Clinical trial results:
A phase II trial of ibrutinib, lenalidomide and rituximab for patients with relapsed/refractory mantle cell lymphoma.

Summary

EudraCT number	2013-005541-36
Trial protocol	SE FI DK
Global end of trial date	31 December 2019

Results information

Result version number	v1 (current)
This version publication date	29 October 2020
First version publication date	29 October 2020

Trial information

Trial identification

Sponsor protocol code	NLG-MCL6

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02460276
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Nordic Lymphoma Group represented by Skåne University Hospital
Sponsor organisation address	Gettingevägen, Lund, Sweden,
Public contact	Jan Sundberg, Lund University Hospital, +46 4617 70 34, jan.sundberg@skane.se
Scientific contact	Jan Sundberg, Lund University Hospital, +46 4617 70 34, jan.sundberg@skane.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	29 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 January 2018
Global end of trial reached?	Yes
Global end of trial date	31 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluation of overall response rate, based on PET and CT, with lenalidomide, ibrutinib and rituximab in relapsed/refractory mantle cell lymphoma patients.

Protection of trial subjects:

The study was conducted according to the guidelines for Good Clinical Practice, issued by The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The protocol was approved by the local, regional or national Ethical Review Boards according to the existing national and local regulatory requirements. The study was conducted in agreement with the declaration of Helsinki, Tokyo, Venice and Hong Kong amendments and the laws and the regulations of the respective countries.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 April 2015
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: 13
Country: Number of subjects enrolled	Sweden: 16
Country: Number of subjects enrolled	Denmark: 18
Country: Number of subjects enrolled	Finland: 3
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)	13
From 65 to 84 years	36
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The trial was activated at a common start meeting held on 13th April 2015 for PIs and study nurses from the 10 participating sites. The first patient was included shortly after, on 30th April 2015. The last patient was included on 1st June 2016. Overall 50 patients were included in the trial over a period of 13 months.

Pre-assignment

Screening details:

Patients are screened for the complete list of inclusion and exclusion criteria according to the protocol.

Period 1

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

Arms

Arm title	Experimental

Arm description:

Induction therapy consisted of 12 cycles of 28 days:

- Lenalidomide: 15 mg p o daily days 1-21, every 28 days, cycles 1-12
- Ibrutinib: 560 mg daily p o days 1-28, cycles 1-12
- Rituximab 375 mg/m2 iv Day 1 in cycle 1
- Rituximab 1400 mg s c (or 375 mg/m2 iv) days 8, 15 and 22 in cycle 1. Then given day 1 in cycles 3, 5, 7, 9 and 11

Maintenance therapy consisted of 12 cycles of 56 days:

- Ibrutinib: 560 mg daily p o days 1-56, cycles 1-12
- Rituximab 1400 mg s c (or 375 mg/m2 iv) day 1, cycles 1-12

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

Dosage and administration details:

560 mg p o daily

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

Dosage and administration details:

15 mg p o daily on days 1-21 of 28 days, 12 cycles

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:

Induction therapy:
375 mg/m2 iv days 1, 8, 15, 22 in cycle 1; thereafter 375 mg/m2 on day 1 of cycle 3,5,7,9,11
Alternatively, 1400 mg sc on days 8,15,22 in cycle 1 and day 1 of cycles 3,5,7,9,11
Maintenance therapy:
1400 mg sc (or 375 mg/m2 iv) day 1 of each cycle

Number of subjects in period 1	Experimental
Started	50
Completed	11
Not completed	39
Adverse event, serious fatal	2
Consent withdrawn by subject	3
Physician's Decision	1
Adverse event, non-fatal	8
Patient's Decision	1
Allogeneic Stem Cell Transplantation	4
Lack of efficacy	20

Baseline characteristics

Reporting groups	
Reporting group title	Experimental

Reporting group description: -

Reporting group values	Experimental	Total	
Number of subjects	50	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		0	
85 years and over		0	
Age continuous Units: years			
median	69		
full range (min-max)	45 to 85	-	
Gender categorical Units: Subjects			
Female	14	14	
Male	36	36	
ECOG Performance Status Score Units: Subjects			
0-1	45	45	
>1	5	5	
MIPI Score Units: Subjects			
Low risk (<5.7)	8	8	
Intermediate risk (5.7 - 6.1)	15	15	
High risk (>6.2)	23	23	
Missing	4	4	
Ann Arbor Stage Units: Subjects			
Stage IV disease	42	42	
Stage I-III disease	8	8	
Bone Marrow Involvement Units: Subjects			
Yes	34	34	
No	16	16	
Refractory Disease Units: Subjects			

