Clinical trial results:
A multicentre, phase II, open label, single arm study of pixantrone in patients with CD20-positive relapsed or refractory aggressive non-Hodgkin lymphoma treated with rituximab, ifosfamide and etoposide.

Summary

EudraCT number	2017-000719-17
Trial protocol	FR BE
Global end of trial date	19 December 2024

Results information

Result version number	v1 (current)
This version publication date	29 March 2026
First version publication date	29 March 2026

Trial information

Trial identification

Sponsor protocol code	PIVeR

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03458260
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LYSARC
Sponsor organisation address	CH Lyon Sud – Bat 2D - 69495 PIERRE-BENITE Cedex - France, PIERRE-BENITE , France, 69495
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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	24 December 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 December 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess the efficacy of Pixantrone with rituximab, ifosfamide and etoposide as measured by the overall metabolic response (OMR) rate after 2 cycles of treatment or at permanent treatment discontinuation, whichever occurs first.

Protection of trial subjects:

sentence on rescue treatment ?

Background therapy:

Anthracycline-based regimens in combination with Rituximab are the standard of care in first-line for aggressive NHL. However, 30-40% will be refractory to first-line therapy or relapsed after standard first-line immunochemotherapy (R/R patients). Salvage chemotherapy followed by high-dose therapy and autologous stem-cells transplantation (HDT-ASCT) is the standard of care for eligible R/R patients.

Evidence for comparator:

There is currently no standard of care for patients with R/R aggressive NHL who are not eligible for HDT-ASCT procedure. Studies have demonstrated the possibility to combine Pixantrone with rituximab and other chemotherapeutic compounds in indolent and aggressive NHL. The combination of Rituximab, Ifosfamide and Etoposide is the backbone of several salvage regimens for relapsed/refractory DLBCL and will be tested in this study.

Actual start date of recruitment	01 January 2018
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	France: 71
Country: Number of subjects enrolled	Belgium: 3
Worldwide total number of subjects	74
EEA total number of subjects	74

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	17
From 65 to 84 years	55
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Enrollment of PIVeR study was to be stopped once 84 evaluable patients were enrolled with an estimated recruitment period of 3 years. However, the recruitment was not as efficient as expected and it has been stopped on December 31st, 2021. A total of 74 patients were enrolled.

Pre-assignment

Screening details:

A total of 74 patients were enrolled.
16 patients were screen failed

Period 1

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

Arms

Arm title	Pixantrone - rituximab - ifosfamide - etoposide

Arm description:

Treatment will consist of 2 to 6 cycles of Pixantrone with rituximab, ifosfamide and etoposide (21-day cycle)

Arm type	Experimental
Investigational medicinal product name	Pixantrone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Dose for patients aged 18-69 : 80 mg/m2
Dose for patients aged 70 and + : 60 mg/m2

After reconstitution should be administered as a slow IV infusion over a period of 1 hour (+/- 10 minutes)

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

Dosage and administration details:

Dosage 375 mg/m2
Administration : Chemotherapy products have been used according to summary of product characteristics.

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

Dosage and administration details:

Chemotherapy products have been used according to summary of product characteristics.
Dose for pateints aged 18-69 : 1500 mg/m2
Dose for patients aged 70 and + : 1000mg/m2

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

Dosage and administration details:

Chemotherapy products are to be used according to summary of product characteristics.
Dosage for patients aged 18-69 : 150 mg/m2
Dosage for patients aged 70 and + : 100 mg/m2

Number of subjects in period 1	Pixantrone - rituximab - ifosfamide - etoposide
Started	74
Completed	19
Not completed	55
Consent withdrawn by subject	1
Physician decision	1
CAR-T cells	3
NO RESPONDER PATIENT	3
Adverse event, non-fatal	10
Death	1
PERSONAL REASON FOR THE PATIENT	1
PATIENT DECIDES TO STOP ALL LYMPHOMAS TREATMENTS	1
DEAUVILLE 4	1
INSUFFICIENT RESPONSE AND CARDIAC COMORBIDITIES	1
ASCT	3
Lack of efficacy	29

Baseline characteristics

Reporting groups	
Reporting group title	Treatment

Reporting group description: -

Reporting group values	Treatment	Total	
Number of subjects	74	74	
Age categorical Units: Subjects			
From 18-70 years	38	38	
71 years and over	36	36	
Age continuous Units: years			
median	70		
full range (min-max)	35 to 87	-	
Gender categorical Units: Subjects			
Female	28	28	
Male	46	46	
Ann Arbor stage Units: Subjects			
_I	3	3	
II	9	9	
III	9	9	
IV	53	53	
ECOG Units: Subjects			
_0	27	27	
_1	35	35	
_2	12	12	
IPI Units: Subjects			
0-2	25	25	
3-5	45	45	
Missing	4	4	
aaIPI Units: Subjects			
0-1	28	28	
2-3	42	42	
Missing	4	4	

