A phase Ib, multicenter, open-label study of HCD122 administered intravenously in combination with bendamustine in patients with CD40+ follicular lymphoma who are refractory to rituximab

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Objective PrimaryDose escalation phase only: To determine the MTD of HCD122 when administered in combination with bendamustineDose expansion phase only: To assess the safety and tolerability of HCD122 in combination with bendamustine SecondaryDose...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Lymphomas non-Hodgkin's B-cell
Study type	Interventional

Summary

ID

NL-OMON36558

Source
ToetsingOnline

Brief title
LIFT study

Condition

- Lymphomas non-Hodgkin's B-cell
- Lymphomas non-Hodgkin's B-cell

Synonym
folliculair lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V.

Intervention

Keyword: Bendamustine, CD40+ folliculair lymfoma, combination therapy HCD122, maximum tolerated dose, Phase 1b

Outcome measures

Primary outcome

- Frequency and characteristics of DLTs at each dose level

- Type, frequency, and severity of AEs, changes in hematology and blood

chemistry values, assessments of physical examinations, vital signs, and

electrocardiograms

Secondary outcome

secondary

-Type, frequency, and severity of AEs, changes in hematology and blood

chemistry values, assessments of physical examinations, vital signs, and

electrocardiograms

-Overall response rate (CR and PR)

-HCD122 and bendamustine plasma concentrations and basic PK parameters

(AUC0-tlast, Cmax, t1/2)

-Serum concentrations of antibodies to HCD122

exploratory

-Whole blood DNA Fc*RIIIa haplotype

-Tumor biopsy CD40 IHC H scores and CD40+ cell percentages

-Levels of CD40 receptor occupancy by HCD122

-Blood biomarker levels (e.g.sCD40); IHC H-scores (e.g. CD40L and CD3),

cytogenetics [e.g. t(14;18)], and gene expression profiling in tumor biopsy

specimens

-Blood biomarker levels (e.g. CRP, IL-6, IL-8)

-IHC H-scores for pharmacodynamic and cellular response markers (e.g. pAKT,

Ki67, CC3); gene expression

Study description

Background summary

Follicular lymphoma (FL) is the most common indolent non-Hodgkin*s lymphoma (NHL) and the second most common form of NHL worldwide
Therapy options for symptomatic patients after initial diagnosis include chemotherapy, rituximab monotherapy, rituximab and chemotherapy, or radioimmunotherapy (National Comprehensive Cancer Network [NCCN] guidelines v.1.2010).
Upon clinical relapse or for nonresponsive disease, second-line treatment options include rituximab plus chemotherapy (e.g. R-CHOP, R-CVP), fludarabine-based chemotherapy, bendamustine, or high-dose chemotherapy with autologous or allogeneic stem-cell rescue.
The anti-CD20 monoclonal antibody, rituximab, has been a valuable addition to the treatment of B-cell NHL and has improved response rates in FL. However, 50% of patients with relapsed or refractory CD20-positive FL do not respond to initial therapy with rituximab, and approximately 60% of patients who were previously treated with rituximab no longer benefit from retreatment (Tay et al 2010). The alkylating agent, bendamustine, was recently approved as a single agent for rituximab-refractory NHL, and is an effective treatment option for indolent B-cell NHLs that are refractory to rituximab (Friedberg et al 2008a, Kahl et al 2010). In the first-line setting, preliminary studies with bendamustine plus rituximab demonstrate improved progression free survival (PFS) and complete response (CR) rates compared with R-CHOP (Rummel et al 2009).
Although the introduction of these new agents and regimens for the treatment of NHL has resulted in improved CR rates and survival rates in some settings, the lack of any significant improvement in overall survival indicates a continued need for novel drugs and interventions (Tay et al 2010).

Study objective

Objective
Primary
Dose escalation phase only: To determine the MTD of HCD122 when administered in combination with bendamustine
Dose expansion phase only: To assess the safety and tolerability of HCD122 in combination with bendamustine

Secondary
Dose escalation phase only: To assess the safety and tolerability of HCD122 in combination with bendamustine
To assess the preliminary anti-tumor activity of HCD122 in combination with bendamustine
To characterize the PK profile of HCD122 and bendamustine
To assess the immunogenicity of HCD122

Exploratory
To assess Fc*RIIIa polymorphism status
To assess CD40 expression levels
Dose expansion phase only: To characterize CD40 occupancy of HCD122 on peripheral CD19+ B cells
To investigate candidate markers predictive of response found in blood and malignant lymphoid tissue
To investigate if post-treatment pharmacodynamic changes in blood inflammatory and immune markers correlate with clinical response
To explore candidate pharmacodynamic markers, cellular response markers, and gene expression changes in malignant lymphoid tissue pre- and post-treatment

Study design

This phase Ib, multicenter, open-label study will investigate the safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of HCD122 in combination with bendamustine in patients with CD40+ FL that is refractory to treatment with rituxmab.
In dose escalation (n=15-30), successive cohorts of newly enrolled patients will receive increasing doses of HCD122 in combination with bendamustine until the MTD of HCD122 is determined (Figure 3-1). Once the MTD has been established, additional patients will be enrolled into the dose expansion phase of the study to better characterize the safety, tolerability, and make a preliminary assessment of anti-tumor activity of the combination. A minimum of 20 total patients (escalation + expansion) will be treated at the MTD.
DLTs that will primarily contribute to the determination of the MTD will be identified during cycle 1 of dose escalation (Section 5.1.2.6). All patients will remain on treatment until disease progression, unacceptable toxicity, or

patient withdrawal.

Intervention

HCD122 infusion will be administered once every 14 days at the assigned dose (during dose escalation) or at the MTD (during dose expansion). Bendamustine infusion will be administered on the first two days of each 28-day combination treatment cycle.

Study burden and risks

Toxicity of the combination-therapy and HCD122 Bendamustine
- Radiation exposure of CT scan / MRI
-Frequent visits and blood sampling
- (optional) tumorbiopsy
-Bone marrow punction (if necessary)

An overview of all visits during the procedure are given in Appendix B of the patient information.
The side effects can be found in Appendix C of the patient information.
It is not certain that participation in the study will lead them directly benefit the patient, the data can be useful for the future.
The burden on the patients is as expected from a Phase 1 study.

Contacts

Public
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Scientific
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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 must have a confirmed diagnosis of follicular lymphoma, according to the Revised European American Lymphoma/World Health Organization [REAL/WHO] classification
-Patients must have a recent (< 6 months) restaging tissue specimen available for CD40 expression confirmation or willingness to undergo a core biopsy for confirmation of CD40 expression
-Patients must have documented CD40+ follicular lymphoma
-Patients must have progressive disease
-Patients must be refractory to rituximab, defined as:
-Progression during rituximab treatment; OR
* Progression within 6 months of last rituximab dose
-Patients must have received at least 1 prior chemotherapeutic regimen
-Patients must have a life expectancy > 3 months

Exclusion criteria

- Grade 3b follicular lymphoma or evidence that the indolent lymphoma has transformed to aggressive lymphoma (i.e. DLBCL)
-Patients who have a history of another primary malignancy that is currently clinically significant or currently requires active intervention
-Patients who have received prior allogeneic stem cell transplantation
-Impaired cardiac function or clinically significant cardiac disease, including any one of the following:
* New York Heart Association Class III or IV cardiac disease, including pre-existing clinically significant arrhythmia, congestive heart failure, or cardiomyopathy
* Angina pectoris * 3 months before starting study treatment
* Acute myocardial infarction * 3 months before starting study treatment
* Other clinically significant heart disease (e.g. uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)
-Patients who have a history of acute or chronic pancreatitis, surgery of the pancreas, or any risk factors that may increase the risk of pancreatitis

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	HCD122
Generic name:	lucatumumab
Product type:	Medicine
Brand name:	Ribomustine / Levact
Generic name:	Bendamustine

Ethics review

Approved WMO Date:	01-02-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-04-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-09-2011

Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2010-022350-17-NL
ClinicalTrials.gov	NCT01275209
CCMO	NL35168.029.11