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

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Primary Objectives- 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...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Lymphomas non-Hodgkin's unspecified histology
Study type	Interventional

Summary

ID

NL-OMON49078

Source
ToetsingOnline

Brief title
HOVON 144 NHL / P[R]EBEN

Condition

- Lymphomas non-Hodgkin's unspecified histology

Synonym
NHL, Non-hodgkin lymphoma

Research involving

Human

Sponsors and support

Primary sponsor: Aarhus University Hospital
Source(s) of monetary or material Support: Er is KWF subsidie aangevraagd

Intervention

Keyword: non-Hodgkin lymphoma, pixantrone, relapse, rituximab

Outcome measures

Primary outcome

Phase 2:

-Objective ORR in both *fit* and *frail* relapsed aNHL pts

Secondary outcome

Phase 2:

- Safety and tolerability of the combination of pixantrone,

rituximab, etoposide and bendamustine

- CRR

- DOR

- Progression-free survival (PFS)

- Overall survival (OS)

- Successful bridging to stem cell therapy (e.g. 2nd auto- and/or 1st allo-SCT)

or other cell therapy (e.g. chimeric antigen receptor [CAR]-T cell therapy)

Study description

Background summary

Patients with aggressive non-Hodgkin lymphoma (aNHL) relapsing after 1st line

therapy and too frail for platinum-based salvage therapy followed by autologous stem cell transplant (ASCT), those primary refractory to platinum-based salvage regimens or those experiencing a 2nd relapse after ASCT consolidation represent an unmet clinical need. Thus, three clinically and biologically distinct patient categories can be identified: frail, not transplant eligible (group 1); fit, transplant eligible but refractory to salvage therapy (group 2) and fit, transplant eligible, chemo-sensitive to salvage regimen and ASCT, but relapsing after ASCT (group 3). Based on population-based data from the Danish Lymphoma Registry, the 1-year survival expectation (from the time of relapse) within the aforementioned 3 groups is 33%, 21% and 42%, respectively. Pixantrone is an aza-anthracenadione recently approved in Europe for patients with relapsed/refractory aNHL based on phase 3 data comparing pixantrone with physician*s best choice. Etoposide, bendamustine and, in CD20 positive tumors, rituximab were chosen as companion compounds due to available feasibility and efficacy data in combination with pixantrone.

Study objective

Primary Objectives
- 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.

Secondary objectives
- 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.
-To perform molecular analyses at nucleic acid (DNA, RNA, microRNA) and protein level to see if specific molecular features can predict responder versus non-responder status.

Study design

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.

Intervention

In phase 2 the treatment will depend on if the patient is either classified as fit or frail.
Fit patients will be treated with the in the phase 1 part of the study determined MTD of Pixantrone, Etoposide and Bendamustine. Frail patients will be treated with the baseline regimen of Pixantrone, Etoposide and Bendamustine.

Study burden and risks

Patients with aggressive non-Hodgkin lymphoma (NHL) relapsing after 1st line therapy and too frail for platinum-based salvage therapy followed by autologous stem cell transplant (ASCT) represent an unmet clinical need. The PREBEN regimen is a new combination of the chemotherapeutics pixantrone, bendamustine, etoposide and rituximab. In a small pilot study the PREBEN regimen gave promising results and was well tolerated in a heavily pretreated patient population. The burden for the patient to participate into this study is not different from the burden of a treatment outside this clinical trial, except for 5 extra CT scans during follow-up. If the results that were found in the pilot study are confirmed in this study then PREBEN could be the new standard treatment for this patient group. Also PREBEN could serve as a backbone regimen for the combination with new drugs. Lastly, some young patients might be offered an allogeneic stem cell transplantation with curative intent.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Patients with a histologically confirmed relapse of an aggressive lymphoma of T- or B-cell phenotype (including follicular lymphoma grade 3b).;- Phase 1 + Phase 2 *fit* patients:
--Age 18-70 years at the time of inclusion
--ECOG performance score (PS) 0-1 at protocol entry
--Deemed *fit* by the treating physician
- Phase 2 *frail* patients:
--Age 71-85 years at the time of inclusion
and/or
--ECOG PS 2-3 at protocol entry
and/or
--Deemed *frail* by the treating physician;- At least 6 months response duration since last given course of treatment
- Estimated life expectancy of 3 months or longer
- Measurable disease
- Hemoglobin >= 8 g/dL (>=5 mmol/l) (can be post transfusion)
- Platelets >= 100 x 109/L; >= 75 x 109/L permitted if bone marrow involvement
- Absolute neutrophil count >= 1.5 x 109/L; >= 1.0 x 109/L permitted if documented bone marrow involvement
- Serum bilirubin <= 1.5 x upper limit of normal (ULN); patients with proven Gilbert*s syndrome (<= 5 x
ULN) may be enrolled.
- Serum glutamic-oxaloacetic transaminase (AST) and/or serum glutamic-pyruvic transaminase (ALT) <= 2.5 x ULN, or <= 5 x ULN if elevation is due to hepatic involvement by lymphoma
- Serum creatinine <= 2 x ULN
- Women of childbearing potential must use safe anticonception (e.g. contraceptive pills, intrauterine devices etc.) during the study and 12 months after the last administration of study drugs
- Male patients must use contraception for the duration of the study and 6 months after the last administration of study drugs if his partner is of childbearing potential
- Written informed consent

Exclusion criteria

- Patients with primary refractory disease (e.g. progressing under platinum-containing or

similar salvage therapy) defined as < 6 months response duration from last given course of treatment.
- High-dose therapy with autologous stem cell rescue within the last 6 months prior to study entry.
- Following T-cell lymphoma entities:
--T-cell lymphoblastic lymphoma
--Hepatosplenic T-cell lymphoma
--Extranodal NK/T, nasal type
--Subcutaneous panniculitis-like
--Primary cutaneous T-cell lymphoma
--Primary leukemic T-cell lymphoma
- Following B-cell lymphoma entities:
--Transformed indolent B-cell lymphomas
--Post-transplant B-cell lymphoproliferative disease
--HIV-associated B-cell lymphoma
- Concurrent severe and/or uncontrolled medical disease which is not lymphoma-related
- Left ventricular ejection fraction (LVEF) < 45%
- Suspected or documented central nervous system involvement by NHL
- Patients known to be antigen positive for HIV and/or hepatitis B and/or hepatitis C
- Patients with active, uncontrolled infections
- Vaccination with live, attenuated vaccines within 4 weeks of inclusion
- Pregnant and/or breastfeeding women
- History of active cancer during the past 5 years, except basal carcinoma of the skin or stage 0 cervical carcinoma
- Known hypersensitivity to one or more of the study drugs
- Unwillingness or inability to comply with the protocol

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruiting

Start date (anticipated):	28-11-2018
Enrollment:	35
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Etoposide Sandoz
Generic name:	Etoposide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Levact
Generic name:	Bendamustine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Pixuvri
Generic name:	Pixantrone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Rituximab
Generic name:	Rituximab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	14-05-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-07-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	07-12-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-12-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-000758-39-NL
CCMO	NL60809.078.17