
Reporting group description:	
Lenalidomide 25 mg, methotrexate and cytarabine dose level 2	
Reporting group title	3. Dose level 2-2
Reporting group description:	
Lenalidomide 20 mg, methotrexate and cytarabine dose level 2	
Reporting group title	4. Dose level 2-3
Reporting group description:	
Lenalidomide 20 mg, methotrexate and cytarabine dose level 3	
Reporting group title	Phase 2 at MTD level (2-2)
Reporting group description:	
Treatment at MTD level and comparison with published results for lenalidomide monotherapy	

Reporting group values	1. Dose level 3-1	2. Dose level 3-2	3. Dose level 2-2
Number of subjects	4	4	8
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	2	4
From 65-84 years	4	2	4
85 years and over	0	0	0
Age continuous Units: years			
median	72	68	68
full range (min-max)	70 to 74	56 to 80	56 to 80
Gender categorical Units: Subjects			
Female	4	1	2
Male	0	3	6

Reporting group values	4. Dose level 2-3	Phase 2 at MTD level (2-2)	Total
Number of subjects	6	12	34
Age categorical Units: Subjects			
In utero	0	0	0

Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	7	16
From 65-84 years	3	5	18
85 years and over	0	0	0
Age continuous			
Units: years			
median	64	61	
full range (min-max)	49 to 72	40 to 82	-
Gender categorical			
Units: Subjects			
Female	1	7	15
Male	5	5	19

End points

End points reporting groups

Reporting group title	1. Dose level 3-1
Reporting group description:	
Lenalidomide 25 mg, methotrexate and cytarabine dose level 1	
Reporting group title	2. Dose level 3-2
Reporting group description:	
Lenalidomide 25 mg, methotrexate and cytarabine dose level 2	
Reporting group title	3. Dose level 2-2
Reporting group description:	
Lenalidomide 20 mg, methotrexate and cytarabine dose level 2	
Reporting group title	4. Dose level 2-3
Reporting group description:	
Lenalidomide 20 mg, methotrexate and cytarabine dose level 3	
Reporting group title	Phase 2 at MTD level (2-2)
Reporting group description:	
Treatment at MTD level and comparison with published results for lenalidomide monotherapy	

Primary: Dose-limiting toxicity

End point title	Dose-limiting toxicity[1][2]

End point description:

Treatment tolerance was assumed if none of three or only one of six patients experienced dose limiting toxicity (DLT).
Definition of DLT: Neutrophils <0.5 /nl, platelets <25 /nl, creatinine clearance <60 ml/min, bilirubine ≥3 mg/dl, serum AST or ALT ≥6× ULN, or mucositis grade ≥3 on day 8 (plus a maximum of 3 extra days), day 15 (plus ≤6 days), or day 29 (plus ≤7 days). Failure to reach these thresholds at the indicated time-points prevented timely administration of methotrexate and cytarabine. Adverse events requiring dose reduction in cycle 1 or 2, receipt of <21 lenalidomide doses per cycle, cycle length >35 days, and any adverse event preventing continuation according to the protocol were also rated as DLT. Patients without DLT terminating treatment in cycle 1 or 2 prematurely due to disease progression were replaced by new patients. They were rated as not evaluable.
The maximum tolerated dose (MTD) was the dose level immediately below the level where DLT occurred.

End point type	Primary

End point timeframe:

Phase 1, first two treatment cycles (56-70 days from first treatment day)

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 first four arms represent groups of patients treated at escalating dose levels and are not meant to be compared by standard statistical methods. Dose escalation followed the 3+3 design whereby dose-limiting toxicity (DLT) was defined as an occurrence of toxicity in ≥1 of 3 or ≥2 of 6 patients treated at a given dose level. The maximum tolerated dose (2-2) was the level immediately below the level at which DLT occurred (2-3).
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The first four arms represent groups of patients treated at escalating dose levels and are not meant to be compared by standard statistical methods. Dose escalation followed the 3+3 design whereby dose-limiting toxicity (DLT) was defined as an occurrence of toxicity in ≥1 of 3 or ≥2 of 6 patients treated at a given dose level. The maximum tolerated dose (2-2) was the level immediately below the level at which DLT occurred (2-3).

End point values	1. Dose level 3-1	2. Dose level 3-2	3. Dose level 2-2	4. Dose level 2-3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	8	6
Units: Patients				
No DLT	3	1	5	4
DLT	0	2	1	2
Not evaluable	1	1	2	0

Statistical analyses

No statistical analyses for this end point

Primary: Objective response rate

End point title	Objective response rate[3][4]

End point description:

End point type	Primary

End point timeframe:

End of treatment (4 weeks after the last LeMLAR cycle)

Notes:

[3] - 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 study aimed at including 20 patients treated at the maximum tolerated dose (MTD = level 2-2). These were 8 patients from phase 1 and 12 patients additionally recruited in phase 2. These groups were not meant to be compared with each other, but to be combined to describe the objective response rate (ORR). The hypothesis of the phase 2 part was that the published ORR of lenalidomide monotherapy (20%) would be increased to ≥40% by combining lenalidomide with MLAR. This was confirmed (ORR=55%).
[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The study aimed at including 20 patients treated at the maximum tolerated dose (MTD = level 2-2). These were 8 patients from phase 1 and 12 patients additionally recruited in phase 2. These groups were not meant to be compared with each other, but to be combined to describe the objective response rate (ORR). The hypothesis of the phase 2 part was that the published ORR of lenalidomide monotherapy (20%) would be increased to ≥40% by combining lenalidomide with MLAR. This was confirmed (ORR=55%).

End point values	3. Dose level 2-2	Phase 2 at MTD level (2-2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	12		
Units: Patients				
Objective response	3	8		
No objective response	3	4		
Not evaluable	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete remission rate

End point title	Complete remission rate[5]

End point description:

End point type	Secondary

End point timeframe:

End of treatment (4 weeks after the last LeMLAR cycle)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The study aimed at including 20 patients treated at the maximum tolerated dose (MTD = level 2-2). These were 8 patients from the phase 1 part and 12 patients additionally recruited in the phase 2 part. These groups were not meant to be compared with each other, but to be combined to describe the complete remission rate.

End point values	3. Dose level 2-2	Phase 2 at MTD level (2-2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	12		
Units: Patients				
Complete remission	1	4		
Partial remission	2	4		
Stable disease	2	1		
Progressive disease	1	3		
Not evaluable	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response[6]

End point description:

This analysis includes patients from Phase 1, Arm 3 (dose level 2-2) and Phase 2 at MTD level (2-2) combined

End point type	Secondary

End point timeframe:

From achievement of an objective response to progression or last follow-up

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The study aimed at including 20 patients treated at the maximum tolerated dose (MTD = level 2-2). These were 8 patients from phase 1 and 12 patients additionally recruited in phase 2. These groups were not meant to be compared with each other, but to be combined to describe the duration of response. This was compared to other therapies in similar patient groups (see LeMLAR publication, Blood Cancer J 11:95, 2021)

End point values	3. Dose level 2-2	Phase 2 at MTD level (2-2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	12		
Units: Months				
median (full range (min-max))	19 (1 to 32)	19 (1 to 32)		

Attachments (see zip file)	Duration of response to LeMLAR/Figure 2 - LeMLAR.jpg

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing the consent form for trial participation to 4 weeks after the last treatment cycle
Only for overall deaths: From signing the consent form to death or last follow-up (median follow-up: 31 months)

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Phase 1
Reporting group description: -	
Reporting group title	Phase 2
Reporting group description: -	

Serious adverse events	Phase 1	Phase 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 22 (63.64%)	6 / 12 (50.00%)	
number of deaths (all causes)	22	7	
number of deaths resulting from adverse events	1	0	
Vascular disorders			
Thromboembolism			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	2 / 22 (9.09%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	2 / 22 (9.09%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Worsening of general condition			
subjects affected / exposed	1 / 22 (4.55%)	2 / 12 (16.67%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter-related infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 22 (9.09%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hyperbilirubinuria			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal			

disorders			
Lung infection			
subjects affected / exposed	2 / 22 (9.09%)	2 / 12 (16.67%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial obstruction			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	1 / 22 (4.55%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Phase 1	Phase 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 22 (77.27%)	6 / 12 (50.00%)	
Blood and lymphatic system disorders			
Anemia, grade 3 or 4			
subjects affected / exposed	4 / 22 (18.18%)	3 / 12 (25.00%)	
occurrences (all)	4	3	
Leukopenia, grade 3 or 4			
subjects affected / exposed	2 / 22 (9.09%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Neutropenia, grade 3 or 4			
subjects affected / exposed	2 / 22 (9.09%)	2 / 12 (16.67%)	
occurrences (all)	2	2	
Thrombocytopenia, grade 3 or 4			
subjects affected / exposed	4 / 22 (18.18%)	3 / 12 (25.00%)	
occurrences (all)	4	3	
Gastrointestinal disorders			
Diarrhea, grade 3 or 4			
subjects affected / exposed	2 / 22 (9.09%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Infections and infestations			
Infection, grade 3 to 4			
subjects affected / exposed	3 / 22 (13.64%)	0 / 12 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 October 2014	Deescalation of lenalidomide dose from 25 mg to 20 mg and from 20 mg to 15 mg, if chemotherapy dose level 1 cannot be escalated at a lenalidomide dose of 25 mg or 20 mg, respectively

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34001867