Clinical trial results:
Randomized Phase III study evaluating the non-inferiority of a treatment adapted to the early response evaluated with 18F-FDG PET compared to a standard treatment, for patients aged from 18 to 80 years with low risk (aa IPI = 0) diffuse large B-cells non hodgkin's lymphoma CD 20+

Summary

EudraCT number	2009-017279-77
Trial protocol	FR BE
Global end of trial date	23 May 2020

Results information

Result version number	v1 (current)
This version publication date	24 November 2023
First version publication date	24 November 2023

Trial information

Trial identification

Sponsor protocol code	LNH2009-1B

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01285765
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHU de Nancy – Direction de la Recherche et de l'Innovation
Sponsor organisation address	Hôpital Saint Julien – Rue Foller – Case Officielle 60034, Nancy, France,
Public contact	Fabienne MORAND - Project Manager, LYSARC, +33 (0)472 66 93 33, lnh09-1b@lysarc.org
Scientific contact	Serge Bologna, LYSARC, +33 (0)472 66 93 33, s.bologna@oncog.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	23 May 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate by PFS at 3 years the non-inferiority of a chemotherapy treatment with 4 or 6 cycles of R-CHOP 21, determined according to early response assessed by PET at the end of 2 cycles versus standard chemotherapy of 6 cycles of R-CHOP 21 in patients with DLBCL lymphoma CD20+ with no factors of the IPI age adjusted.

Protection of trial subjects:

No rescue treatment during this study

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 December 2010
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	Belgium: 74
Country: Number of subjects enrolled	France: 576
Worldwide total number of subjects	650
EEA total number of subjects	650

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)	473
From 65 to 84 years	177
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

576 patients were recruited in France between december 2010 and may 2017
74 patients were recruited in Belgium between august 2011 and april 2017

Pre-assignment

Screening details:

650 patients were randomized. Among them, 646 patients received at least dose of treatment regimen.

Period 1

Period 1 title	Treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard

Arm description:

6 cycles of R-CHOP 21

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Experimental

Arm description:

4 or 6 cycles of R-CHOP 21
The number of cycle to be administered is depending on the results assessed by PET after the cycle 2 and 4 :
- If the PET is negative after cycle 2 and cycle 4, 4 cycles will be administered in total.
- If the PET is positive after cycle 2 and negative after cycle 4, 6 cycles will be administered in total.
- If the PET is positive after cycle 2 and 4 (or negative after cycle 2 and positive after cycle 4), the patient will be withdrawn from the study with a pathological confirmation by biopsy of the lesion if possible. A Salvage treatment will be administered.

Arm type	Experimental
Investigational medicinal product name	R-CHOP 21
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Prednisone 60 mg/m2
Rituximab 375 mg/m2
Doxorubicin 50 mg/m2
Cyclophosphamide 750 mg/m2
Vincristine 1.4 mg/m2
G-CSF (SC) 5 ug/kg/day (optional)

Number of subjects in period 1	Standard	Experimental
Started	331	319
Completed	289	275
Not completed	42	44
Consent withdrawn by subject	2	-
death	2	1
progression	4	1
Other	4	8
concurrent illness	5	2
toxicity of study treatment	3	-
Lack of efficacy	17	23
Protocol deviation	5	9

Period 2

Period 2 title	Follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard

Arm description:

6 cycles of R-CHOP 21

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Experimental

Arm description:

4 or 6 cycles of R-CHOP 21
The number of cycle to be administered is depending on the results assessed by PET after the cycle 2 and 4 :
- If the PET is negative after cycle 2 and cycle 4, 4 cycles will be administered in total.
- If the PET is positive after cycle 2 and negative after cycle 4, 6 cycles will be administered in total.
- If the PET is positive after cycle 2 and 4 (or negative after cycle 2 and positive after cycle 4), the patient will be withdrawn from the study with a pathological confirmation by biopsy of the lesion if possible. A Salvage treatment will be administered.

Arm type	Experimental
Investigational medicinal product name	R-CHOP 21
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Prednisone 60 mg/m2
Rituximab 375 mg/m2

Doxorubicin 50 mg/m2
Cyclophosphamide 750 mg/m2
Vincristine 1.4 mg/m2
G-CSF (SC) 5 ug/kg/day (optional)

Number of subjects in period 2	Standard	Experimental
Started	289	275
Completed	289	275

Baseline characteristics

Reporting groups	
Reporting group title	Standard
Reporting group description:	
6 cycles of R-CHOP 21	
Reporting group title	Experimental
Reporting group description:	
4 or 6 cycles of R-CHOP 21 The number of cycle to be administered is depending on the results assessed by PET after the cycle 2 and 4 : - If the PET is negative after cycle 2 and cycle 4, 4 cycles will be administered in total. - If the PET is positive after cycle 2 and negative after cycle 4, 6 cycles will be administered in total. - If the PET is positive after cycle 2 and 4 (or negative after cycle 2 and positive after cycle 4), the patient will be withdrawn from the study with a pathological confirmation by biopsy of the lesion if possible. A Salvage treatment will be administered.	

Reporting group values	Standard	Experimental	Total
Number of subjects	331	319	650
Age categorical Units: Subjects			
Adults (18-64 years)	244	229	473
From 65-84 years	87	90	177
Gender categorical Units: Subjects			
Female	132	137	269
Male	199	182	381

Subject analysis sets	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients randomized	

Reporting group values	Intention to treat		
Number of subjects	650		
Age categorical Units: Subjects			
Adults (18-64 years)	473		
From 65-84 years	177		
Gender categorical Units: Subjects			
Female	269		
Male	381		

End points

End points reporting groups

Reporting group title	Standard
Reporting group description:	
6 cycles of R-CHOP 21	
Reporting group title	Experimental
Reporting group description:	
4 or 6 cycles of R-CHOP 21 The number of cycle to be administered is depending on the results assessed by PET after the cycle 2 and 4 : - If the PET is negative after cycle 2 and cycle 4, 4 cycles will be administered in total. - If the PET is positive after cycle 2 and negative after cycle 4, 6 cycles will be administered in total. - If the PET is positive after cycle 2 and 4 (or negative after cycle 2 and positive after cycle 4), the patient will be withdrawn from the study with a pathological confirmation by biopsy of the lesion if possible. A Salvage treatment will be administered.	
Reporting group title	Standard
Reporting group description:	
6 cycles of R-CHOP 21	
Reporting group title	Experimental
Reporting group description:	
4 or 6 cycles of R-CHOP 21 The number of cycle to be administered is depending on the results assessed by PET after the cycle 2 and 4 : - If the PET is negative after cycle 2 and cycle 4, 4 cycles will be administered in total. - If the PET is positive after cycle 2 and negative after cycle 4, 6 cycles will be administered in total. - If the PET is positive after cycle 2 and 4 (or negative after cycle 2 and positive after cycle 4), the patient will be withdrawn from the study with a pathological confirmation by biopsy of the lesion if possible. A Salvage treatment will be administered.	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients randomized	

Primary: Progression-free survival

End point title	Progression-free survival
End point description:	
End point type	Primary
End point timeframe:	
From the date of randomization to the date of first documented disease progression, relapse or death from any cause, whichever occurs first	

End point values	Standard	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	319		
Units: percent				
number (confidence interval 90%)				
3 years	89.2 (85.3 to 92.2)	92.0 (88.3 to 94.5)		

Attachments (see zip file)	PFS/Figure 160001.png

Statistical analyses

Statistical analysis title	PFS non-inferiority
Statistical analysis description: Non-inferiority on PFS	
Comparison groups	Experimental v Standard
Number of subjects included in analysis	650
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.724
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.504
upper limit	1.04

Notes:

[1] - The trial was designed based on a non-inferiority margin of 10% (corresponding to a 3-year PFS of 80% in the control arm vs >70% in the experimental arm, HR=1.6).

If the upper limit of the confidence interval is strictly lower than the non-inferiority margin (HR = 1.6), the non-inferiority of experimental arm vs standard arm will be demonstrated.

Statistical analysis title	PFS superiority
Comparison groups	Standard v Experimental
Number of subjects included in analysis	650
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0702 [2]
Method	Logrank

Notes:

[2] - Superiority of experimental arm

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

From the date of randomization to the date of death from any cause

End point values	Standard	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	319		
Units: percent				
number (confidence interval 95%)				
3 years	95.7 (92.8 to 97.4)	97.7 (95.3 to 98.9)		

Attachments (see zip file)	OS/Figure 170001.png

Statistical analyses

Statistical analysis title	OS
Comparison groups	Standard v Experimental
Number of subjects included in analysis	650
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.127 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.612
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.323
upper limit	1.157

Notes:

[3] - Bilateral p-value

Secondary: Event-free survival

End point title	Event-free survival

End point description:

End point type	Secondary

End point timeframe:

From the date of randomization to the date of first documented disease progression, relapse, initiation of new anti-lymphoma therapy or death from any cause.

End point values	Standard	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	319		
Units: percent				
number (confidence interval 95%)				
3 years	82.6 (78.0 to 86.3)	84.8 (80.3 to 88.3)		

Attachments (see zip file)	EFS/Figure 170019.png

Statistical analyses

Statistical analysis title	EFS
Comparison groups	Experimental v Standard
Number of subjects included in analysis	650
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3412 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.847
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.598
upper limit	1.198

Notes:

[4] - Bilateral p-value

Secondary: Duration of response

End point title	Duration of response

End point description:

End point type	Secondary

End point timeframe:

Duration of response will be measured from the time of attainment of CR or PR to the date of first documented disease progression, relapse or death from any cause.

End point values	Standard	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	318[5]	303[6]		
Units: percent				
number (confidence interval 95%)				
3 years	91.1 (87.4 to 93.8)	93.6 (90.1 to 95.9)		

Notes:

[5] - Patients who reached CR or PR during study

[6] - Patients who reached CR or PR during study

Attachments (see zip file)	DoR/Figure 170034.png

Statistical analyses

Statistical analysis title	DoR
Comparison groups	Experimental v Standard
Number of subjects included in analysis	621
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.151 [7]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.709
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.443
upper limit	1.136

Notes:

[7] - Bilateral p-value

Secondary: Complete response rate

End point title	Complete response rate

End point description:

Response was assessed according to Cheson 2007 criteria.

End point type	Secondary

End point timeframe:

End of treatment = 4 or 6 cycles if patient received all planned cycles otherwise at withdrawal

End point values	Standard	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	319		
Units: Percentage				
number (confidence interval 95%)	86.0 (81.79 to 89.58)	87.5 (83.32 to 90.89)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 30 days after the last study drug administration

Adverse event reporting additional description:

All events that meet one or more criteria of seriousness occurred after the informed consent up to 30 days after the last study drug administration, regardless the relationship to the study treatment, will be reported as SAE. A SAE that occurs after this time, including during the follow-up period, if considered related to the study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15

Reporting groups

Reporting group title	Standard

Reporting group description:

6 cycles of R-CHOP 21

Reporting group title	Experimental

Reporting group description:

4 or 6 cycles of R-CHOP 21
The number of cycle to be administered is depending on the results assessed by PET after the cycle 2 and 4 :
- If the PET is negative after cycle 2 and cycle 4, 4 cycles will be administered in total.
- If the PET is positive after cycle 2 and negative after cycle 4, 6 cycles will be administered in total.
- If the PET is positive after cycle 2 and 4 (or negative after cycle 2 and positive after cycle 4), the patient will be withdrawn from the study with a pathological confirmation by biopsy of the lesion if possible. A Salvage treatment will be administered.

Serious adverse events	Standard	Experimental	
Total subjects affected by serious adverse events			
subjects affected / exposed	47 / 330 (14.24%)	30 / 316 (9.49%)	
number of deaths (all causes)	26	15	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm benign, malignant and unspecified			
subjects affected / exposed	8 / 330 (2.42%)	7 / 316 (2.22%)	
occurrences causally related to treatment / all	3 / 9	4 / 7	
deaths causally related to treatment / all	0 / 2	0 / 2	
General disorders and administration site conditions			
General disorders and administration site conditions			

subjects affected / exposed	5 / 330 (1.52%)	3 / 316 (0.95%)	
occurrences causally related to treatment / all	8 / 8	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	5 / 330 (1.52%)	4 / 316 (1.27%)	
occurrences causally related to treatment / all	5 / 5	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	5 / 330 (1.52%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	5 / 5	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	3 / 330 (0.91%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	4 / 330 (1.21%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	4 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye disorders			
subjects affected / exposed	0 / 330 (0.00%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	6 / 330 (1.82%)	5 / 316 (1.58%)	
occurrences causally related to treatment / all	6 / 6	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Hepatobiliary disorders			
subjects affected / exposed	1 / 330 (0.30%)	1 / 316 (0.32%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	3 / 330 (0.91%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	1 / 330 (0.30%)	0 / 316 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and infestations			
subjects affected / exposed	10 / 330 (3.03%)	10 / 316 (3.16%)	
occurrences causally related to treatment / all	8 / 10	9 / 10	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	4 / 330 (1.21%)	2 / 316 (0.63%)	
occurrences causally related to treatment / all	5 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Standard	Experimental	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	327 / 330 (99.09%)	306 / 316 (96.84%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm benign, malignant and unspecified			
subjects affected / exposed	6 / 330 (1.82%)	3 / 316 (0.95%)	
occurrences (all)	6	3	

Vascular disorders Vascular disorders subjects affected / exposed occurrences (all)	11 / 330 (3.33%) 11	4 / 316 (1.27%) 4	
General disorders and administration site conditions General disorders and administration site conditions subjects affected / exposed occurrences (all)	27 / 330 (8.18%) 27	25 / 316 (7.91%) 25	
Immune system disorders Immune system disorders subjects affected / exposed occurrences (all)	9 / 330 (2.73%) 9	9 / 316 (2.85%) 9	
Respiratory, thoracic and mediastinal disorders Respiratory, thoracic and mediastinal disorders subjects affected / exposed occurrences (all)	2 / 330 (0.61%) 2	3 / 316 (0.95%) 3	
Cardiac disorders Cardiac disorders subjects affected / exposed occurrences (all)	2 / 330 (0.61%) 2	0 / 316 (0.00%) 0	
Nervous system disorders Nervous system disorders subjects affected / exposed occurrences (all)	82 / 330 (24.85%) 82	60 / 316 (18.99%) 60	
Blood and lymphatic system disorders Blood & lymphatic system disorders/investigations subjects affected / exposed occurrences (all)	310 / 330 (93.94%) 310	272 / 316 (86.08%) 272	
Gastrointestinal disorders Gastro-intestinal disorders subjects affected / exposed occurrences (all)	102 / 330 (30.91%) 102	80 / 316 (25.32%) 80	
Hepatobiliary disorders Hepatobiliary disorders subjects affected / exposed occurrences (all)	16 / 330 (4.85%) 16	7 / 316 (2.22%) 7	

Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	 43 / 330 (13.03%) 43	 44 / 316 (13.92%) 44	
Renal and urinary disorders Renal and urinary disorders subjects affected / exposed occurrences (all)	 14 / 330 (4.24%) 14	 9 / 316 (2.85%) 9	
Infections and infestations Infections and infestations subjects affected / exposed occurrences (all)	 12 / 330 (3.64%) 12	 11 / 316 (3.48%) 11	
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	 19 / 330 (5.76%) 19	 17 / 316 (5.38%) 17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 March 2011	Addition of Data Safety Monitoring Committee Addition of quality of life questionnaire (QLQ-C30)
15 May 2012	Sponsor change (GELARC to CHU de Nancy) "GELARC" replaced by "LYSARC" ; "GELA" replaced by "LYSA" reflecting change to names of these organizations
13 March 2013	Addition of neurological examination at each clinical examination Addition of instructions in case of PML suspicion following rituximab intake Updated AE part with addition of complementary information about expected toxicities Lumbar puncture at baseline not mandatory anymore. Optional and at the discretion of the investigator, except in cases of involvement of ovary, testis, breast or ORL and in the absence of clinical neurological signs Extension of inclusion period because of slower recruitment than expected
08 July 2015	Increase of number of patients to include in the study: addition of 230 patients Extension of recruitment period to reach 650 randomized patients Modification of an exclusion criteria to allow the inclusion of patient with HBV: Positive HIV, HBV and HCV serologies before inclusion (except after hepatitis B vaccination or for patients who are HBs Ag negative, anti-HBs positive and/or anti-HBc positive but viral DNA negative). Patients with positive serology of hepatitis B virus (old disease) should be referred to a hepatologist or gastroenterologist before start of treatment and should be monitored and managed following local standards such as European Association of the Study of the Liver guidelines to prevent hepatitis reactivation. Updated list of PET reviewers Updated description of PET acquisition and reconstruction Modification of SAE reporting rules part to clarify the process Modification of informed consent part to remove the collection of third copy by LYSARC

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported