A prospective, open-label, multicenter randomized phase-II trial to evaluate the efficacy and safety of a sequential regimen of Gazyvaro (obinutuzumab) followed by obinutuzumab and venetoclax, followed by either standard venetoclax maintenance or MRD guided venetoclax maintenance in first-line patients with CLL and unfit for FCR-like regimens. (GIVE trial)

Published: 09-06-2016
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This study has been transitioned to CTIS with ID 2024-511048-22-00 check the CTIS register for the current data. -Primary objective- To separately study the efficacy, defined as MRD negative bone marrow and no progression according to the IWCLL...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON54803

Source
ToetsingOnline

Brief title
HOVON 139 CLL

Condition

- Leukaemias

Synonym
Chronic Lymphocytic Leukemia, CLL

Research involving
Human

Sponsors and support

Primary sponsor: HOVON
Source(s) of monetary or material Support: Hoffmann-La Roche,Roche;subsidie wordt aangevraagd bij KWF

Intervention

Keyword: CLL, Minimal Residual Disease (MRD), Obinutuzumab, Venetoclax

Outcome measures

Primary outcome

• MRD negative bone marrow after maximum 24 cycles of (planned) venetoclax and

no progression according to IWCLL criteria at any earlier timepoint.

Secondary outcome

• Efficacy as assessed by additional outcome measures, including overall

response, PFS, EFS and OS;

• MRD in blood

• Toxicity of venetoclax after pre-induction, especially tumorlysis and

neutropenia

• Quality of life

• Geriatric assessment

• P16 expression in skin biopsy

• Predictive factors for response and resistance mechanisms:

- NGS at baseline and at progression

- Flow-based subset analysis on expression levels of Bcl-2 proteins at

baseline, during therapy and at progression

- Analyses of malignant and non-malignant immune cells in PB and in LN at

baseline and during treatment

Study description

Background summary

With current therapy, progression free survival of CLL in patients unfit for FCR is around 2 years. Venetoclax treatment, especially when initially combined with an anti-CD20 monoclonal antibody (mAb) has high efficacy and in contrast to kinase inhibitors, has the potency to result in MRD-negative disease status, which possibly allows drug discontinuation.
Obinutuzumab has the potency to debulk and therefore when used prior to venetoclax might efficiently prevent the occurrence of tumor lysis tyndrome (TLS).

Study objective

This study has been transitioned to CTIS with ID 2024-511048-22-00 check the CTIS register for the current data.

-Primary objective
- To separately study the efficacy, defined as MRD negative bone marrow and no progression according to the IWCLL criteria, of the two arms of the study of either venetoclax maintenance or MRD-guided venetoclax maintenance after sequential regimens of obinutuzumab (pre-induction) followed by 6 cycles obinutuzumab with venetoclax and 6 cycles of venetoclax (induction) in first-line patients with CLL and unfit for FCR-like regimens

Secondary objectives
- To determine efficacy as assessed by additional outcome measures, including overall response, PFS, EFS , OS;
- To determine the impact of the study treatment on quality of life and geriatric scores (including a biological senescence marker of skin biopsy)
- Toxicity of venetoclax after pre-induction, especially tumorlysis and neutropenia

- To identify predictive factors for response and resistance mechanisms

Study design

A prospective, multicenter, open-label, randomized phase -II trial.

Intervention

After pre-induction with obinituzumab, patients will receive induction treatment with obinutuzumab and/or venetoclax followed by 1 year maintenance with venetocax (arm A) or MRD guided maintenance with venetoclax (arm B)

Study burden and risks

Participation in this study will only be associated with minimal extra investigations compared to standard patient care. Extra investigations consist of MRD measurement in blood and bone marrow. MRD measurement is currently regarded as the most sensitive parameter to predict quality and duration of response. Hence, it may be implemented in the near future. It is therefore of vital importance to include MRD analysis into this trial. Blood and bone marrow samples for MRD measurement will be obtained during moments of routine blood and bone marrow analysis. Minimal amounts of blood and bone marrow are required to perform MRD analysis .
For side studies a skin biopsy and FNA or biopsy of an easy accessible lymph node will be taken.
Furthermore, patients will be requested to participate in Quality of Life studies and studies for geriatric assessements.

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

- Diagnosis of symptomatic CLL (according to IWCLL guidelines);
- Patients without prior treatment for CLL (Corticoid treatment administered due to necessary immediate intervention is allowed; within the last 10 days before start of study treatment only dose equivalents of max 20 mg prednisolone are permitted);
- Patients aged >= 18 years, not fit for FCR-like regimens;
- Able to adhere to the study visit schedule and other protocol requirements;
- WHO performance status of <= 2;
- Laboratory test results within these ranges:
- absolute neutrophil count >= 1.0 x 109/l and platelet count >= 50 x 109/l unless due to bone marrow infiltration,
- creatinine clearance >= 45 ml/min,
- total bilirubin 1,5 x ULN unless considered due to Gilbert*s syndrome,
- transaminases <= 3 x ULN;
-Negative serum or urine pregnancy test within 28 days prior to registration (all females of childbearing potential) ;
- Written informed consent
- Patient is capable of giving informed consent

Exclusion criteria

- Current inclusion in other clinical trials
- Intolerance of exogenous protein administration;
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies. Known sensitivity or allergy to murine products
- Positive hepatitis serology (serology testing required at screening), as follows:

- Hepatitis B virus (HBV): Patients with positive serology for hepatitis B defined as positivity for
hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (anti-HBc).
- Hepatitis C virus (HCV): Patients with positive hepatitis C serology unless HCV- (RNA) is
confirmed negative.
- HIV positive patients;
- • Active fungal, bacterial, and/or viral infection that requires systemic therapy;
- Vaccination with a live vaccine a minimum of 28 days prior to registration.
- Use of any other experimental drug or therapy within 28 days of baseline;
- Concurrent use of other anti-cancer agents or treatments;
- History of prior malignancy, except for conditions as listed below if patients have recovered from the acute side effects incurred as a result of previous therapy:
- Malignancies surgically treated with curative intent and with no known active disease present for 3 years before randomization
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated cervical carcinoma in situ without evidence of disease
- Severe cardiovascular disease (arrhythmias requiring chronic treatment, congestive heart failure or symptomatic ischemic heart disease) (CTCAE grade III-IV);
- Severe pulmonary dysfunction (CTCAE grade III-IV);
- Severe neurological or psychiatric disease (CTCAE grade III-IV);
- Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, hypertension, hyperthyroidism or hypothyroidism , etc.)
- Women who are pregnant or lactating
- Fertile men or women of childbearing potential unless: (1). surgically sterile or >= 2 years after the onset of menopause (2). willing to use a highly effective contraceptive method (Pearl Index <1) during study treatment and in female patients for 18 months after end of antibody treatment and male patients for 6 months after end of treatment.
- Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

Study design

Design

Study phase: 2

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-10-2016
Enrollment:	70
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	Venetoclax
Product type:	Medicine
Brand name:	Gazyvaro
Generic name:	Obinutuzumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	09-06-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-09-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-04-2017

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-09-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-12-2020

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-12-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-04-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	11-05-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214

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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
EU-CTR	CTIS2024-511048-22-00
EudraCT	EUCTR2015-004985-27-NL
CCMO	NL56096.018.16