Clinical trial results:
Lenalidomide, bendamustine and rituximab as first-line therapy for patients >65 years with mantle cell lymphoma

Summary

EudraCT number	2008-007246-60
Trial protocol	SE FI DK
Global end of trial date	12 April 2017

Results information

Result version number	v1 (current)
This version publication date	03 June 2021
First version publication date	03 June 2021
Summary attachment (see zip file)	Publication (LENA BERIT.Blood.pdf)

Trial information

Trial identification

Sponsor protocol code	NLG-MCL4 (LENA-BERIT)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00963534
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Lund University Hospital
Sponsor organisation address	Lund University Hospital, Department of Oncology, Lund, Sweden, 221 85
Public contact	Jan Sundberg, Lund University Hospital, Department of Oncology, Clinical Trial Unit, +46 46 17 70 34, jan.sundberg@skane.se
Scientific contact	Mats Jerkeman, Lund University Hospital, Department of Oncology, +46 46 17 75 20, mats.jerkeman@med.lu.se

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	12 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 April 2017
Global end of trial reached?	Yes
Global end of trial date	12 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• Phase I: Establishing maximally tolerable dose (MTD) of lenalidomide in combination with bendamustine and rituximab.
• Phase II: The primary efficacy variable was the evaluation of progression-free survival with lenalidomide, bendamustine and rituximab as frontline therapy in mantle cell lymphoma patients.

Protection of trial subjects:

Dose-limiting toxicity (DLT) was defined as any grade 3 to 5 non hematologic adverse event (AE) within the first 2 cycles of lenalidomide, bendamustine and rituximab, with the exception of thromboembolic events grade 3 to 4, nonpersisting nausea, diarrhea, elevated transaminases, or events attributed to progressive disease. Arecovery to absolute neutrophil count ≥ 1.0 x 109/L and platelet count ≥ 100 x 109/L was required before the next cycle was started.
Initially, the protocol included premedication with corticosteroids before rituximab infusion exclusively in cycle 1, but after protocol amendment corticosteroids were administered before every rituximab infusion, and in cycle 2, all patients received oral prednisone 20 mg days 1 to 14, followed by 1 week tapering of the dose. The use of granulocyte colonystimulating factor was mandatory in cycles 1 to 6, because the addition of lenalidomide was expected to augment hematologic toxicity.
Antibiotic prophylaxis was not initially recommended. After the first case of Pneumocystis carinii pneumonia (PCP), co-trimoxazole was prescribed to all patients.
All patients received allopurinol 300 mg per day by mouth, days 1 to 3 in cycle 1, but not thereafter because of the risk of cutaneous reactions in combination with bendamustine.
Thrombosis prophylaxis was recommended to all patients during the treatment phase, unless contraindicated (aspirin 75 mg/day, or low-molecularweight heparin to patients with a history of a thromboembolic event and/or a known hypercoagulable state).

Background therapy:

Prophylaxis
1. In the first cycle, all patients receive prophylactic steroid medication with 4 mg of betamethasone p o / i v (or comparable corticosteroid dose), the evening before, and one hour prior to rituximab. All patients receive prophylaxis with paracetamol 1000 mg p o and antihistamine, according to local routine, prior to rituximab in all cycles.
2. In cycle 2, all patients will receive oral prednisolone 20 mg x 2 days 1-14, then taper in one week. Corticosteroids are allowed, at the discretion of the investigator, also in the following cycles.
3. The use of G-CSF, such as inj pegfilgrastim 6 mg s c day 3, is mandatory after LBR in cycles 1-6.
4. Due to the possibility of an increased risk for Pneumocystis pneumonia, co-trimoxazole according to local guidelines, should be administered from the start of treatment until at least three months after finishing protocol therapy.
5. All patients receive allopurinol 300 mg/day p o days 1-3 cycle 1, and are encouraged to keep well hydrated during the first cycle of LBR due to potential risk of tumor lysis syndrome. Allopurinol should not be continued further due to risk of cutaneous reactions in combination with bendamustine.
6. All patients receive thrombosis prophylaxis with aspirine (acetyl salicylic acid, ASA) 75

mg/day during the treatment phase, unless contraindicated.
7. Patients with a history of a thromboembolic event and/or a known hypercoagulable state, or patients in whom ASA is contraindicated, should instead receive prophylaxis with low molecular weight heparin (LMWH), at the discretion of the investigator

Evidence for comparator:

Not applicable. No comparators were used.

Actual start date of recruitment	12 October 2009
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	Norway: 14
Country: Number of subjects enrolled	Sweden: 27
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Finland: 5
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	0
From 65 to 84 years	50
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a phase I- II, multicenter, open label trial. The study was divided into 2 parts; in part 1 the end point was to establish maximum tolerated dose for lenalidomide in combination with bendamustine and rituximab, while in the part 2 the main end point was evaluating progression-free survival.

Pre-assignment

Screening details:

Patients were eligible if they were 65 years or ≤ 65 years but unable to tolerate high-dose chemotherapy, with a confirmed diagnosis of mantle cell lymphoma stage II to IV and World Health Organization Performance status 0-3, requiring treatment as a result of at least one of the following symptoms: bulky disease, nodal or extra nodal mass .

Period 1

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

Arms

Arm title	Treatment period
Arm description: -	
Arm type	Single arm trial.
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

During the phase I portion of the study, dose-limiting toxicity was defined as a grade 3 or greater non-hematologic toxicity within the first two cycles of therapy, as specified below. The phase I portion of the study follows a sequential dose escalation, '3 + 3' design.
The maximum tolerated dose was defined as the highest dose studied for which the incidence of dose limiting toxicity was less than two out of the six subjects during the first cycle of therapy.

Phase 1: Phase I: Planned dose levels of lenalidomide were 5, 10, 15, 20 and 25 mg/day during cycles 1-6. In cycles 7-13, all patients will receive an initial dose of 25 mg/day.

Phase 2: Lenalidomide was used at maximum tolerated dose level from the phase I portion during cycles 1-6. In cycles 7-13, the dose is 25 mg/day. Maximum tolerated dose was established to 10 mg.

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

Dosage and administration details:

90 mg/m2 i v, days 1-2 (cycle 1-6). Cycle length 28 days.

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

Dosage and administration details:
375 mg/m2, i v, day 1, (cycle 1-6). Cycle length 28 days.

Number of subjects in period 1	Treatment period
Started	50
Completed	14
Not completed	36
Adverse event, serious fatal	2
Adverse event, non-fatal	28
Progressive disease	6

Baseline characteristics

Reporting groups

Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	50	50	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	50	50	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	71		
full range (min-max)	62 to 84	-	
Gender categorical Units: Subjects			
Female	13	13	
Male	37	37	

Subject analysis sets

Subject analysis set title	Non treatment
Subject analysis set type	Full analysis

Subject analysis set description:

Comparison group. Did not receive treatment.

Reporting group values	Non treatment		
Number of subjects	50		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		

From 65-84 years	50		
85 years and over	0		

Age continuous Units: years			
arithmetic mean	71		
full range (min-max)	62 to 84		
Gender categorical Units: Subjects			
Female	13		
Male	37		

End points

End points reporting groups

Reporting group title	Treatment period
Reporting group description: -	
Subject analysis set title	Non treatment
Subject analysis set type	Full analysis
Subject analysis set description: Comparison group. Did not receive treatment.	

Primary: Progression free survival

End point title	Progression free survival[1]

End point description:

Progression-free survival was defined as the interval between registration date and date of documented progression, lack of response, first relapse, or death of any cause.Overall survival was defined as time fromregistration to death from any cause. The Kaplan-Meier method was used to estimate survival curves for PFS and OS. Comparison of frequency of adverse events in different groups was based on x2 tests.

End point type	Primary

End point timeframe:

During the time the patient participated in the trial. Defined as the interval between registration date and date of documented progression or lack of response, first relapse, or death of any cause.

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: Progression-free survival was defined as the interval between registration date and date of documented progression, lack of response, first relapse, or death of any cause.Overall survival was defined as time fromregistration to death from any cause. The Kaplan-Meier method was used to estimate survival curves for PFS and OS. Comparison of frequency of adverse events in different groups was based on x2 tests.

End point values	Treatment period			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: Time.				
number (not applicable)	50			

Statistical analyses

No statistical analyses for this end point

Primary: Phase I: Establishing maximally tolerable dose (MTD) of lenalidomide in combination with bendamustine and rituximab.

End point title	Phase I: Establishing maximally tolerable dose (MTD) of lenalidomide in combination with bendamustine and rituximab.[2]

End point description:

End point type	Primary

End point timeframe:

Phase I: Establishing maximally tolerable dose (MTD) of lenalidomide in combination with bendamustine and rituximab.

Notes:

[2] - 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: In phase 1, the treatment plan followed a sequential dose escalation according to a 3+3 design. The initial dose of LEN in cycles 1 to 6 was 5 mg, escalated by 5 mg in each step. In cycles 7 to 13, the dose of LENwas 25mg.
Dose-limiting toxicity (DLT) was defined as any grade 3 to 5 nonhematologic adverse event (AE) within the first 2 cycles of LBR, with the exception of thromboembolic events grade 3 to 4, nonpersisting nausea, diarrhea, elevated transaminases, or events attributed to PD.

End point values	Treatment period	Non treatment		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	20	20		
Units: mg				
number (not applicable)	20	20		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the time the patient participated in the trial, and during the follow up period (37 months after end of treatment).

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Treatment period

Reporting group description: -

Serious adverse events	Treatment period		
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 50 (56.00%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
New primary tumor			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
ALP elevation			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial flutter			

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			
Cerebral infarction			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Anorexia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
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	2 / 50 (4.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	4 / 50 (8.00%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection			
subjects affected / exposed	8 / 50 (16.00%)		
occurrences causally related to treatment / all	8 / 8		
deaths causally related to treatment / all	2 / 2		

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

Non-serious adverse events	Treatment period		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 50 (100.00%)		
Investigations			
Hypoalbuminemia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Creatinine elevation			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Hyperglycemia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Cardiac disorders			

Hypotension subjects affected / exposed occurrences (all) Edema subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1 2 / 50 (4.00%) 2		
Nervous system disorders Neuropathy subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2		
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	6 / 50 (12.00%) 42 6 / 50 (12.00%) 42 4 / 50 (8.00%) 4		
General disorders and administration site conditions Allergic reaction to excipient subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Sweating subjects affected / exposed occurrences (all)	7 / 50 (14.00%) 7 4 / 50 (8.00%) 4 1 / 50 (2.00%) 1		
Immune system disorders Cytokine release reaction subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Gastrointestinal disorders			

Abdominal pain subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Constipation subjects affected / exposed occurrences (all)	7 / 50 (14.00%) 7		
Rectal bleeding subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 4		
Mucositis subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2		
Weight loss subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Renal and urinary disorders Urinary tract obstruction subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Infections and infestations Infection subjects affected / exposed occurrences (all)	5 / 50 (10.00%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 May 2009	Version 2: Corrections of inclusions- and exclusions criteria.
08 September 2009	Version 2: Modification of dose adjustments, additions of investigators.
14 September 2011	Version 4.1: Addition of corticosteroids. Addition of co-trimoxazole.
19 April 2012	Version 4.2: A change in study design in the phase 1 portion.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported