Clinical trial results:
TARGETED INTENSIFICATION BY A PREPARATIVE REGIMEN FOR PATIENTS WITH HIGH-GRADE B-CELL LYMPHOMA UTILIZING STANDARD-DOSE YTTRIUM-90 IBRITUMOMAB TIUXETAN (ZEVALIN) RADIOIMMUNOTHERAPY (RIT) COMBINED WITH HIGH-DOSE BEAM FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT):Z BEAM 2

Summary

EudraCT number	2007-000270-23
Trial protocol	BE
Global end of trial date	29 January 2014

Results information

Result version number	v1 (current)
This version publication date	14 October 2017
First version publication date	14 October 2017

Trial information

Trial identification

Sponsor protocol code	Z BEAM 2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00689169
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LYSA
Sponsor organisation address	CH Lyon Sud - Service d'Hématologie - Bâtiment 1F - 3ème étage , Pierre-Bénite Cedex, France, 69495
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Scientific contact	Christophe Fruchart, LYSA, fruchart-c@chu-caen.fr

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	28 June 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and the safety of a preparative regimen utilizing standard-dose Yttrium-90 Ibritumomab Tiuxetan (Zevalin) radioimmunotherapy combined with high-dose BEAM followed by ASCT after first line treatment in patients aged from 18 to 65 years CD20 positive Diffuse Large B-Cell lymphoma with poor prognosis

PRIMARY ENDPOINT:
Event free survival (EFS) at 2 years: events being death from any cause, relapse for complete responders and unconfirmed complete responders, progression during and after treatment and changes of therapy.

Protection of trial subjects:

Supportive treatments administered according to the standard use of each center.
Treatment for progression/relapse administered at the discretion of treating physician.

Background therapy:

No background therapy.

Evidence for comparator:

No comparator.

Actual start date of recruitment	21 August 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	France: 66
Country: Number of subjects enrolled	Switzerland: 2
Worldwide total number of subjects	75
EEA total number of subjects	73

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)	75
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period : from 21/08/2007 to 18/12/2008.
Patients recruited in France, Belgium and Switzerland.

Pre-assignment

Screening details:

pathologically proven large B-Cell lymphoma CD20 positive (without transformation from low grade), in CR or PR after induction treatment (R CHOP like or R ACVBP), eligible for autologous stem cell transplantation
75 patient included

Period 1

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

Arms

Arm title	Z-BEAM + ASCT

Arm description:

Conditioning regiment rituximab + ZBEAM followed by ASCT

Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

250 mg/m² administered at D-21 and D-14 before ASCT

Investigational medicinal product name	90Y ibritumomab tiuxetan
Investigational medicinal product code	
Other name	Zevalin
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

0,4 mCi/kg administered at D-14 before ASCT

Investigational medicinal product name	Carmustine
Investigational medicinal product code	
Other name	BCNU
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

300 mg/m² administered at D-6 before ASCT

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

Dosage and administration details: 100 mg/m²/12h administered from D-6 to D-3 before ASCT	
Investigational medicinal product name	cytarabine
Investigational medicinal product code	
Other name	aracytine
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 200 mg/m²/12h administered from D-6 to D-3 before ASCT	
Investigational medicinal product name	melphalan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 140 mg/m² administered at D-2 before ASCT	

Number of subjects in period 1	Z-BEAM + ASCT
Started	75
Enrollment of patient	75
Study treatment	73
ASCT	71
Completed	71
Not completed	4
No study treatment received	2
Lack of efficacy	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	75	75	
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	49		
full range (min-max)	19 to 64	-	
Gender categorical Units: Subjects			
Female	43	43	
Male	32	32	
Performance status (ECOG) at baseline Units: Subjects			
00	24	24	
01	27	27	
02	16	16	
03	7	7	
04	1	1	
Age Units: Subjects			
<= 60	68	68	
> 60	7	7	
Ann Arbor Stage Units: Subjects			
Stage 1	1	1	
Stage 2	4	4	
Stage 3	12	12	
Stage 4	58	58	
B symptoms Units: Subjects			
No	35	35	

Yes	40	40	
LDH Units: Subjects			
<= 1N	7	7	
> 1N	68	68	
Age-ajusted IPI Units: Subjects			
00	0	0	
01	5	5	
02	53	53	
03	17	17	
Number of extranodal sites involved Units: Subjects			
<= 1	31	31	
>1	44	44	
IPI Units: Subjects			
01	1	1	
02	27	27	
03	31	31	
04	15	15	
05	1	1	
Bone Marrow biopsy at dignosis Units: Subjects			
Not involved	56	56	
Involved	15	15	
Not done	4	4	
PET Scan at diagnosis Units: Subjects			
Positive	53	53	
Not done	22	22	
Performance Status (ECOG) at registration Units: Subjects			
00	50	50	
01	24	24	
02	1	1	
Response after induction treatment Units: Subjects			
COMPLETE RESPONSE	30	30	
UNCONFIRMED COMPLETE RESPONSE	33	33	
PARTIAL RESPONSE	12	12	
Bone marrow biopsy after induction Units: Subjects			
Not involved	25	25	
Not done	50	50	
PET scan after induction Units: Subjects			
Negative	54	54	
Positive	21	21	
Induction treatment - type of			

chemotherapy Units: Subjects			
R-CHOP like	36	36	
R-ACVBP like	39	39	
Weight Units: kg			
median	63		
full range (min-max)	45 to 100	-	
Height Units: cm			
median	170		
full range (min-max)	140 to 195	-	
Body area Units: m²			
median	1.74		
full range (min-max)	1.44 to 2.29	-	
Number of extranodal sites at diagnosis Units: number			
median	2		
full range (min-max)	0 to 9	-	
Number of sites used for response evaluation at diagnosis Units: number			
median	2		
full range (min-max)	1 to 6	-	
Number of sites used for response evaluation at registration Units: number			
median	2		
full range (min-max)	1 to 6	-	

End points

End points reporting groups

Reporting group title	Z-BEAM + ASCT
Reporting group description:	
Conditioning regiment rituximab + ZBEAM followed by ASCT	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population comprises all patients registred and having received the dose of study treatment (Zevalin).	
Subject analysis set title	Patient with transplantation
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All patients registred and having received ZBEAM and transplantation.	

Primary: Event Free survival from ASCT

End point title	Event Free survival from ASCT[1]
End point description:	
Event free survival (EFS) at 2 years: events being death from any cause, relapse for complete responders and unconfirmed complete responders, progression during and after treatment and changes of therapy. Event-Free survival is measured both from date of inclusion and from date of transplantation to date of first event.	
End point type	Primary
End point timeframe:	
24 months after ASCT	

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: Since there is only one treatment arm, it is not possible to indicate comparative statistical analysis as required by EudraCT system.

End point values	Patient with transplantation			
Subject group type	Subject analysis set			
Number of subjects analysed	71			
Units: percent				
number (confidence interval 5%)	78.8 (67.4 to 86.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate

End point title	Overall Response Rate
End point description:	
Overall response rate (ORR) (complete response CR and partial response PR) at day 100 after ASCT. Overall response rate (ORR) will be defined as defined according to Cheson 1999 criteria. Patients without response assessment are considered as non-responder.	

End point type	Secondary

End point timeframe:

Overall Response rate at D100 after ASCT or at withdrawal.

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	73			
Units: percent				
number (confidence interval 5%)	83.6 (73 to 91.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival is measured from the date of inclusion or from evaluation at month 3 post-transplant to the date of death, irrespective of the cause. Patients who have not died at the time of analysis will be censored at the most recent date they were known to be alive or at the stopping date if the most recent date is later.

End point type	Secondary

End point timeframe:

Overall survival 24 months after ASCT.

End point values	Patient with transplantation			
Subject group type	Subject analysis set			
Number of subjects analysed	71			
Units: percent				
number (confidence interval 5%)	83.1 (72.1 to 90)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) occurring during the treatment period will be recorded until 100 days after the end of the
last dose of treatment

Adverse event reporting additional description:

Due to the expected toxicity of these treatments, only grade 3,4 and 5 toxicities (Common Terminology Criteria for Adverse Events (CTCAE) v3.0) or grade 2 for infections, and toxicities (grade 1 to 5) related to a
Serious Adverse Event, must be reported as "Adverse Event".

