Clinical trial results:
A phase 1/2 study of the combination of pixantrone, etoposide, bendamustine and, in CD-20 positive tumors, rituximab in patients with relapsed aggressive non-Hodgkin lymphomas of B- or T-cell phenotype - the P[R]EBEN study

Summary

EudraCT number	2015-000758-39
Trial protocol	DK SE FI NO NL
Global end of trial date	31 January 2025

Results information

Result version number	v1 (current)
This version publication date	07 September 2025
First version publication date	07 September 2025

Trial information

Trial identification

Sponsor protocol code	PREBEN

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02678299
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle Juul-Jensens Boulevard 35, Aarhus N, Denmark, 8200
Public contact	Clinical Trial Office, Department of Hematology, Aarhus University Hospital, 45 78455855, a-cto@auh.rm.dk
Scientific contact	Clinical Trial Office, Department of Hematology, Aarhus University Hospital, 45 78455855, a-cto@auh.rm.dk

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	08 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 January 2021
Global end of trial reached?	Yes
Global end of trial date	31 January 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determine the MTD of pixantrone, rituximab (only in CD20 positive tumors), etoposide, and bendamustine in 'fit' patients with rel aNHL of B- or T-cell phenotype.

Evaluate the ORR and PFS using the combination of pixantrone, rituximab (only in CD20 positive tumors), etoposide, and bendamustine either at the identified MTD (P[R]EBEN-fit) in 'fit' patients or at the baseline dose level (P[R]EBEN-frail) in 'frail' patients with rel aNHL.

Evaluate the CR, PR, duration of response, and OS using the combination of pixantrone, rituximab (only in CD20 positive tumors), etoposide, and bendamustine in patients with B- or T-cell NHL.

Evaluate the safety and tolerability of combination therapy with pixantrone, rituximab (only in CD20 positive tumors), etoposide, and bendamustine in patients with aggressive B- or T-cell NHL.

Protection of trial subjects:

The study was conducted according to the guidelines for Good Clinical Practice issued by the International Conference on Harmonisation of the Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). The protocol was approved by the local, regional or national ethical review boards according to the existing natinal and local requirements. The study was conducted in agreement with the declaration of Helsinki and the laws and regulations of the respective countries.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 June 2016
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	Netherlands: 4
Country: Number of subjects enrolled	Norway: 4
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Denmark: 34
Country: Number of subjects enrolled	Finland: 15
Worldwide total number of subjects	60
EEA total number of subjects	60

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)	11
From 65 to 84 years	49
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall 60 patients were included in the trial. The first patient was included on 03-Jun-2016 and the last patient was included on 21-Jul-2020

Pre-assignment

Screening details:

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

Period 1

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

Arms

Arm title	Treatment

Arm description:

Single arm study. All patients received a maximum of 6 cycles of 3 weeks duration. Pixantrone, etoposide, bendamustine was given to all patients and rituximab was added for patients with CD20 positive tumors

Arm type	Experimental
Investigational medicinal product name	Pixantrone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 mg/m2 i.v. day 1+8 in 6 cycles of 3 weeks

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

Dosage and administration details:

100 mg/m2 i.v. day 1 of 6 cycles of 3 weeks duration

Investigational medicinal product name	Bendamustine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

90 mg/m2 i.v. day 1 of 6 cycles of 3 weeks

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:

375 mg/m2 i.v. day 1 of 6 cycles of 3 weeks, only in patients with CD20 positive tumors

Number of subjects in period 1	Treatment
Started	60
Completed	46
Not completed	14
Adverse event, serious fatal	1
Physician decision	1
Adverse event, non-fatal	4
Lack of efficacy	6
Protocol deviation	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	60	60	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	11	11	
From 65-84 years	49	49	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	26	26	
Male	34	34	

End points

End points reporting groups

Reporting group title	Treatment

Reporting group description:

Single arm study. All patients received a maximum of 6 cycles of 3 weeks duration. Pixantrone, etoposide, bendamustine was given to all patients and rituximab was added for patients with CD20 positive tumors

Primary: Overall Response Rate

End point title	Overall Response Rate[1]

End point description:

End point type	Primary

End point timeframe:

Response at end of treatment

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 overall response rate is reported as number of subjects responding

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: Subjects	34			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from day 1 of cycle 1 to 6 months after last administration of study drugs.

Adverse event reporting additional description:

Number of non-serious adverse events are reported only for anemia, neutropenia and thrombocytopenia

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Treatment

Reporting group description:

All patients received a maximum of 6 cycles of 3 weeks duration. Pixantrone, etoposide, bendamustine was given to all patients and rituximab was added for patients with CD20 positive tumors

Serious adverse events	Treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 60 (63.33%)		
number of deaths (all causes)	44		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Troponin C increased			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tachycardia			

subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
heart failure				
subjects affected / exposed	2 / 60 (3.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Coronary artery stenosis				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Left ventricular dysfunction				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Ataxia				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bone marrow disorder	Additional description: Only observed in patients with PTCL of TFH type with probable pre-existing clonal haematopoieses (well-known to be frequently present in PTCL of TFH type)			
subjects affected / exposed	2 / 60 (3.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Dehydration				

subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Impaired general condition				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	5 / 60 (8.33%)			
occurrences causally related to treatment / all	3 / 5			
deaths causally related to treatment / all	3 / 5			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	3 / 60 (5.00%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
rectal bleeding				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pleural effusion				
subjects affected / exposed	3 / 60 (5.00%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			

Dyspnoea			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Enterocolitis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	11 / 60 (18.33%)		
occurrences causally related to treatment / all	14 / 14		
deaths causally related to treatment / all	0 / 0		
fever			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
cytomegalovirus reactivation			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Influenza				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes simplex				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	2 / 60 (3.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	11 / 60 (18.33%)			
occurrences causally related to treatment / all	11 / 11			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	2 / 60 (3.33%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 1			
Upper respiratory tract infection				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				

subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 60 (100.00%)		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	30 / 60 (50.00%)		
occurrences (all)	30		
Thrombocytopenia			
subjects affected / exposed	31 / 60 (51.67%)		
occurrences (all)	31		
Anaemia			
subjects affected / exposed	39 / 60 (65.00%)		
occurrences (all)	39		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2017	End of the Phase 1 part, selection of the phase 2 dose schedule, sc rituximab administration allowed from cycle 2

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported