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Protocol description of the HOVON 141/VISION trial: a prospective, multicentre, randomised phase II trial of ibrutinib plus venetoclax in patients with creatinine clearance ≥30 mL/min who have relapsed or refractory chronic lymphocytic leukaemia (RR-CLL) with or without TP53 aberrations

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ABSTRACT

Introduction Literature is scarce on the combination treatment of ibrutinib and venetoclax (IV) is scarce in relapsed or refractory chronic lymphocytic leukaemia (RR-CLL). Especially, the possibility of stopping ibrutinib in RR-CLL patients in deep remission is unclear.

Methods and analysis In the HOVON 141/VISION trial, patients with RR-CLL are treated with 12 cycles of IV after a short induction with ibrutinib. Patients reaching undetectable minimal residual disease (uMRD) after 12 cycles of IV are randomised 1:2 to continue ibrutinib or stop treatment. The persistence of uMRD after stopping IV is studied. In addition, in patients who become positive for MRD again after stopping, IV treatment is reinitiated. The efficacy of this approach with regard to progression-free survival 12 months after randomisation is the primary endpoint of the study.

Ethics and dissemination This protocol respects the Helsinki declaration and has been approved by the ethical committee of the Amsterdam Medical Center. Study findings will be disseminated through peer-reviewed papers. All patients who fulfil the inclusion criteria and no-exclusion criteria, and have signed the informed consent form are included in the study.

Trial registration number ClinicalTrials.gov Registry (NCT03226301).

Strengths and limitations of this study

- Prospective intervention study of ibrutinib and venetoclax in chronic lymphocytic leukaemia.
- Primary study question on stopping ibrutinib in undetectable minimal residual disease patients.
- Central laboratory assessment of minimal residual disease (MRD) in only two academic laboratories.
- A randomised phase II study, but no phase III study.
- Safety measure of reinitiating treatment if patients become MRD positive.

INTRODUCTION

The standard of care in treatment of patients with relapsed or refractory chronic lymphocytic leukaemia (RR-CLL) is rapidly changing. For patients with a relapse later than 2 years from first-line therapy, repeated therapy with a first-line or an alternative chemoimmunotherapy regimen has been regularly used.[1]

Novel agents such as ibrutinib and venetoclax (IV) alone or in combination with anti-CD20 antibodies are regularly used nowadays to treat relapse with high response rates. Ibrutinib treatment effectively targets the lymph node (LN) compartment but rarely results in deep clearance of peripheral blood (PB) and bone marrow (BM), which necessitates prolonged treatment with concomitant high costs and increasing rates of discontinuation due to either side effects[2] or development of resistance.[3 4] In contrast, venetoclax proved highly active in clearing CLL cells from blood and BM, but less so from LN.[5] Treatment of relapse with a combination of rituximab and venetoclax demonstrated superior efficacy and less toxicity than rituximab and bendamustine.[5 6] In addition, treatment with ibrutinib in patients with relapse demonstrated superior outcome in relation to ofatumumab.[7]

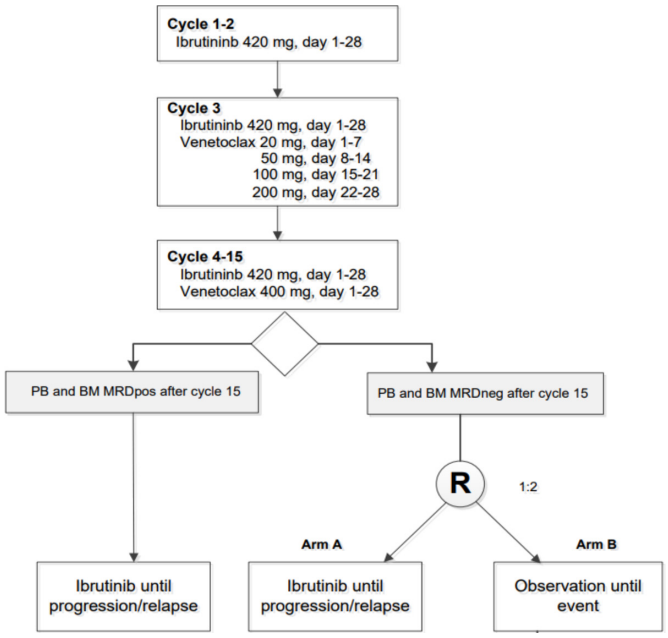

Figure 1 Scheme of treatment until cycle 15 and randomisation of MRD-negative patients. BM, bone marrow; MRD, minimal residual disease; neg, negative; PB, peripheral blood; pos, positive.

