A prospective, multicenter, phase-II trial of ibrutinib plus venetoclax in patients with creatinine clearance ≥ 30 ml/min who have relapsed or refractory chronic lymphocytic leukemia (RR-CLL) with or without TP53 aberrations

HOVON 141 CLL / VIsion Trial of the HOVON and Nordic CLL study groups

PROTOCOL

Principal Investigator	:	**Arnon P Kater (HOVON)** **Carsten U Niemann (Nordic CLL study Group))**
Sponsor	:	HOVON
EudraCT number	:	2016-002599-29

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

28/8/18

Signature of Principal Investigator Date

Carsten U. Niemann, MD, PhD, Nordic CLL study group

Principal Investigator

27 AUG 18

Signature of Principal Investigator Date

Arnon P. Kater, MD, PhD, HOVON

Principal Investigator

LOCAL INVESTIGATOR SIGNATURE PAGE

Local site name: _____

_____ _____

Signature of Local Investigator Date

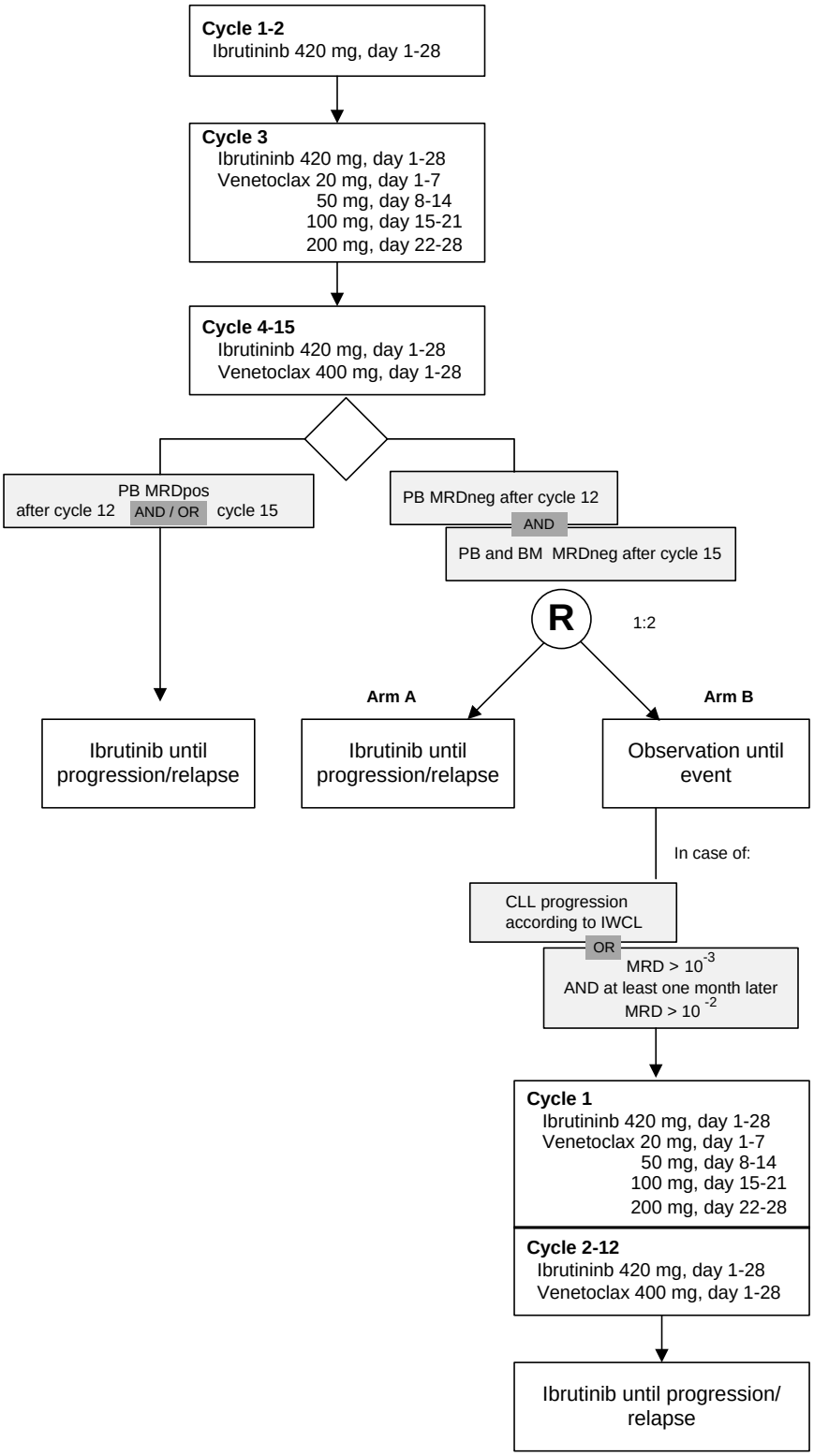
_____

Printed Name of Local Investigator

By my signature, I agree to personally supervise the conduct of this study in my affiliation and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, ICH Good Clinical Practices guideline, the EU directive Good Clinical Practice (2001-20-EG), and local regulations governing the conduct of clinical studies.

1 Scheme of study

Fit and unfit patients with creatinine clearance ≥ 30 ml/min who have relapsed or refractory CLL with or without TP53 aberrations, requiring treatment.



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3 Synopsis

Study aim	The aim of the current trial is to evaluate if combination treatment with venetoclax + ibrutinib in patients with relapsed or refractory chronic lymphocytic leukemia (RR CLL) can lead to MRD negativity, which may induce long lasting remissions for MRD-negative patients randomized to stopping treatment after 15 induction cycles.
Study objectives	The primary objective: - Evaluate efficacy of ibrutinib + venetoclax (VI) in terms of proportion of patients fulfilling the criteria for progression free survival (PFS) at 12 months after stopping therapy (27 months after starting treatment) for patients randomized to stop treatment (arm B of the study), reinitiated treatment due to MRD positivity not