



Clinical trial results:

A multicentric phase II study evaluating the benefit of a short induction treatment by Bendamustine and Rituximab followed by maintenance therapy with rituximab In Elderly (60 years old) patients with untreated Follicular lymphoma patients, with an intermediate or high FLIPI score
Summary

EudraCT number	2010-020757-14
Trial protocol	BE
Global end of trial date	01 July 2016

Results information

Result version number	v1 (current)
This version publication date	27 March 2019
First version publication date	27 March 2019

Trial information

Trial identification

Sponsor protocol code	BRIEF
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01313611
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LYSARC
Sponsor organisation address	CHU LYON SUD PAVILLON 6D, PIERRE BENITE, France,
Public contact	Chairman of the study, Professor Pierre Feugier, +33 383 15 32 82, p.feugier@chu-nancy.fr
Scientific contact	Project Management, LYSARC, +33 4 72 66 93 33, affaires-reglementaires@lysarc.org

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	01 July 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 July 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the complete response rate according to Cheson criteria 1999 after a short induction treatment by Rituximab and Bendamustine in 1st line follicular lymphoma patients, ≥ 60 years old, with an intermediate or high FLIPI score, and without high tumor burden (according to GELF criteria)

Protection of trial subjects:

Standard care

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 February 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	France: 61
Worldwide total number of subjects	63
EEA total number of subjects	63

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	63
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

clinical examination (weight, BSA, pulse, blood pressure, Temp, physical examination, ECOG PS, Biochemical test, blood celle count), inclusion/exclusion criteria

Period 1

Period 1 title	Induction (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Experimental
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	bendamustine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

- Two cycles of bendamustine (LEVACT®) at the dose of 90 mg/m² intravenously over 60 minutes on days 1 and 2, with a four weeks interval (28 days) between the two cycles.

Investigational medicinal product name	rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

- Four cycles of rituximab (MABTHERA®) 375 mg/m² intravenously at the appropriate infusion rate on days 1, 8, 15, and 22.

Number of subjects in period 1	Experimental
Started	63
Completed	37
Not completed	26
no drug received	1
Protocol deviation	25

Baseline characteristics

Reporting groups

Reporting group title	Induction
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Reporting group description: -

Reporting group values	Induction	Total	
Number of subjects	63	63	
Age categorical Units: Subjects			
Adults (18-64 years)		0	
Age continuous Units: years			
arithmetic mean	69.6		
inter-quartile range (Q1-Q3)	64 to 75	-	
Gender categorical Units: Subjects			
Female	34	34	
Male	29	29	

End points

End points reporting groups

Reporting group title	Experimental
Reporting group description: -	

Primary: Complete Response Rate according to Cheson 2007

End point title	Complete Response Rate according to Cheson 2007 ^[1]
End point description:	

End point type	Primary
End point timeframe: end of induction phase	

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: 1 arm = no comparative statistical analysis

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	63			
Units: percent				
arithmetic mean (confidence interval 5%)	54 (40.9 to 66.6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

28 days after end of treatment

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Experimental
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Reporting group description: -

Serious adverse events	Experimental		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 62 (33.87%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelofibrosis			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma of prostate			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myelodysplastic syndrome			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Auricular fibrillation			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Heart failure			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Transurethral bladder resection			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Neuralgia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stroke			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Adenocarcinoma			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Neutropenia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile aplasia			

subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Reduced general condition			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Pyrexia			
subjects affected / exposed	3 / 62 (4.84%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Scrotal hernia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhea			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Interstitial pneumonia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnea			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoxia			

subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pyuria			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Streptococcus pneumoniae pneumonia			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Bronchitis			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Infective myositis			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Progressive multifocal leucoencephalopathy			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection urinary tract			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia Pseudomonas aeruginosa			
subjects affected / exposed	1 / 62 (1.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	2 / 62 (3.23%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Experimental		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 62 (83.87%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) NEOPLASM BENIGN, MALIGNANT AND UNSPECIFIED			
subjects affected / exposed	9 / 62 (14.52%)		
occurrences (all)	9		
Vascular disorders VASCULAR DISORDERS			
subjects affected / exposed	6 / 62 (9.68%)		
occurrences (all)	6		
General disorders and administration site conditions GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			

subjects affected / exposed occurrences (all)	26 / 62 (41.94%) 26		
Immune system disorders IMMUNE SYSTEM DISORDERS subjects affected / exposed occurrences (all)	4 / 62 (6.45%) 4		
Respiratory, thoracic and mediastinal disorders RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS subjects affected / exposed occurrences (all)	12 / 62 (19.35%) 12		
Investigations INVESTIGATIONS subjects affected / exposed occurrences (all)	31 / 62 (50.00%) 31		
Cardiac disorders CARDIAC DISORDERS subjects affected / exposed occurrences (all)	4 / 62 (6.45%) 4		
Nervous system disorders NERVOUS SYSTEM DISORDERS subjects affected / exposed occurrences (all)	18 / 62 (29.03%) 18		
Blood and lymphatic system disorders BLOOD & LYMPHATIC SYSTEM DISORDERS/INVESTIGATIONS subjects affected / exposed occurrences (all)	52 / 62 (83.87%) 147		
Gastrointestinal disorders GASTRO-INTESTINAL DISORDERS subjects affected / exposed occurrences (all)	38 / 62 (61.29%) 38		
Hepatobiliary disorders HEPATOBIILIARY DISORDERS subjects affected / exposed occurrences (all)	3 / 62 (4.84%) 3		
Skin and subcutaneous tissue disorders			

SKIN AND SUBCUTANEOUS TISSUE DISORDERS subjects affected / exposed occurrences (all)	12 / 62 (19.35%) 12		
Renal and urinary disorders RENAL AND URINARY DISORDERS subjects affected / exposed occurrences (all)	5 / 62 (8.06%) 5		
Infections and infestations INFECTIOUS AND INFESTATIONS subjects affected / exposed occurrences (all)	32 / 62 (51.61%) 32		
Metabolism and nutrition disorders METABOLISM AND NUTRITION DISORDERS subjects affected / exposed occurrences (all)	9 / 62 (14.52%) 9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 April 2011	Addition and precision of secondary objectives : 12 infusion in maintenance instead of 13, as recommended in the MA
06 September 2012	Clarification of GELF criteria Addition of platelet count every 4 weeks during maintenat as required by IDMC
10 January 2013	Treatment STOP

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
13 November 2012	Two cycles of bendamustine administered concomitantly with 4 weekly cycles of rituximab may result in a high response rate and PFS. Due to the observed toxicity-related deaths, this scheme may not be recommended in LTBFL. Further research aiming at proposing short-term treatments with low toxicity and prolonged PFS should be encouraged for these patients. Because of 3 deaths evaluated to be related to the experimental treatment, the Scientific Board of the LYSA met on November 13, 2012, and decision was made to definitively stop rituximab treatment during maintenance phase, according to DSMC recommendations	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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Notes: