A phase 3 multicentre, randomized, prospective, open-label trial of Ibrutinib monotherapy versus fixed-duration Venetoclax plus Obinutuzumab versus fixed-duration Venetoclax plus Ibrutinib in patients with previously untreated chronic lymphocytic leukaemia (CLL).

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This study has been transitioned to CTIS with ID 2022-500439-35-00 check the CTIS register for the current data. The primary objective of the study is to compare the efficacy of continuous ibrutinib monotherapy with fixed-duration venetoclax plus...

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

Summary

ID

NL-OMON52308

Source
ToetsingOnline

Brief title
CLL17/HO500 CLL

Condition

- Leukaemias

Synonym
Chronic Lymphatic Leukemia CLL

Research involving
Human

Sponsors and support

Primary sponsor: HOVON
Source(s) of monetary or material Support: AbbVie B.V.,Hoffmann-La Roche,Janssen-Cilag,Janssen-Cilag;Hoffman LaRoche;AbbVie

Intervention

Keyword: CLL, Ibrutinib, Obinutuzumab, Venetoclax

Outcome measures

Primary outcome

Progression-free survival (PFS)

Secondary outcome

• Rates of undetectable MRD (uMRD, i.e. <10-4) in peripheral blood (PB) and bone marrow (BM) at final restaging (RE), which will be at cycle 18 after start of treatment, and additional BM assessment approx. 12 months after RE

• MRD levels in PB at different time points (cycle 1 before start of therapy, start of cycle 7, start of cycle 13 [-> end of VG treatment], start of cycle 16 [-> end of VI treatment], final restaging [cycle 18], afterwards every 6 months to end of study)

• Duration of undetectable MRD (uMRD)

• Overall response rate (ORR; defined as rate of a response of CR, CRi, or PR) as per iwCLL guidelines] at final restaging

• Complete response rate (CRR; defined as rate of a response of CR or CRi) at final restaging as per iwCLL guidelines

• Overall survival (OS)

• Event-free survival (EFS) (I vs VG and I vs VI)

• Time to next treatment (TTNT)

• PFS2 (i.e. PFS after second-line treatment)

Safety parameters:

• Type, frequency, and severity of

o adverse events (AEs) and

o adverse events of special interest (AESI)

o adverse events of particular interest (AEPI)

and their relationship to study treatment

• Tumour lysis syndrome (TLS) risk category after G or I lead-in (before

venetoclax ramp up)

Exploratory analyses:

• Evaluation of relationship between various baseline markers and clini-cal

outcome parameters (e.g. PFS, OS, ORR relative to del17p/TP53, IGHV, fitness,

etc)

• MRD by methods other than flow cytometry

• Correlation between MRD in BM and PB

• Correlation between MRD in BM and PFS/ EFS/ OS

Correlation between MRD in PB and PFS/ EFS/ OS

• Health-related quality of life by EORTC QLQC30 and QLQ-CLL17 questionnaires

• Medical Resource Utilization

• SARS-CoV-2-antibody levels before and 30 days, 6 months and 12

months after vaccination

Study description

Background summary

Recently several trials indicated that chemotherapy-free regimens can yield at least similar or even higher efficacy than chemoimmunotherapy

Two treatment paradigms have emerged when trying to establish chemotherapyfree regimens in CLL: continous treatment to maintain disease control or to achieve long term disease control without need for continuous therapy. For the latter, a more intensive treatment should be given over a defined period of time in order to reduce MRD to undetectable levels in most patients.
Fixed duration combination therapy with ibrutinib and obinutuzab or ibrutiniab and venetoclax have shown good results with regards to PFS

Given these two different treatment paradigms, i.e. continuous treatment with ibrutinib versus limited combinational treatment with venetoclax and obinutuzumab or venetoclax and ibrutinib, the main aim of the CLL17 trial will be to provide a randomized comparison of I versus VG and VI based on the duration of progression free survival in previously untreated patients of all age and fitness levels. This will also include a comparison of drug-related toxicities, discontinuations and quality of life parameters. Ultimately, the trial will help physicians to identify the best of the currently available individual treatment options for their patients

Also see page 4 protocol

Study objective

This study has been transitioned to CTIS with ID 2022-500439-35-00 check the CTIS register for the current data.

The primary objective of the study is to compare the efficacy of continuous ibrutinib monotherapy with fixed-duration venetoclax plus obinutuzumab and fixed-duration ibrutinib plus venetoclax by measuring progression-free survival (PFS) in patients with previously untreated CLL.

Study design

Phase-III trial, prospective, multicentre, open-label, randomized

Intervention

Patients are randomized to receive
- Ibrutinib continuous therapy until progression (max 7 years)
- Venetoclax-Ibrutinib combination therapy for 15 cycles
- Ibrutinib-Obinutuzamb combination therapy for 12 cycles

Study burden and risks

The risk for the patient consists of side effects of treatment.
Important side effects of ibrutinib are bleeding tendency and atrial fibrillation.
The risk of tumor lysis syndrome (TLS) in case of high tumorload with venetoclax is diminished by dosis ramp up. Obinutuzumab has a risk for infusion related reactions (IRR) which tends to be less frequent when it is given in combination with ibrutinib.
The risk from venapuncture, BM biopsy, is minimal. Discomfort from BM biopspy/aspirate is substantial but temporarily. From these procedures important knowledge will be gained for disease monitoring by assessing depth of response.

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

1. Documented CLL/SLL requiring treatment according to iwCLL criteria.
2. Age at least 18 years.
3. Life expectancy >= 6 months.
4. Ability and willingness to provide written informed consent and to adhere to the study visit schedule and other protocol requirements.
5. Adequate bone marrow function independent of growth factor or transfusion support within 2 weeks of screening initiation as follows,unless cytopenia is due to CLL:
a. Absolute neutrophil count >= 1.0 × 109/L
b. Platelet counts >= 30 × 109/L; in cases of thrombocytopenia clearly due to CLL (per the discretion of the investigator), platelet count should be >= 10 × 109/L
c. Total haemoglobin >= 8 g/dL (without transfusion support, unless anaemia is due to CLL)
6. GFR >30ml/min directly measured with 24hr urine collection, calculated according to the modified formula of Cockcroft and Gault or an equally accurate method.
a. For patients with creatinine values within the normal range the calculation of the clearance is not necessary. Dehydrated patients with an estimated creatinine clearance less than 30 ml/min may be eligible if a repeat estimate after adequate hydration is > 30 ml/min.
7. Adequate liver function as indicated by a total bilirubin <= 2 x, AST/ ALT <= 2.5 x the institutional ULN value, unless directly attributable to the patient's CLL or to Gilbert's Syndrome.
8. Negative serological testing for hepatitis B (HbsAg negative and anti-HBc negative; patients positive for anti-HBc may be included if PCR for HBV DNA is negative and HBV-DNA PCR is performed every month until 12 months after last treatment cycle), and for hepatitis C (anti-HCV-ab negative; in case of positive HCV anti-body test, negative HCV-PCR is required).
9. Eastern Cooperative Oncology Group Performance Status (ECOG) performance status 0-2.

Exclusion criteria

1. Any prior CLL-specific therapies (except corticosteroid treatment

administered due to necessary immediate intervention; within the last 10 days before start of study treatment, only dose equivalents up to 20 mg prednisolone are permitted).
2. Transformation of CLL (Richter transformation). When Richter transformation is suspected, PET-CT and/or biopsy should be performed to rule out transformation.
3. Patients with a history of PML.
4. An individual organ/ system impairment score of 4 as assessed by the CIRS definition limiting the ability to receive the study treatment or any other life-threatening illness, medical condition or organ system dysfunction that, in the investigator*s opinion, could compromise the patients' safety or interfere with the absorption or metabolism of the study drugs (e.g. inability to swallow tablets or impaired resorption in the gastrointestinal tract).
5. Malignancies other than CLL currently requiring systemic therapies, not being treated with curative intent before (unless the malignant disease is in a stable remission due to the discretion of the treating physician or showing signs of progression after curative treatment.
6. Uncontrolled or active infection.
7. Patients with known infection with human immunodeficiency virus (HIV).
8. Requirement of therapy with strong CYP3A4 and CYP3A5 inhibitors/ inducers (incl. up to 7 days prior to study treatment start).
9. Anticoagulant therapy with warfarin or phenprocoumon, (alternative anticoagulation is allowed e.g. DOACs, but patients must be properly informed about the potential risk of bleeding under treatment with ibrutinib).
10. History of stroke or intracranial hemorrhage within 6 months prior to registration for study screening.
11. Known bleeding disorders
12. Child B / C liver cirrhosis
13. Use of investigational agents which might interfere with the study drug within 28 days prior to registration for study screening.
14. Vaccination with live vaccines 28 days prior to registration for study screening.
15. Major surgery less than 30 days before start of study treatment.
16. History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies, known sensitivity or allergy to murine products.
17. Known hypersensitivity to any active substance or to any of the excipients of one of the drugs used in the trial.
18. Pregnant women and nursing mothers (a negative pregnancy test is required for all women of childbearing potential within 7 days before start of study treatment; further pregnancy testing will be performed monthly).
19. Fertile men or women of childbearing potential unless:
a. surgically sterile or >= 2 years after the onset of menopause
b. willing to use two methods of reliable contraception including one highly effective contraceptive method (Pearl Index <1) and one additional effective (barrier) method during study treatment and for 18 months after the end of study treatment.
20. Legal incapacity.

21. Prisoners or subjects who are institutionalized by regulatory or court order.
22. Persons who are in dependence to the sponsor or an investigator.

Study design

Design

Study phase:	3
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):	17-03-2021
Enrollment:	110
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Gazyvaro
Generic name:	obinutuzumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	IMBRUVICA
Generic name:	ibrutinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Venclyxto

Generic name:	venetoclax
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	16-11-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-12-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-09-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-06-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-10-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-10-2022
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-01-2023
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:	10-02-2023
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	CTIS2022-500439-35-00
EudraCT	EUCTR2019-003854-99-NL
CCMO	NL75009.018.20