considered progression (see section 13.1 for details). Secondary objectives (for all treatment groups): - Evaluation of the efficacy in terms of minimal residual disease (MRD) at 12 months after stopping treatment (month 27), - Evaluation of efficacy in terms of PFS (IWCLL criteria), - Time to next CLL treatment, - MRD after cycle 12 (PB), at day 15 of cycle 15 (PB and BM) and at later time points in PB, - Overall Survival (OS), - Complete response (CR)/ Partial Response (PR)/ Stable disease (SD) after cycle 3, 9, 12, 15, and at month 27 and month 51 (3 years after stopping treatment), - Duration of response, – To evaluate safety with regards to type, frequency, and severity of adverse events (AEs) and adverse events of special interest (AESI) and their relationship to study

	treatment, – To evaluate patient related outcomes, measured in terms of health-related quality of life (QoL) by EORTC QLQ-C30 and QLQ-CLL16 questionnaires. Secondary objectives (Arm B group) - Time to and number of patients reinitiating treatment, - Time to treatment failure after reinitiated treatment.
Study design	Phase-II trial, prospective, multicenter, open-label, randomized.
Patient population	Fit (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.
Intervention	All patients receive ibrutinib + venetoclax (with delayed start and ramp up of venetoclax from cycle 3) for the 15 cycles. Patients not achieving MRD negativity after cycle 12 (PB) AND/OR day 15 cycle 15 (PB+BM) continue on ibrutinib maintenance (non-randomized group). Patients achieving MRD negativity after cycle 12 (PB) ANDday 15 cycle 15 (PB+BM) are randomized 1:2 between ibrutinib maintenance (arm A) and stopping treatment (observation, arm B). Patients randomized to arm B who become MRD positive or have symptomatic CLL according to IWCLL critera during the observation period reinitiate treatment with both ibrutinib and venetoclax for 12 cycles and continue ibrutinib treatment until toxicity or progression. Only patients randomized for observation (arm B) are considered for the primary endpoint without formal comparison between arms.
Duration of treatment	All patients receive ibrutinib + venetoclax (with delayed start

	and ramp up of venetoclax from cycle 3) for the first 15 cycles. Thereafter Ibrutinib maintenance until progression/toxicity or observation without treatment. Patients randomized to arm B who become MRD positive or have symptomatic CLL according to IWCLL critera during the observation period reinitiate treatment ibrutinib + venetoclax for 12 months and continue ibrutinib treatment until toxicity or progression. Subsequently all patients will be followed until 7 years after registration
Target number of patients	207 eligible patients. In order to take into account possible dropout due to ineligibility, 230 patients will be registered
Expected duration of accrual	Expected start of recruitment Q2/2017 Expected end of recruitment Q2/2020
Main study endpoints	Primary endpoints: (Only considered for arm B of the study) - Proportion of patients fulfilling the criteria for progression free survival (PFS) at 12 months after stopping therapy (27 months after starting treatment) for patients randomized to stop treatment , reinitiated treatment due to MRD positivity not considered progression (see section 13.1 for details). Secondary endpoints (for all treatment groups): - Minimal residual disease (MRD) at 12 months after stopping treatment (month 27) for patients randomized to stop treatment, - PFS (IWCLL criteria), - Time to and number of patients reinitiating treatment, - Time to treatment failure after reinitiated treatment, - Time to next CLL treatment, - MRD after cycle 12 (PB), day 15 cycle 15 (PB and

BM) and at later time points in PB,
- Overall survival (OS),
- Complete response (CR)/ Partial Response (PR)/ Stable disease (SD) after cycle 3, 9, 12, 15 and month 27 and 51 (3 years after stopping treatment,
- Duration of response,
- Safety parameters: Type, frequency, and severity of
    - adverse events (AEs) and
    - adverse events of special interest (AESI) and their relationship to study treatment
- Health-related quality of life by EORTC QLQ-C30 and QLQ-CLL16 questionnaires.

Exploratory endpoints:
- Evaluation of relationship between various baseline markers and clinical outcome parameters,
- Various markers at time of progression,
- Correlation between MRD in BM and PB,
- Correlation between MRD in BM and PFS//OS,
- Correlation between MRD in PB and PFS/OS.

Benefit and nature and extent of the burden and risks associated with participation

The standard of care in treatment of patients with relapsed or refractory CLL (RR CLL) is rapidly changing. For patients with a relapse later than 1-2 years from first line therapy, repeated therapy with a first line regimen is used. This poses the risk of significant immunosuppression and infectious complications as well as a shorter progression free survival than for first line treatment is expected. For patients with refractory disease, early relapse or emerging of TP53 aberrated subclones, targeted treatment with ibrutinib or idelalisib + rituximab is used. However, literature to date only supports treatment until progression or toxicity with significant impact on quality of life and significant socioeconomic implications as well as conferring the risk of clonal evolution and development of resistance with continuous exposure to treatment.
Thus, there is an urgent need for alternatives, especially

	chemotherapy-free regimens without the need for prolonged maintenance. As CD20 targeting agents are currently part of standard first line treatment for CLL, testing of a regimen for RR CLL without repeated CD20 targeting, thus presenting targets for treatment that have not been targeted previously for the patients, is a rational approach. Ibrutinib is approved for treatment of patients with CLL as first line treatment and for patients with relapsed or refractory disease with a manageable safety profile. Venetoclax has been approved for treatment of patients with CLL and del(17p), with a manageable safety profile as long as precautions concerning the risk of tumor lysis syndrome are followed as stated for this trial. Several hundreds of patients have been treated with the combination of ibrutinib and venetoclax in clinical trials, no unexpected safety signals differing from the safety profile described for each drug have been reported. However, data on long term safety and the outcome upon stopping treatment is still immature, thus the current study especially addresses these aspects in addition to the primary endpoint. 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, which may induce long lasting remissions for those patients randomized for observation after cycle 15.
Planned interim analysis and DSMB	The interim analyses of the trial are described in section 14.4.4. Real time monitoring of the outcome for patients randomized for stopping treatment will continue based on the MRD results. MRD data will be collected at the 2 central laboratories and shared with central data management.

4 Investigators and study administrative structure

Responsibility	Name	Affiliation/Address
Sponsor	HOVON	VU University Medical Center, P.O.Box 7057 1007 MB Amsterdam The Netherlands Tel: +31-204443797
Co-sponsor	NCLLSG	Rigshospitalet, Copenhagen University Hospital Department of Hematology, Building 4042 Blegdamsvej 9 2100 Copenhagen Denmark Tel: +45-35455657
Representative of Sponsor (HOVON)	J.J. Cornelissen, chairman N.M.A Blijlevens, treasurer	Erasmus MC, Rotterdam Radboud University, Nijmegen
Principal Investigator	C.U. Niemann	Copenhagen University hospital, Rigshospitalet Department of Hematology, building 4042 Blegdamsvej 9 DK2100 Copenhagen , Denmark Tel :+45-35457830 Mail: carsten.utoft.niemann@regionh.dk
	A.P. Kater	Academic Medical Center University of Amsterdam Department of Hematology F4-224 Meibergdreef 9 1105 AZ Amsterdam,The Netherlands Tel:+31- 205665785 Mail: a.p.kater@amc.uva.nl
Co-investigators	MD Levin	Albert Schweitzer hospital Department of Internal Medicine Albert Schweitzerplaats 25 3318 AT Dordrecht, The Netherlands Tel: +31-786523787 Mail: m-d.levin@asz.nl
	M. Mattsson	Uppsala University Hospital Blodmottagningen/Avd. 50 C 751 85 Uppsala, Sweden Tel: +46-186115047 Mail: mattias.mattsson@akademiska.se

Coordinating investigator	*The Netherlands* A.P. Kater	Academic Medical Center, Amsterdam
	Denmark C.U. Niemann	Rigshospitalet, Copenhagen University Hospital, Copenhagen
	Sweden M. Mattsson	Uppsala University Hospital, Uppsala
	Norway H. Tran	Akershus University Hospital, Lørenskog
	Finland T. Salmi	Turku University Central Hospital, Turku
HOVON CLL working group chair	A.P. Kater	Academic Medical Center, Amsterdam
Writing Committee	MD Levin A.P. Kater S. Kersting M. Mattsson C.U. Niemann T. Salmi H. Tran	Albert Schweitzer hospital, Dordrecht Academic Medical Center, Amsterdam Haga Hospital, The Hague Uppsala University Hospital, Uppsala Copenhagen University hospital, Copenhagen Turku University Central Hospital, Turku Akershus University Hospital, Lørenskog
Statistician	K. Nasserinejad	Erasmus MC – Cancer Institute HOVON Data Center
Registration	HOVON Data Center	Erasmus MC Cancer Institute P.O.Box 2040 3000 CA ROTTERDAM The Netherlands https://www.hdc.hovon.nl/top Tel. +31-107041560 Fax +31-107041028
Monitoring	HOVON Data Center GCP unit (Denmark) Clinical Trial Unit	Erasmus MC Cancer Institute Copenhagen University Hospital Uppsala University Hospital
Central Laboratory	HOVON: Academic Medical Center Amsterdam Nordic: Rigshospitalet, Copenhagen University Hospital	
Trial management	HOVON Data Center	Erasmus MC Cancer Institute
Data management	HOVON Data Center	Erasmus MC Cancer Institute
Serious Adverse Events (SAEs) notification	HOVON Data Center	Erasmus MC Cancer Institute

