Short-term combined acalabrutinib and venetoclax treatment of newly diagnosed patients with CLL at high risk of infection and/or early treatment, who do not fulfil IWCLL treatment criteria for treatment. A randomized study with extensive immune phenotyping.

Published: 18-08-2020
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This study has been transitioned to CTIS with ID 2024-511072-33-00 check the CTIS register for the current data. The aim is thereby to reduce the risk of serious infections and the need for regular CLL treatment.

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

Summary

ID

NL-OMON52681

Source
ToetsingOnline

Brief title
PreVent-ACaLL

Condition

- Leukaemias

Synonym
bloodcancer, Chronic Lymphocytic Leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Rigshospitalet/Copenhagen University hospital
Source(s) of monetary or material Support: Ministerie van OC&W,AbbVie B.V.,Acerta Pharma,Novo Nordisk,Novo Nordisk foundation;Acerta Pharma and Abbvie

Intervention

Keyword: Chronic Lymphocytic Leukemia, Infection, IWCLL treatment criteria

Outcome measures

Primary outcome

• Grade >=3-Infection-free survival in the treatment arm compared to the observation arm 12 weeks after finishing treatment, (24 weeks after treatment initiation). This is a non-inferiority analysis as detailed in the statistical analysis plan to assure safety of the combination treatment in this preemptive trial population.

Secondary outcome

• Grade >=3-infection free and CLL-treatment-free survival at end of treatment, 1 year and 2 years after enrollment

• Rate of overall survival (OS) and cause of death

• Treatment free survival

• Rate and CTCAE V5.0 grade of infections

• Response rate and duration according to IWCLL criteria

• Treatment related adverse events, type, frequency and severity during and for 2 years after treatment

• Immune function as assessed by immune phenotyping, functional TruCulture

assays and measurements of cytokine levels

Study description

Background summary

Many patients with CLL have a weakened immune system due to their disease. CLL increases the risk of developing serious infections requiring treatment or in the worst case CLL can result in fatalities. Recently, however, several publications have demonstrated a high risk population for infection or CLL treatment by a machine learning algoritm.
The study will investigate whether three months treatment with a combination of two types of oral medication can reduce the risk of infection and the need for regular CLL treatment when it is given to newly diagnosed CLL patients.
Two drugs will be given as preventive treatment prior to the patients needing any chemotherapy. In this way, it is tested whether the cancer disease can be *reset* and the immune system, which is inhibited by CLL, can be restored.

Study objective

This study has been transitioned to CTIS with ID 2024-511072-33-00 check the CTIS register for the current data.

The aim is thereby to reduce the risk of serious infections and the need for regular CLL treatment.

Study design

Subjects will be assigned by chance (like flipping a coin) to one of two treatment groups, randomized. Subjects have an equal (1 to 1) change of being assigned to either the study treatment group or the standard observation (no treatment) group.

In the study treatment group, subjects will be treated with a combination of the drugs acalabrutinib and venetoclax. The treatment will be started within 14 days after they have been randomised. They will be treated for three cycles, each cycle lasts 28 days.

Intervention

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Study burden and risks

It is not known whether being in the study will be a direct benefit to the patient. About half of the patients in the study will get the study treatment. If a patient is in the treatment group, he/she will receive a treatment not usually used for newly diagnosed CLL patients. The treatment might decrease the risk of infections and postpone the need for chemotherapy. The treatment may also cause side effects, which you would not have experienced with the standard of care where no medication is given.

If you are participating in the study, additional tests and procedures may impose risks including minor bleeding or infection from blood drawings and radiation due to CT scans, which equals approximately the background radiation that you would otherwise be exposed to in a few years. The CT scans performed as part of the study will expose you to approx.10 mSv per scan. For comparison, the annual natural background radiation exposure (the amount of radiation in the air, etc.) is approx. 4 mSV.

Disadvantages of participating in the research can
- possible side effects of acalabrutinib and venetoclax
- additional tests and procedures may impose risks

Participation in research also means:
- the subject has to spent extra time in the hospital
- (extra) testing;
- there are pre-arranged agreements to which the subject must keep

Contacts

Public
Rigshospitalet/Copenhagen University hospital

Blegdamsvej 9
Copenhagen DK-2100
DK
Scientific
Rigshospitalet/Copenhagen University hospital

Blegdamsvej 9
Copenhagen DK-2100
DK

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. CLL diagnosed according to IWCLL criteria within one year prior to randomization
2. High risk of infection and/or progressive treatment within 2 years according to CLL-TIM
3. IWCLL treatment indication not fulfilled
4. Life expectancy > 2 years
5. Age at least 18 years
6. Ability and willingness to provide written informed consent and adhere to study procedures and treatment
7. Adequate bone marrow function as indicated by platelets above 100 x 10E9, hemoglobin above 10 g/dL and neutrophils above 1 x 10E9
8. Creatinine clearance above 30 mL/min directly measured with 24hr urine collection or calculated according to the modified formula of Cockcroft and Gault
9. Adequate liver function as indicated by a total bilirubin<= 2 x, AST or ALT <= 2.5 x the institutional ULN value, unless directly attributable to the patient*s CLL or to Gilbert*s Syndrome.
10. 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), negative testing for hepatitis C RNA within 6 weeks prior to registration.
11. Eastern Cooperative Oncology Group Performance Status (ECOG) performance status 0-2.
12. Woman of childbearing potential (WOCBP) who are sexually active must use highly effective methods of contraception during treatment and for 30 days after the last dose of investigational drugs.
13. Willing and able to participate in all required evaluations and procedures

in this study protocol including swallowing capsules without difficulty.
14. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information.

Exclusion criteria

1. Prior CLL treatment (including monoclonal antibodies, chemotherapy, small molecules, including CD20 antibodies, BTK inhibitors and bcl-2 inhibitors for any indication)
2. Transformation of CLL (Richter*s transformation)
3. Previous autoimmune disease as AIHA (autoimmune hemolytic anemia) or ITP (idiopathic thrombocytopenic purpura) treated with immune suppression or uncontrolled AIHA or ITP
4. History of progressive multifocal leukoencephalopathy
5. HIV infection (a negative test required)
6. Known active infection
7. Malignancies other than CLL requiring systemic therapies (except anti-hormonal therapies) or considered to impact survival
8. Requirement of therapy with strong CYP3A4 and CYP3A5 inhibitors/inducers or anticoagulant therapy with vitamin K antagonists
9. History of bleeding disorders or current platelet inhibitors or anticoagulant therapy
10. History of clinically significant cardiovascular disease such as arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association
Functional Classification, or corrected QT interval (QTc) > 480 msec at screening.
11. History of stroke or intracranial hemorrhage within 6 months prior to registration.
12. Use of investigational agents which might interfere with the study drug within 28 days prior to registration.
13. Vaccination with live vaccines within 28 days prior to registration.
14. Major surgery less than 30 days before start of treatment. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.
15. Known hypersensitivity to any active substance or to any of the excipients of one of the drugs used in the trial.
16. Pregnant women and nursing mothers (a negative pregnancy test is required for all women of childbearing potential within 7 days before start of treatment; further pregnancy testing will be performed regularly).
17. Fertile men or women of childbearing potential unless: surgically sterile or >= 2 years after the onset of menopause or 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 30 days after the end of study treatment.
18. Legal incapacity.
19. Persons who are in dependence to the sponsor or an investigator
20. Persons not considered fit for the trial by the investigator
21. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.
22. Prothrombin time/INR or aPTT (in the absence of Lupus anticoagulant) > 2x ULN.
23. Requires treatment with proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Subjects receiving proton pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-05-2022
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine

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

Ethics review

Approved WMO Date:	18-08-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-01-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-01-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-06-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-07-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	20-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-09-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-02-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-03-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	CTIS2024-511072-33-00
EudraCT	EUCTR2019-000270-29-NL
CCMO	NL72316.078.20