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Safety population

Reporting group description:

The safety population comprises all patients registred and having received the dose of study treatment (Zevalin).

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 73 (24.66%)		
number of deaths (all causes)	14		
number of deaths resulting from adverse events	1		
Cardiac disorders			
Myopericarditis			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Lung disorder			
subjects affected / exposed	3 / 73 (4.11%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure acute			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Septic shock				
subjects affected / exposed	2 / 73 (2.74%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	1 / 1			
Arthritis bacterial				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes virus infection				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes oesophagitis				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis fungal				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchopulmonary aspergillosis				
subjects affected / exposed	1 / 73 (1.37%)			
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 / 73 (1.37%)		
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	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 73 (93.15%)		
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	35 / 73 (47.95%)		
occurrences (all)	35		
Asthenia			
subjects affected / exposed	3 / 73 (4.11%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Lung disorder			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	4		
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences (all)	2		
Psychiatric disorders			

Depression			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences (all)	2		
Liver function test abnormal			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Cardiac disorders			
Myopericarditis			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	39 / 73 (53.42%)		
occurrences (all)	39		
Neutropenia			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Eye disorders			
Keratitis			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Diplopia			

subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 73 (6.85%)		
occurrences (all)	5		
Anal inflammation			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Dysphagia			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Enterocolitis			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Enteritis			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences (all)	2		
renal failure acute			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Infections and infestations			
Infection			
subjects affected / exposed	8 / 73 (10.96%)		
occurrences (all)	8		
Neutropenic infection			

subjects affected / exposed	5 / 73 (6.85%)			
occurrences (all)	5			
Urinary tract infection				
subjects affected / exposed	5 / 73 (6.85%)			
occurrences (all)	5			
Diarrhoea infectious				
subjects affected / exposed	4 / 73 (5.48%)			
occurrences (all)	4			
Herpes zoster				
subjects affected / exposed	3 / 73 (4.11%)			
occurrences (all)	3			
Staphylococcal infection				
subjects affected / exposed	3 / 73 (4.11%)			
occurrences (all)	3			
Rhinitis				
subjects affected / exposed	3 / 73 (4.11%)			
occurrences (all)	3			
Tooth abscess				
subjects affected / exposed	3 / 73 (4.11%)			
occurrences (all)	3			
Pneumonia				
subjects affected / exposed	2 / 73 (2.74%)			
occurrences (all)	2			
Escherichia infection				
subjects affected / exposed	2 / 73 (2.74%)			
occurrences (all)	2			
Septic shock				
subjects affected / exposed	2 / 73 (2.74%)			
occurrences (all)	2			
Staphylococcal sepsis				
subjects affected / exposed	2 / 73 (2.74%)			
occurrences (all)	2			
Escherichia urinary tract infection				
subjects affected / exposed	2 / 73 (2.74%)			
occurrences (all)	2			
Bronchitis				

subjects affected / exposed	2 / 73 (2.74%)			
occurrences (all)	2			
Herpes oesophagitis				
subjects affected / exposed	2 / 73 (2.74%)			
occurrences (all)	2			
Cystitis				
subjects affected / exposed	2 / 73 (2.74%)			
occurrences (all)	2			
Arthritis bacterial				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Oral candidiasis				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Ear infection				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Enterococcal infection				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Genital infection				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Oral fungal infection				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Klebsiella infection				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Proteus infection				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Enterocolitis infectious				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Herpes virus infection				

subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Respiratory tract infection				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Enterocolitis fungal				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Candidiasis				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Bacteremia				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Pharyngitis				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Fungal infection				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Pseudomonal sepsis				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Bronchopulmonary aspergillosis				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Sinusitis				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Streptococcal sepsis				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Nasopharyngitis				

subjects affected / exposed occurrences (all)	1 / 73 (1.37%) 1		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Dehydration subjects affected / exposed occurrences (all)	 2 / 73 (2.74%) 2 2 / 73 (2.74%) 2 1 / 73 (1.37%) 1		

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/25072780