5 Introduction and rationale

5.1 Description of disease and current treatment

Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults. CLL is characterized by clonal proliferation and accumulation of neoplastic B-cells within the blood, bone marrow and secondary lymphatic organs (Chiorazzi, Hatzi et al. 2005). The B-cell receptor (BCR) pathway has in recent years been at the core for development of new therapeutics for patients with CLL. High efficacy of novel kinase inhibitors (the of Brutons Tyrosine Kinase (BTK) inhibitor ibrutinib and the PI3K inhibitor idelalisib) targeting the BCR pathway led to approval for patients with relapsed/refractory CLL, including first line treatment of CLL patients with del(17p) or TP53 mutations(Byrd, Furman et al. 2013, Furman, Sharman et al. 2014, Farooqui, Valdez et al. 2015). Besides the significance of the BCR pathway, CLL cells show resistance to apoptosis due to upregulation of the anti-apoptotic protein Bcl-2, which can be inhibited in the clinical setting with the Bcl-2 inhibitor venetoclax, recently approved for clinical use by the FDA(Roberts, Davids et al. 2016).
The standard of care in treatment of patients with relapsed or refractory CLL (RR CLL) is rapidly changing. For patients with a relapse later than 2 years from first line therapy, repeated therapy with a first line regimen is used. This poses the risk of significant immunosuppression and infectious complications as well as a shorter event free survival than for first line treatment is expected. For patients with refractory disease, early relapse or emerging TP53 aberrated subclones, targeted treatment with ibrutinib, idelalisib + rituximab or venetoclax is used. However, published studies to date only supports treatment until progression or toxicity with significant impact on quality of life and significant socioeconomic implications. Thus, there is an urgent need for alternatives, especially chemotherapy-free regimens without the need for prolonged maintenance in the setting of RR CLL.

5.2 Investigational Medicinal Products

5.2.1 Venetoclax

Venetoclax is an oral bcl-2-antagonist, which in contrast to ABT-263 is specific for bcl-2 and induces death in bcl-2 dependent tumor cells while sparing thrombocytes (Souers, Leverson et al. 2013, Ng and Davids 2014). Venetoclax was shown be potent in cell-killing and anti-tumor effects, but also enhanced the efficacy of drugs like bendamustine and rituximab in xenograft mouse models. It is co-developed for the treatment of hematological and immunological diseases by the pharmaceutical companies F. Hoffmann-La Roche LTD and AbbVie Inc. Venetoclax has been approved for treatment of CLL by the FDA in April 2016. Concerning detailed information on Venetoclax please refer to the current version of the IB.

Venetoclax is currently investigated in trials including patients with relapsed/refractory CLL/ small lymphocytic lymphoma (SLL), that were heavily pretreated and harbor adverse prognostic features, such as del(17p) and unmutated IGHV status. In the first-in-human trial even a single dosage lead to a rapid reduction of tumor burden. However, the overwhelming and rapid dying of malignant cells caused severe and sometimes even fatal tumor lysis syndromes (TLS), which could be managed or even prevented with certain measures of precaution, especially during the first days of treatment and during the dose-escalation phase. Thus, the target dose of 400 mg venetoclax per day has been kept in ongoing trials without significant safety findings concerning tumor lysis syndrome, as long as the careful dose-escalation also implicated in the current study is followed.
Aside from these TLS, venetoclax was found to be safe and well tolerated. Preliminary results from trials evaluating venetoclax as a monotherapy and combined with rituximab were very encouraging: an overall response rate of 79% and CR rate of 34% and even some cases of minimal residual disease (MRD) negativity were achieved with single agent venetoclax, however, these results appeared to be independent of adverse factors such as IGHV and cytogenetics as well as refractoriness to fludarabine (Roberts, Davids et al. 2016). In an ongoing dose-escalation study, the combination of venetoclax and rituximab showed no additional toxicities, of note, no further TLS occurred after dosing and monitoring was changed due to one fatal hyperkalemia due to TLS. (Roberts, Ma et al. 2015) An overall response rate of 88% and a CR/CRi rate of 31% were achieved. Of 15 patients with CR/Cri and 22 patients with PR 17 were MRD-negative in the bone marrow.

5.2.2 Ibrutinib

Ibrutinib is an oral, first-in-class selective, irreversible small molecular inhibitor of Bruton´s Tyrosine Kinase (BTK) currently under development in B-cell malignancies. Ibrutinib is being co-developed by Pharma-cyclics, Inc. and Janssen Research & Development, LLC (JRD). Ibrutinib was approved by the FDA in February 2014 and by the EMA in October 2014 for the treatment of CLL patients who have received at least one previous therapy and also for patients with del(17p) or TP53 mutations. For detailed in-formation on ibrutinib please see the current version of the investigator´s brochure and the SmPC.
Ibrutinib showed excellent responses and a safe toxicity profile and therefore warrants to be implemented into clinical trials (Byrd, Furman et al. 2013).

5.3 Rationale of the study

Preclinical data supports the combination of the BTK inhibitor ibrutinib and the bcl-2 inhibitor venetoclax. The combination of ibrutinib and venetoclax showed synergy in a diffuse large B cel lymphoma (DLBCL) cell line model (Mathews Griner, Guha et al. 2014) and in primary CLL cells

(Deng, Isik et al. 2015) as well as in Mantle Cell Lymphoma (MCL) cell lines.(Portell, Axelrod et al. 2014) CD20 targeting agents are currently part of standard first line treatment for CLL. Testing of a regimen for RR CLL without repeated CD20 targeting, thus presenting targets for treatment that has not been targeted previously for these patients, is a rational approach. Furthermore, several clinical trials are currently testing the combination of venetoclax and ibrutinib 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, which may induce long lasting remissions.

6 Study objectives

The primary objective:

- Evaluate efficacy of ibrutinib + venetoclax (VI) in terms of proportion of patients fulfilling the criteria for progression free survival (PFS) at 12 months after stopping therapy (27 months after starting treatment) for patients randomized to stop treatment (arm B of the study), reinitiated treatment due to MRD positivity not considered progression (see section 13.1 for details).

Secondary objectives (for all treatment groups):

- Evaluation of the efficacy in terms of minimal residual disease (MRD) at 12 months after stopping treatment (month 27),
- Evaluation of efficacy in terms of PFS (IWCLL criteria),
-
- Time to next CLL treatment,
- MRD after cycle 12 (PB), day 15 cycle of 15 (PB and BM) and at later time points in PB,
- Overall Survival (OS),
- Complete response (CR)/Partial response (PR)/Stable disease (SD) after cycle 3, 9, 12, 15, and at month 27 and month 51 (3 years after stopping treatment),
- Duration of response,
– To evaluate safety with regards to type, frequency, and severity of adverse events (AEs) and adverse events of special interest (AESI) and their relationship to study treatment,
– To evaluate patient related outcomes, measured in terms of health-related quality of life (QoL) by EORTC QLQ-C30 and QLQ-CLL16 questionnaires.

Secondary objectives (Arm B group)

- Time to and number of patients reinitiating treatment,
- Time to treatment failure after reinitiated treatment.

7 Study design

This study is designed as a phase 2 study with a late randomization in patients MRD negative after cycle 12 and15, no formal comparisons between the two randomized treatment arms will be made.

During the treatment period all patients receive 15 cycles (28 days each) of oral ibrutinib + venetoclax treatment. During the first 2 cycles, only ibrutinib 420 mg a day is administered. From day 1 in cycle 3, ramp up over five weeks of venetoclax from 20 mg per day to the target of 400 mg per day is administered.

Patients achieving MRD negativity after cycle 12 in peripheral blood (PB) and at day 15 of cycle 15 in PB and bone marrow (BM) are randomized 1:2 between contious ibrutinib treatment until toxicity or progression (arm A) and treatment free observation (arm B). Patients not reaching MRD negativity after cycle 12 and/orat day 15 of cycle 15 continue ibrutinib treatment until toxicity or progression (non-randomized patients).

MRD negative patients will be closely monitored for relapse/progression during the first 3 years after randomization by means of rapid reporting as described in section 16.1.1.
Patients becoming MRD positive (defined as MRD≥10^{-3} and at least one month later MRD ≥10^{-2}), or have symptomatic CLL according to IWCLL critera (appendix A) during the observation period reinitiate treatment with both ibrutinib and venetoclax for 12 cycles and continues ibrutinib treatment until toxicity or progression.
Patients failing on reinitiating therapy (not reaching any response (CR/PR/SD) according to IWCLL critera as assessed by the local investigator after 3 cycles of reinitiated therapy (or after reinitiation therapy until 12 months after randomization if progression occurred within 9 months from randomization) are considered as having progressive disease and will go off protocol treatment.

Details of all treatments (dose and schedule) are given in section 9.

8 Study population

8.1 Eligibility for registration

All patients must be registered before start of treatment and must meet all of the following eligibility criteria, which will be checked at registration.

