A prospective, open-label, multicenter randomized phase-II trial to evaluate the efficacy and safety of a sequential regimen of obinutuzumab (Gazyvaro) 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

No registrations found.

Ethical review	Not applicable
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON23205

Source
NTR

Brief title
HOVON 139 CLL

Health condition

Chronic Lymphocytic Leukemia (CLL)

Sponsors and support

Primary sponsor: HOVON data center
Source(s) of monetary or material Support: HOVON, Abbvie, Roche

Intervention

Outcome measures

Primary outcome

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 outcome

♦ To determine efficacy as assessed by additional outcome measures, including overall response, PFS, event free survival (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 via:

- Next-generation sequencing (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

Background of the study:

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 design:

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

Study population:

First-line patients with CLL and unfit for FCR-like regimens.

Intervention

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

Primary study parameters/outcome of the study

MRD negative bone marrow after maximum 24 cycles of (planned) venetoclax and no progression according to IWCLL criteria at any earlier timepoint.

Study design

♦ Before enrollment: within 28 days before registration, as specified in 10.2

♦ After each cycle

♦ Induction cycle 1: Before start venetoclax

♦ Weekly during venetoclax ramp up in induction cycle 1

♦ 15 months after randomization

♦ During follow up every 3 months until 3 years after registration. Therafter every 6 months until 7 years after registration or until progression, whatever comes first.

Intervention

After induction treatment venetoclax maintenance will be given for either 1 year (arm A) of or until MRD-negativity with a maximum of 1 year (arm B)

Contacts

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Eligibility criteria

Inclusion criteria

- Diagnosis of symptomatic CLL (according to IWCLL guidelines, including minimal required markers (CD5/CD19/CD23 triple positive with light chain restriction))

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 maximum 20 mg prednisolone are permitted);

♦ Patients aged ¡Ý 18 years, not fit for FCR-like regimens, according to the treating physician;

♦ Able to adhere to the study visit schedule and other protocol requirements;

♦ WHO performance status of ¡Ü 2 (see appendix C);

♦ Laboratory test results within these ranges: - absolute neutrophil count ¡Ý 1.0 x 109/l and

platelet count ¡Ý 50 x 109/l, unless due to bone marrow infiltration, - creatinine clearance ¡Ý 45 ml/min .(using 24-hour creatinine clearance or modified Cockcroft−Gault equation (see appendix E) - total bilirubin ¡Ü 1,5 x ULN unless considered due to Gilbert¡¯s syndrome, - transaminases ¡Ü 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; Note: active controlled as well as chronic/recurrent infections are at risk of reactivation/infection during teatment with obinutuzumab and/or venetoclax);

♦ 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 ¡Ý 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, see appendix D);

♦ Severe pulmonary dysfunction (CTCAE grade III-IV, see appendix D);

♦ Severe neurological or psychiatric disease (CTCAE grade III-IV, see appendix D);

♦ 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 ¡Ý 2 years after the onset of menopause (2). willing to use a highly effective contraceptive method (Pearl Index <1) such as oral contraceptives, intrauterine device, sexual abstinence or barrier method of contraception in conjunction with spermicidal jelly 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 type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-12-2016
Enrollment:	70
Type:	Anticipated

Ethics review

Not applicable
Application type: Not applicable

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
NTR-new	NL5871
NTR-old	NTR6043
Other	2015-004985-27 : HO139 CLL

Study results

Summary results
N/A