End points

End points reporting groups

Reporting group title	Pixantrone - rituximab - ifosfamide - etoposide

Reporting group description:

Treatment will consist of 2 to 6 cycles of Pixantrone with rituximab, ifosfamide and etoposide (21-day cycle)

Primary: OMR rate after 2 cycles according to local investigator

End point title	OMR rate after 2 cycles according to local investigator[1]

End point description:

Overall Metabolic Response rate by local investigator based on PET-CT scan according to Lugano classification (Cheson B. et al, JCO 2014).
Patients without response assessment (i.e. response not evaluated or missing) due to whatever reason will be considered as non-responders.

End point type	Primary

End point timeframe:

After 2 cycles or at permanent treatment discontinuation, whichever occurs first.

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 PIVeR trial was designed in order to detect an OMR increase in favor of the Pixantrone from 40% (null hypothesis) to 55% (alternative hypothesis), assuming an 80% power at a 5% (1-sided) significance level using a two-stage phase II design.
The null hypothesis was to be rejected if the lower limit of the 90%CI was ≥ 40%.

End point values	Pixantrone - rituximab - ifosfamide - etoposide			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: percent				
number (confidence interval 90%)	59.5 (49.2 to 69.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: CMR rate after 2 cycles according to local investigator

End point title	CMR rate after 2 cycles according to local investigator

End point description:

Complete Metabolic Response rate by local investigator based on PET-CT scan according to Lugano classification (Cheson B. et al, JCO 2014).
Patients without response assessment (i.e. response not evaluated or missing) due to whatever reason will be considered as non-responders.

End point type	Secondary

End point timeframe:

After 2 cycles or at permanent treatment discontinuation, whichever occurs first.

End point values	Pixantrone - rituximab - ifosfamide - etoposide			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: percent				
number (confidence interval 95%)	18.9 (10.7 to 29.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: OMR rate after 2 cycles according to central review

End point title	OMR rate after 2 cycles according to central review

End point description:

Overall Metabolic Response rate according to central review based on PET-CT scan according to Lugano classification (Cheson B. et al, JCO 2014).
Patients without response assessment (i.e. response not evaluated or missing) due to whatever reason will be considered as non-responders.

End point type	Secondary

End point timeframe:

After 2 cycles or at permanent treatment discontinuation, whichever occurs first.

End point values	Pixantrone - rituximab - ifosfamide - etoposide			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: percent				
number (confidence interval 95%)	47.3 (35.6 to 59.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: OMR rate at the timepoint of interest according to local investigator

End point title	OMR rate at the timepoint of interest according to local investigator

End point description:

Overall Metabolic Response rate by local investigator based on PET-CT scan according to Lugano classification (Cheson B. et al, JCO 2014).
Patients without response assessment (i.e. response not evaluated or missing) due to whatever reason will be considered as non-responders.

End point type	Secondary

End point timeframe:

After 2 cycles, for patients who did not respond after 2 cycles.
After 2 cycles, for patients responders after 2 cycles and eligible for ASCT.
After 6 cycles, for patients responders after 2 cycles and not eligible for ASCT.

End point values	Pixantrone - rituximab - ifosfamide - etoposide			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: percent				
number (confidence interval 95%)	39.2 (28 to 51.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: OMR rate at the end of treatment according to local investigator

End point title	OMR rate at the end of treatment according to local investigator

End point description:

Overall Metabolic Response rate by local investigator based on PET-CT scan according to Lugano classification (Cheson B. et al, JCO 2014).
Patients without response assessment (i.e. response not evaluated or missing) due to whatever reason will be considered as non-responders.

End point type	Secondary

End point timeframe:

At the end of treatment or at permanent treatment discontinuation, whichever occurs first.

End point values	Pixantrone - rituximab - ifosfamide - etoposide			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: percent				
number (confidence interval 95%)	37.8 (26.8 to 49.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival

End point title	Progression Free Survival

End point description:

PFS is defined as the time (years) from inclusion into the study to the first observation of documented disease progression or death due to any cause.
If a subject has not progressed or died, PFS will be censored at the date of tumor assessment.

End point type	Secondary

End point timeframe:

Since inclusion.

End point values	Pixantrone - rituximab - ifosfamide - etoposide			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: percent				
median (confidence interval 95%)	0.26 (0.21 to 0.47)			

Attachments (see zip file)	PFS/Figure 170302.jpeg

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival will be measured (in years) from the date of inclusion to the date of death from any cause.
Alive patients will be censored at the date of last contact.

End point type	Secondary

End point timeframe:

Since inclusion.

End point values	Pixantrone - rituximab - ifosfamide - etoposide			
Subject group type	Reporting group			
Number of subjects analysed	74			
Units: percent				
median (confidence interval 95%)	1.6 (1.16 to 3.04)			

Attachments (see zip file)	OS/Figure 170402.jpeg

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From the date of informed consent signature to 30 days after last drug administration.	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups	
Reporting group title	Pixantrone - rituximab - ifosfamide - etoposide
Reporting group description: Treatment will consist of 2 to 6 cycles of Pixantrone with rituximab, ifosfamide and etoposide (21-day cycle)	

Serious adverse events	Pixantrone - rituximab - ifosfamide - etoposide		
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 74 (39.19%)		
number of deaths (all causes)	48		
number of deaths resulting from adverse events	13		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 4		
Injury, poisoning and procedural complications			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
CARDIAC DISORDERS			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences causally related to treatment / all	5 / 7		
deaths causally related to treatment / all	0 / 1		

Nervous system disorders NERVOUS SYSTEM DISORDERS subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 74 (1.35%) 0 / 1 0 / 0		
Blood and lymphatic system disorders BLOOD AND LYMPHATIC SYSTEM DISORDERS subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 8 / 74 (10.81%) 7 / 9 0 / 0		
General disorders and administration site conditions GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 4 / 74 (5.41%) 3 / 4 1 / 2		
Gastrointestinal disorders GASTROINTESTINAL DISORDERS subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 74 (1.35%) 1 / 1 1 / 1		
Respiratory, thoracic and mediastinal disorders RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 4 / 74 (5.41%) 0 / 4 0 / 1		
Renal and urinary disorders RENAL AND URINARY DISORDERS subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 2 / 74 (2.70%) 0 / 2 0 / 0		
Infections and infestations INFECTIONS AND INFESTATIONS			

subjects affected / exposed	17 / 74 (22.97%)		
occurrences causally related to treatment / all	6 / 19		
deaths causally related to treatment / all	0 / 4		
Metabolism and nutrition disorders			
METABOLISM AND NUTRITION DISORDERS			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Pixantrone - rituximab - ifosfamide - etoposide		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 74 (75.68%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	6		
Vascular disorders			
VASCULAR DISORDERS			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences (all)	2		
General disorders and administration site conditions			
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
subjects affected / exposed	8 / 74 (10.81%)		
occurrences (all)	9		
Respiratory, thoracic and mediastinal disorders			
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	6		
Investigations			

INVESTIGATIONS subjects affected / exposed occurrences (all)	2 / 74 (2.70%) 2		
Injury, poisoning and procedural complications INJURY, POISONING AND PROCEDURAL COMPLICATIONS subjects affected / exposed occurrences (all)	1 / 74 (1.35%) 1		
Cardiac disorders CARDIAC DISORDERS subjects affected / exposed occurrences (all)	7 / 74 (9.46%) 9		
Nervous system disorders NERVOUS SYSTEM DISORDERS subjects affected / exposed occurrences (all)	4 / 74 (5.41%) 6		
Blood and lymphatic system disorders BLOOD AND LYMPHATIC SYSTEM DISORDERS subjects affected / exposed occurrences (all)	34 / 74 (45.95%) 83		
Gastrointestinal disorders GASTROINTESTINAL DISORDERS subjects affected / exposed occurrences (all)	6 / 74 (8.11%) 8		
Renal and urinary disorders RENAL AND URINARY DISORDERS subjects affected / exposed occurrences (all)	2 / 74 (2.70%) 2		
Musculoskeletal and connective tissue disorders MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS subjects affected / exposed occurrences (all)	1 / 74 (1.35%) 1		
Infections and infestations INFECTIONS AND INFESTATIONS subjects affected / exposed occurrences (all)	22 / 74 (29.73%) 25		
Metabolism and nutrition disorders			

METABOLISM AND NUTRITION DISORDERS			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 July 2018	Protovol v2.0 - addition of a third treatment cycle for patients eligible for autologous stem cell transplantation, prior to conditioning therapy. Initially, only two cycles were planned. The relatively long interval between the second cycle and transplantation allows for the administration of an additional cycle in routine practice.
03 January 2019	Protocol v3.0 - Patient age limitation to 80 years - Modification of the pixantrone dose for patients 70 years of age or older: the IDMC recommends reducing the dose to 60 mg/m² for patients aged 70 years or older
27 September 2024	Protocol v4.0 Reduction of the study duration to 6 years

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
11 January 2022	premature end of recruitment : 74 patients enrolled instead of 89	-

Notes:

Limitations and caveats

None reported