8.1.1 Inclusion criteria

- Documented relapsed/refractory CLL or SLL requiring treatment according to IWCLL criteria (no limits on previous treatment lines; CD20 and steroids are not considered prior therapy lines).
- Age at least 18 years.
- Adequate bone marrow function defined as:
  - Absolute neutrophil count (ANC) >0.75 x 10^9/L
  - Platelet count >30,000 /µL 30 x 10^9/L.
  - Hemoglobin >8.0 g/dL (5 mmol/L)

  Unless directly attributable to CLL infiltration of the bone marrow, proven by bone marrow biopsy
- Creatinine clearance (CrCL) ≥ 30ml/min calculated according to the modified formula of Cockcroft and Gault or directly measured with 24hr urine collection.
- Adequate liver function as indicated
  - Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 3.0 x upper limit of normal (ULN)
  - Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
  - Prothrombin time (PT)/International normal ratio (INR) <1.5 x ULN and PTT (activated partial thromboplastin time [aPTT]) <1.5 x ULN (unless abnormalities are related to coagulopathy or bleeding disorder).
- 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 dose), negative testing for hepatitis C RNA within 42 days prior to registration.
- WHO/ECOG performance status 0-3 (appendix C), stage 3 only if attributable to CLL.
- Negative pregnancy test at study entry (for women of childbearing potential).
- Male and female subjects of reproductive potential must agree to use both a highly effective method of birth control (e.g. implants, injectables, combined oral contraceptives, some

intrauterine devices [IUDs], complete abstinence , or sterilized partner) and a barrier method (e.g., condoms, cervical ring, sponge, etc.) during the period of therapy and for 90 days after the last dose of study drug.

- Ability and willingness to provide written informed consent and to adhere to the study visit schedule and other protocol requirements.
- Written informed consent.

8.1.2 Exclusion criteria

- Any prior therapy with ibrutinib and/or venetoclax.
- Transformation of CLL (Richter's transformation).
- Patients with a history of confirmed progressive multifocal leukoencephalopathy (PML).
- Malignancies other than CLL currently requiring systemic therapies or not being treated in curative intention before or showing signs of progression after curative treatment.
- Known allergy to xanthine oxidase inhibitors and/or rasburicase if no other appropriate prevention of tumorlysis is considered feasible by the treating physician.
- Known bleeding disorders (e.g., von Willebrand's disease or hemophilia).
- Uncontrolled or active infection.
- Patients requiring treatment with a strong cytochrome P450 (CYP) 3A inhibitor (see appendix K). or anticoagulant therapy with warfarin or phenoprocoumon or other vitamin K antagonists.
  Please note: Patients being treated with NOACs can be included, but must be properly informed about the potential risk of bleeding under treatment with ibrutinib.
- History of stroke or intracranial hemorrhage within 6 months prior to registration.
- Major surgery within 28 days prior to registration.
- Use of investigational agents which might interfere with the study drug within 28 days prior to registration.
- Vaccination with live vaccines within 28 days prior to registration
- Steroid therapy within 7 days prior to registration, with the exception of inhaled steroids for asthma, topical steroids, steroids up to 25 mg of prednisolone daily to control autoimmune phenomenon's, or replacement/stress corticosteroids.
- Pregnant women and nursing mothers.
- Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

8.2 Eligibility for randomization

- MRD negative peripheral blood after cycle 12.

- ♦ MRD negative peripheral blood and bone marrow at day 15 of cycle 15.
- ♦ At least SD after cycle 15.

8.3 Eligibility for Ibrutinib monotherapy in MRD-positive patients

- ♦ MRD positive peripheral blood after cycle 12 and/or MRD positive peripheral blood and/or bone marrow at day 15 of cycle 15.
- ♦ At least SD after cycle 15

9 Treatment

9.1 Treatment with ibrutinib and venetoclax

All patients should start protocol treatment (cycle 1, day 1), within 28 days after registration, or in case of new uncontrolled infection occurring after registration, when infection is under control.