Yes	8	8	
No	42	42	
Previous Therapy Units: Subjects			
Autologous Stem Cell Transplantation	21	21	
Allogeneic Stem Cell Transplantation	3	3	
Ibrutinib	4	4	
Lenalidomide	1	1	
Other	21	21	
Number of Previous Therapies Units: Number			
median	2		
full range (min-max)	1 to 7	-	

End points

End points reporting groups

Reporting group title	Experimental

Reporting group description:

Induction therapy consisted of 12 cycles of 28 days:

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Maintenance therapy consisted of 12 cycles of 56 days:

- Ibrutinib: 560 mg daily p o days 1-56, cycles 1-12
- Rituximab 1400 mg s c (or 375 mg/m2 iv) day 1, cycles 1-12

Primary: Overall Response Rate

End point title	Overall Response Rate[1]

End point description:

End point type	Primary

End point timeframe:

Overall response rate at the end of induction therapy

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 analysis is described in the publication of the study in Lancet Haematology 2018; 5: e109-116

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: subjects				
CR	28			
PR	10			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events was recorded from the time the subject signed the informed consent to 28 days after the last dose of study drug.

Adverse event reporting additional description:

Non-serious adverse events were evaluated and reported per patient.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	All subjects

Reporting group description: -

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 50 (66.00%)		
number of deaths (all causes)	24		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
cutaneous basocellular carcinoma			
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			
vascular disorders			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
general disorders			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences causally related to treatment / all	5 / 6		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			

Immune system disorder			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			
subjects affected / exposed	10 / 50 (20.00%)		
occurrences causally related to treatment / all	15 / 15		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	1 / 1		
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
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		
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			

Musculoskeletal disorder			
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	9 / 10		
deaths causally related to treatment / all	1 / 1		
Metabolism and nutrition disorders			
Tumour lysis syndrome			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 50 (100.00%)		
Vascular disorders			
Vascular Adverse Events	Additional description: grade 1-3		
subjects affected / exposed	20 / 50 (40.00%)		
occurrences (all)	20		
General disorders and administration site conditions			
Fatigue	Additional description: grade 1-3		
subjects affected / exposed	28 / 50 (56.00%)		
occurrences (all)	28		
Respiratory, thoracic and mediastinal disorders			
Respiratory Adverse Events	Additional description: grade 1-3		
subjects affected / exposed	25 / 50 (50.00%)		
occurrences (all)	25		
Psychiatric disorders			
Psychiatric Adverse Events	Additional description: grade 1-2		
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	7		

Cardiac disorders			
Atrial fibrillation	Additional description: grade 1-3		
subjects affected / exposed	8 / 50 (16.00%)		
occurrences (all)	8		
Nervous system disorders			
Neurological Adverse Events	Additional description: grade 1-2		
subjects affected / exposed	17 / 50 (34.00%)		
occurrences (all)	17		
Blood and lymphatic system disorders			
Thrombocytopenia	Additional description: grade 1-3		
subjects affected / exposed	17 / 50 (34.00%)		
occurrences (all)	17		
Anaemia	Additional description: grade 1-3		
subjects affected / exposed	10 / 50 (20.00%)		
occurrences (all)	10		
Neutropenia	Additional description: grade 1-3		
subjects affected / exposed	33 / 50 (66.00%)		
occurrences (all)	33		
Eye disorders			
Ocular Adverse Events	Additional description: grade 1-2		
subjects affected / exposed	13 / 50 (26.00%)		
occurrences (all)	13		
Gastrointestinal disorders			
Gastrointestinal disorders	Additional description: grade 1-3		
subjects affected / exposed	48 / 50 (96.00%)		
occurrences (all)	48		
Skin and subcutaneous tissue disorders			
Cutaneous adverse events	Additional description: grade 1-3		
subjects affected / exposed	39 / 50 (78.00%)		
occurrences (all)	39		
Renal and urinary disorders			
Renal Adverse Events	Additional description: grade 1-2		
subjects affected / exposed	9 / 50 (18.00%)		
occurrences (all)	9		
Musculoskeletal and connective tissue disorders			
Muscle Cramps	Additional description: grade 1-3		
subjects affected / exposed	15 / 50 (30.00%)		
occurrences (all)	15		

Infections and infestations			
Infections	Additional description: grade 1-3		
subjects affected / exposed	38 / 50 (76.00%)		
occurrences (all)	38		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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/29396091