



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 national 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