REtreatment with VEnetoclax and Acalabrutinib after venetoclax Limited duration (REVEAL)
A prospective, multicenter, phase-II trial of venetoclax plus acalabrutinib in patients who have relapsed after first line venetoclax + anti-CD20 mAb treatment for chronic lymphocytic leukemia (CLL or SLL)

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

Summary

ID

NL-OMON52450

Source
ToetsingOnline

Brief title
HOVON 159 CLL

Condition

- Leukaemias

Synonym
chronic lymphocytic leukemia, CLL

Research involving
Human

Sponsors and support

Primary sponsor: HOVON
Source(s) of monetary or material Support: AbbVie B.V.,AbbVie;Acerta,Acerta

Intervention

Keyword: Acalabrutinib, CLL, Venetoclax

Outcome measures

Primary outcome

• uMRD in BM by flow cytometry after 26 cycles (2 acalabrutinib and 24 AV).

Secondary outcome

• Depth of MRD measured in BM after cycle 13 and 26.

• Depth of MRD measured in peripheral blood (PB) after cycle 8, 10, 13, 16, 19, 22, 26 and every 3-6 months thereafter.

• Best overall response rate (ORR) defined as the proportion of subjects with a complete response (CR), complete response with incomplete marrow recovery (CRi), or partial response (PR) according to IWCLL 2018 criteria.

• Progression free survival (PFS), defined as time from registration to the first occurrence of disease progression or death from any cause, whichever occurs first.

• Event free survival (EFS), defined as time from registration to date start of

first CLL treatment off protocol, progression or death, whichever comes first.

• Overall survival (OS), defined as the time from registration to death from any cause.

• Treatment free interval (TFI), defined as date of last protocol treatment to date start of first CLL treatment off protocol, or death from any cause, whichever comes first.

• Incidence and severity of adverse events (AEs), with severity determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Exploratory endpoints

• Depth of MRD by different techniques (flow cytometry, circulating tumor DNA (ctDNA), next-generation sequencing).

• TruCulture and flow cytometry for immune subsets and function.

• Grading of hematological toxicity according to IWCLL.

• Disease-related symptoms and health-related quality of life (HRQoL) measured by following questionnaires: EORTC QLQ-C30, EORTC QLQ-CLL17 and PRO-CTCAE.

Study description

Background summary

Fixed-duration regimens containing combinations of venetoclax with CD20 targeting agents are expected to soon become standard practice in first-line patients with chronic lymfocytic leukemia (CLL). The advantage of a fixed duration venetoclax combination as part of first-line treatment is the potential to retreat with venetoclax in patients who develop relapsed disease after a treatment free period. However, efficacy of venetoclax retreatment

following a fixed duration venetoclax combination is still hypothetical as clinical data are lacking. Thus, there is an urgent need for data proving efficacy of venetoclax combinations following venetoclax treatment cessation. Testing of a novel venetoclax-containing regimen for relapsed CLL without the repeat of anti-CD20 monoclonal antibody (mAb) is a rational approach.

Study objective

This study has been transitioned to CTIS with ID 2023-505449-18-00 check the CTIS register for the current data.

Primary objective
• To evaluate efficacy of acalabrutinib/venetoclax (AV) in terms of undetectable minimal residual disease (uMRD) response in bone marrow (BM) after 26 cycles of treatment in patients with CLL previously treated with venetoclax and anti-CD20 mAb.

Secondary objectives
• To evaluate the efficacy of AV.
• To evaluate the safety and tolerability of AV.

Exploratory objectives
• To evaluate prognostic parameters for efficacy
• To evaluate value of different techniques for MRD testing.
• To evaluate the impact on immunological function of AV.
• To evaluate grading for hematological toxicity. according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) by assessing lab values.
• To evaluate quality of life (QoL) with AV.
• To asses impact on venetoclax pharmacokinetics (PK) in combination with acalabrutinib

Study design

Phase-II trial, prospective, multicenter

Intervention

All patients will receive a lead-in with 2 cycles of acalabrutinib 100 mg bid. Hereafter patients will continue with ramp-up of venetoclax followed by daily 400 mg venetoclax in combination with acalabrutinib for 24 cycles. Patients will be treated until they have received a total of 26 cycles or until progression, whichever comes first.

Study burden and risks

The development of novel targeted treatment has led to new chemo-free treatment

options with better PFS than chemo-immunotherapy, reflected by high percentage of CR or uMRD. However, for patients who progress after a fixed-duration of combination treatment of venetoclax with anti-CD20 mAb, clinical data are lacking how to retreat. Based on data about synergistic potential of the combination of a bruton thyrosine kinase (BTK)-inhibitor with venetoclax and a good safety profile of acalabrutinib (a novel more selective BTK-inhibitor), this combination is a promising re-treatment option to induce uMRD and long-lasting remission, without the need for continuous treatment. The risk of TLS in case of high tumorload with venetoclax may be diminished by the lead-in treatment with acalabrutinib monotherapy. Risk of infections may be minimized by granulocyte colony stimulating factor (G-CSF) in case of neutropenia. Another possible side effect of acalabrutinib is enhanced bleeding tendency and rarely atrial fibrillation. Discomfort from venipuncture, BM biopsy, and CT scan is justified by limited risk of procedures and the value of adequate monitoring of disease response in this pretreated patient population and knowledge gained from this.

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

• Documented CLL or SLL requiring treatment according to IWCLL criteria after at least (clinical) partial response as best response after the following initial study treatment: venetoclax-rituximab in HOVON 140/GAIA or venetoclax-obinutuzumab in HOVON 139/GIVE or HOVON 140/GAIA
• WHO/ECOG performance status 0-3), stage 3 only if attributable to CLL
• Age at least 18 years;
• Adequate BM function defined as:
- Hemoglobin >5 mmol/l or Hb > 8 g/dL
- Absolute neutrophil count (ANC) >0.75 x 109/L (750/µL), unless directly attributable to CLL infiltration of the BM, proven by BM biopsy
- Platelet count >30 x 109/L (30,000/µL) without transfusion and irrespective whether it is attributable to CLL infiltration in the BM;
• Estimated Glomerular Filtration Rate (eGFR) (MDRD) or estimated creatinine clearance (CrCl) >= 30ml/min (Cockcroft-Gault);
Please note: in case eGFR or CrCl is <50ml/min the patient needs to be considered high risk for TLS
• Adequate liver function as indicated:
- Serum aspartate transaminase (ASAT) and alanine transaminase (ALAT) <= 3.0 x upper limit of normal (ULN)
- Bilirubin <=1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of nonhepatic origin);
• Prothrombin time (PT)/International normal ratio (INR) <1.5 x ULN and activated partial thromboplastin time (aPTT) <1.5 x ULN;
• Negative serological testing for hepatitis B virus (HBV) (Hepatitis B surface antigen (HBsAg) negative and hepatitis B core antibody (anti-HBc) negative) and hepatitis C virus (hepatitis C antibody). Subjects who are positive for anti-HBc or hepatitis C antibody may be included if they have a negative PCR within 6 weeks before enrollment. Those who are PCR positive will be excluded.
Please note: For patients positive for anti-HBc HBV-DNA PCR has to be repeated every month until 12 months after last dose of study treatment.
• Patient is able and willing to adhere to the study visit schedule and other protocol requirements
• Patient is capable of giving informed consent
• Written informed consent

Exclusion criteria

• Any prior therapy with BTK inhibitor

• Prior treatment with venetoclax other than first line
• Other therapy with exception of chemo-/immunotherapy which is allowed also after venetoclax first line relapse
• Transformation of CLL (Richter*s transformation);
• Patient with a history of confirmed progressive multifocal leukoencephalopathy (PML).
• Malignancies other than CLL currently requiring systemic therapy or not treated in
curative intention or showing signs of progression after curative treatment;
• Known allergy to xanthine oxidase inhibitors and/or rasburicase;
• History of drug-specific hypersensitivity or anaphylaxis to any study drug (including active product or excipient components);
• Active bleeding or history of bleeding diathesis (e.g. hemophilia or von Willebrand disease);
• Active fungal, bacterial, and/or viral infection that requires systemic therapy;
Please note: active controlled as well as chronic/recurrent infections are at risk of reactivation/infection during treatment;
• Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled: infection, auto-immune hemolysis, immune thrombocytopenia, diabetes, hypertension, hyperthyroidism or hypothyroidism etc.);
• Patient known to be HIV-positive;
• Patient requiring treatment with a strong cytochrome P450 (CYP) 3A inhibitor/inducer (see
appendix J) or anticoagulant therapy with warfarin or phenoprocoumon or other vitamin K
antagonists;
Please note: Patients being treated with DOACs apixaban, edoxaban or rivaroxaban can be included, but must be properly informed about the potential risk of bleeding under treatment with acalabrutinib. (see appendix J)
• History of stroke or intracranial hemorrhage within 6 months prior to registration;
• Severe cardiovascular disease (arrhythmias requiring chronic treatment, congestive
heart failure or symptomatic ischemic heart disease, myocardial infarction within 6 months) (CTCAE grade III-IV);
• Severe pulmonary dysfunction (CTCAE grade III-IV);
• Severe neurological or psychiatric disease (CTCAE grade III-IV);
• Patient who has difficulty with or are unable to swallow oral medication, or have significant gastrointestinal disease that would limit absorption of oral medication;
• Vaccination with live vaccines within 28 days prior to registration;
• Use of any other experimental drug or therapy within 28 days of registration
• Major surgery within 28 days prior to registration;
• Steroid therapy within 10 days prior to registration, with the exception of inhaled steroids for
asthma, topical steroids, steroids up to 20 mg or dose equivalents of

prednisolone daily to control autoimmune phenomenon*s, or replacement/stress corticosteroids;
• Pregnant women and nursing mothers.
• 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 during study treatment and for 30 days after end of treatment;
• Current participation in other clinical trial (other than follow up HOVON139/HOVON140);*• 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
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-06-2021
Enrollment:	49
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Venclyxto
Generic name:	Venetoclax
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	x

Generic name:	Acalabrutinib

Ethics review

Approved WMO Date:	30-06-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-07-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-12-2020
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:	25-10-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-11-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660

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Approved WMO Date:	07-08-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

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	CTIS2023-505449-18-00
EudraCT	EUCTR2019-004337-17-NL
CCMO	NL71704.018.19