Data on IV are relatively limited. Recently, a first-line study revealed high response rates, and considerable and progressive minimal residual disease (MRD) negativity.[8] In addition, Rogers *et al*[9] demonstrated activity and tolerability of IV (plus obinutuzumab) in RR-CLL patients in a phase I study. Very recently, Hillmen *et al*[10] showed undetectable MRD (uMRD) of blood in 28 (53%) and of BM in 19 (36%) of 53 patients after 12 months of ibrutinib plus venetoclax, while 27 (51%) patients achieved a complete remission. Side effects were mild and manageable with one event of laboratory tumour lysis syndrome.

Preclinical data support the combination of the Bruton's tyrosine kinase inhibitor ibrutinib and the B-cell lymphoma 2 inhibitor venetoclax by demonstrating synergy in a diffuse large B-cell lymphoma cell line model and in primary CLL cells, as well as in mantle cell lymphoma cell lines.[11] Furthermore, several clinical trials are currently testing IV for clinical use, with no unexpected toxicities reported so far through scientific meetings, publications or internal reports for the marketing holders. Consequently, the aim of the current trial is to evaluate if combination treatment with venetoclax+ibrutinib in patients with RR-CLL can lead to MRD negativity and induce long-lasting remission even after stopping the treatment.

METHODS AND ANALYSIS

Study aim

The aim of the current trial is to evaluate the progression-free survival (PFS) of patients with RR-CLL on combination treatment with IV. In addition, the persistence of uMRD after IV, which may induce long-lasting remission, is evaluated by randomising MRD-negative patients 2:1 to stopping treatment after 15 cycles of induction or continuing ibrutinib.

Overall study design

Phase II trial, prospective, multicentre, open-label and randomised (online supplemental figure 1).

Patient population

Fit (Cumulative Illness Rating Scale (CIRS) ≤6) and unfit (CIRS >6) patients with a creatinine clearance ≥30 mL/min with previously treated CLL, with or without TP53 aberrations requiring treatment.[12–14] For inclusion and exclusion criteria, see online supplemental tables 1 and 2. On 23 January 2019, the last patient was included in the study. Randomisation is still ongoing.

Study design

This is a phase II study with late randomisation after cycle 15 in MRD-negative patients on day 15 of cycle 15; no formal comparisons between the two randomised treatment arms will be made (figure 1).

During the treatment period, all patients received 15 cycles (28 days each) of oral ibrutinib. During the first two cycles, only ibrutinib 420 mg/day was administered. From day 1 in cycle 3, over 5 weeks, venetoclax was ramped up from 20 mg/day to the target of 400 mg/day, with venetoclax 400 mg/day administered for the remaining 12 cycles.

Patients are followed by MRD assessment in PB at the end of cycle 9, end of cycle 12 and on day 15 of cycle 15 (including BM), and thereafter, every 3 months for 2 years, and every 4 months in the third year. MRD assessment is performed by 8-colour flow cytometry according to the European Research Initiative on CLL guidelines.[15] Additional ror1 and CD45 antibodies are added to the panel; analysis by FACSDiva (BD Biosciences, San Jose, California, USA) at the two central laboratories for the trial. Gating strategies and flow cytometry settings are aligned and validated between the two laboratories by parallel analysis of samples.

Patients achieving uMRD (10–4 level by flow cytometry)[15] on day 15 of cycle 15 in PB and BM are randomised 1:2 after completion of cycle 15 between continuous ibrutinib treatment until toxicity or progression (arm A) and treatment-free observation (arm B). An early amendment of the trial defined that it is not required to reach uMRD at the end of cycle 12 in PB to be eligible for randomisation. Patients not reaching MRD negativity in PB and/or BM at day 15 of cycle 15 continue ibrutinib treatment until toxicity or progression (non-randomised patients). This treatment is unblinded to patient and treating physician.

Patients with uMRD will be closely monitored for clinical signs of relapse/progression along with 3-month MRD assessment for the first 2 years and 4-month MRD assessment in the third year after randomisation. Patients becoming MRD positive (defined as MRD $\geq 10^{-3}$ and at least 1 month later as MRD $\geq 10^{-2}$) or having symptomatic

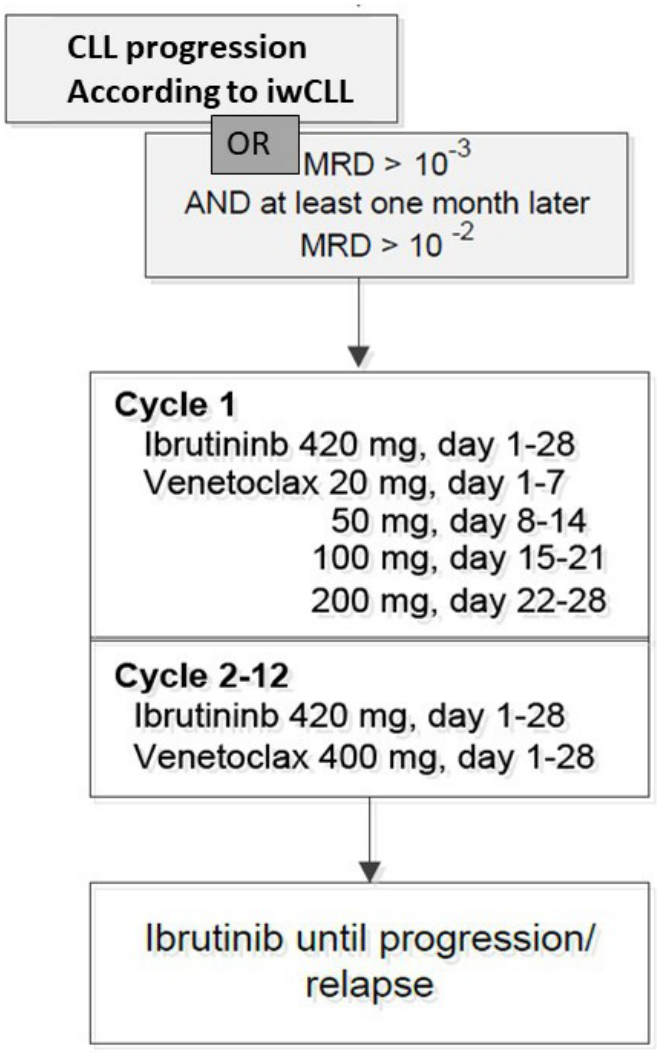

Figure 2 Scheme of reinduction treatment of MRD-negative patients after cycle 15 turning MRD positive after treatment cessation. CLL, chronic lymphocytic leukaemia; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRD, minimal residual disease.

CLL according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria within the first 3 years after randomisation, reinitiate treatment with IV for 12 cycles and continue ibrutinib treatment until toxicity or progression (figure 2).

Patients failing on reinitiation of therapy (not reaching any response (complete response/partial response/stable disease) according to iwCLL criteria as assessed by the local investigator after three cycles of reinitiated therapy, or progressing within 12 months from randomisation) are considered as having progressive disease and will go off protocol treatment.

Randomisation

Patients achieving uMRD on day 15 of cycle 15 (PB and BM) are randomised 1:2 after completion of cycle 15 between continuous ibrutinib treatment until toxicity or progression, and treatment-free observation. Patients not reaching uMRD are not randomised and continue ibrutinib treatment until toxicity or progression. Randomisation has to occur within 14 days after MRD testing after day 15 of cycle 15. Patients need to be randomised through the electronic case report form (eCRF) system provided by the HOVON Data Center.

An amendment in the protocol was made to allow randomisation of patients who were not MRD negative at the end of cycle 12 in PB but became MRD negative (10–4 level) at day 15 of cycle 15 (in PB and BM). Furthermore, this time point was moved 2 weeks in a prior amendment to allow for additional time for the MRD analysis prior to randomisation. These changes in protocol were based on an interim analysis demonstrating a significant number of patients meeting the MRD criterion at cycle 15, despite being MRD positive at the end of cycle 12.

PATIENT AND PUBLIC INVOLVEMENT

No patients or public were involved in the development and execution of this study.

PRIMARY STUDY OBJECTIVE

Evaluate efficacy of IV in terms of proportion of patients fulfilling the criteria for PFS at 12 months after stopping therapy (27 months after starting treatment) for those randomised to stop treatment (arm B of the study); reinitiating treatment due to MRD positivity is not considered progression. (figures 1 and 2).

For secondary study objectives and exploratory study objectives, see online supplemental table 3.

Data collection

Data will be collected on eCRFs to document eligibility, safety and efficacy parameters, compliance to treatment schedules and parameters necessary to evaluate the study endpoints. Data collected on the eCRF are derived from the protocol and will include at least:

- Inclusion and exclusion criteria.
- Baseline status of patient, including medical history and stage of disease.
- Timing and dosage of protocol treatment.
- Baseline concomitant diseases and adverse events.
- Parameters for response evaluation.
- Any other parameters necessary to evaluate the study endpoints.
- Survival status of patient.
- Reason for end of protocol treatment along with information about next line of therapy.

Monitoring

This trial is part of the HOVON Site Evaluation Visit programme. Site evaluation visits will be performed for HOVON trials to review the quality of the site and not specifically the quality of a certain trial. It will enable HOVON to collect quality data and facilitate improvement of the participating sites. Data cleaning or monitoring of the performance of specific trials is not the goal

of the site evaluation visits. Site evaluation visits will be performed according to the site evaluation visit plan. The HOVON site evaluation visit plan applies to sites in the Netherlands, Belgium and Luxembourg only. Monitoring of the quality of trial conducted in participating sites from other countries will be organised by the national coordinating investigator or co-sponsor. The frequency and content of the site visits in other countries will be at least equal to the specifications of the site evaluation visit plan, and are described in a monitoring plan provided by HOVON.

DATA STATEMENT

Al data are gathered in ALEA, the data capturing system used by the HOVON. All data are registered in this electronic data capturing system by local data managers of all sites.

STATISTICS

Efficacy analysis

The PFS primary endpoint will be analysed as soon as all randomised patients have achieved the landmark of 12 months after randomisation. Thus, final analysis will take place as soon as the last patient starting treatment has reached the time point of month 27 and data have been assembled from all study sites. Given an estimated 3-year recruitment period, the time point of final PFS analysis is projected to be 5 years and 6 months after initiation of trial.

The primary efficacy endpoint is the investigator-assessed proportion of patients with PFS at month 27 in arm B (observation arm), the intention-to-treat population for arm B is used for calculation of the proportion. PFS is defined as all patients free of progression or relapse (determined using standard IWCLL guidelines (2008)) or death from any cause, whichever occurs first. Patients in the observation arm becoming MRD positive, and thus restarting treatment, are still considered progression-free as long as they do not progress according to IWCLL criteria after reinitiation of treatment. If patients in the observation arm have clinical progression but achieve response within 3 months of reinitiating treatment, they are still considered progression-free. Patients reinitiating therapy prior to the 12-month time point from randomisation according to the rules outlined above, who have progressed according to IWCLL criteria before reinitiating treatment, are allowed up to 3 months to obtain response after reinitiating therapy. These patients will be considered progression-free at month 27 if a response is achieved within 3 months from reinitiating therapy.

Power calculation

The primary objective of the study is to test the following hypothesis: the PFS rate at 12 months after randomisation for the observation arm (B) is more than 60% (ie, H0: PFS rate at 12 months post randomisation ≤60% vs H1: PFS rate at 12 months post randomisation >60%). PFS and the 95% CI will be estimated using the Kaplan-Meier survival methodology, and a Kaplan-Meier survival curve will be generated to provide a visual illustration of PFS for patients in the different treatment arms separately (from randomisation), and also for all patients together (from registration).

Target number of patients—207 eligible patients. However, in order to take into account possible dropout due to ineligibility, 230 patients will be registered.

Only patients randomised for observation (arm B) are considered for the primary endpoint without formal comparison between the arms.

Before the final analysis, a statistical analysis plan will be prepared by the trial statistician and approved by the principal investigator. It will describe in detail the analyses to be performed. Deviations from the analyses, as specified above, will be discussed with the study coordinators and can only affect the exploratory analyses, but not the primary (confirmatory) analysis on which the sample size is based. All analyses, except the primary analysis, should be considered as hypothesis-generating only.

Interim analyses

See online supplemental table 4.

The results of the interim analyses will be reviewed by the Data Safety and Monitoring Board (DSMB) and, if necessary, additional analyses can be performed depending on the request of the DSMB.

ETHICS AND DISSEMINATION

This protocol respects the Helsinki declaration and has been approved by the ethical committee of the Amsterdam Medical Center. All patients will provide written informed consent (online supplemental figure 2).

Trial results will be submitted for publication in a peer-reviewed scientific journal regardless of the outcome of the trial, unless the trial was terminated prematurely and did not yield sufficient data for publication. Interim analyses will be presented at scientific meetings and may be submitted for publication in peer-reviewed scientific journals.

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Correction notice This article has been corrected since it was published. Middle initial 'P' added in author name Arnon Kater.

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Contributors M-DL, AK and CUN have designed the trial, written the manuscript and conducted the study. MM, SK, JR and HTTT were responsible for locally conducting the study and revising the manuscript. KN made the statistical assumptions and will analyse the results.

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Competing interests M-DL: Advisory board compensation from Janssen, AbbVie and Roche; travel reimbursement from Janssen, AbbVie and Roche. AK: Received research grants from Celgene, Janssen, AbbVie, Roche/Genentech, AstraZeneca; speakers fee from AbbVie and AstraZeneca, and participated in advisory boards of AbbVie, Janssen, AstraZeneca and Roche. CUN: Research grant from AbbVie and Janssen; advisory board compensation from AbbVie, Janssen, Gilead, Roche, AstraZeneca, Acerta and Sunesis; travel reimbursement from Gilead, Roche and Novartis; consultancy compensation from CSL Behring. MM: Lecture remuneration from Janssen and advisory board compensation from AbbVie. JR: Received consultancy fees from AbbVie and Janssen. HTTT: Consultancy fees from Janssen-Cilag, AbbVie, Bayer, Novartis and AstraZeneca.

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