All patients receive 15 cycles of ibrutinib + venetoclax (with ramp up and delayed start, see below). Each cycle has a duration of 28 days.
After 15 cycles of ibrutinib + venetoclax, subsequent treatment will be based on MRD status:

- Patients not achieving MRD negativity after cycle 12 (PB) AND/OR at day 15 of cycle 15 (PB+BM) continue on ibrutinib maintenance (non-randomized patients)
- Patients achieving MRD negativity after cycle 12 (PB) AND at day 15 of cycle15 (PB+BM) are randomized 1:2 between ibrutinib maintenance (Arm A) and stopping treatment (observation) (Arm B).

Ibrutinib will be administered as a daily oral dosage of 420 mg (3 x 140 mg) starting on day 1 of cycle 1.
Venetoclax administration starts in cycle 3. Assessment of subject-specific factors for level of risk of TLS and providing prophylactic hydration and anti-hyperuricemics to subjects prior to first dose of venetoclax to reduce risk of TLS is mandatory (see appendix G). Venetoclax will be administered orally once daily beginning with a dose ramp-up period. The initial venetoclax dose is 20 mg. After one week of treatment at 20 mg, the dose will be escalated to 50 mg, followed by subsequent increases, each after one week, to 100 mg, 200 mg and the maximum dose of 400 mg. The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS.
Patients with a high tumor burden or assessed as high risk for TLS at baseline, should be re-assessed for TLS risk, at the end of cycle 2 (before venetoclax ramp up) including a CT-scan,

absolute leucocyte count (ALC) and creatinine clearance (CrCl, directly measured with 24hr urine collection or calculated according to the modified formula of Cockcroft and Gault, appendix E).
For patients with CrCL between 30-50 ml/min , inclusion in the trial is acceptable if:

- CrCl and ALC count will be re-assessed at end of cycle 2 (before venetoclax ramp up)
- Upon significant (above 15%) creatinine increase, treatment will be put on hold for a work up by a nephrologist to assess whether treatment can be reinitiated
- Re-assessment with a CT scan will be performed at end of cycle 2
  (using contrast is up to local investigator based on kidney function)
- Re-assessment of comorbidities will be performed at end of cycle 2

Please note: patients with a CrCl between 30 ml/min and 50 ml/min are considered as patients at greater risk for TLS and must be hospitalized during ramp-up independently of their disease burden.

In order to correctly diagnose a laboratory or clinical TLS at an early stage certain safety measures must be followed (see appendix G) for further information.

Patients will continue treatment until suspected progressive disease according to IWCLL after start of cycle 6. In case of suspected progression, this needs to be confirmed by CT and bone marrow biopsy. Patients with at least stable disease (SD) will continue on trial; patients with progressive disease will go off protocol treatment
In the case of signs of progression *before* start of cycle 6 i.e. Richter's, progression needs to be confirmed by CT and bone marrow biopsy. If progression is proven after at least 2 cycles of venetoclax the patient should go off protocol.

9.1.1 Treatment schedule

Treatment schedule for cycle 1-15.

Agent	Dose/day	Route of administration	Cycle	Days
Ibrutinib	420 mg	Orally	1-15	1-28
Venetoclax	-	-	1-2	-
Venetoclax	20 mg	Orally	3	1-7
Venetoclax	50 mg	Orally	3	8-14
Venetoclax	100 mg	Orally	3	15-21
Venetoclax	200 mg	Orally	3	22-28
Venetoclax	400 mg	Orally	4-15	1-28

9.1.2 Administration of treatment

During cycles with ibrutinib combination dosing, ibrutinib and venetoclax should be taken together at the same time (in the morning), ibrutinib will be taken before breakfast, venetoclax during breakfast.

Ibrutinib

Patients should be instructed to take 3 capsules (for a dose of 420 mg), orally with a glass of water, once daily at about the same time each day. Patients should avoid consumption of foods or beverages containing grapefruit or Seville oranges or starfruit, as these contain certain ingredients that inhibit CYP 3A activity. The capsules are to be taken with water. The capsules should be swallowed intact and patients should not attempt to open capsules or dissolve them in water
If a dose is missed, it can be taken up to 8 hours after the scheduled time with a return to the normal schedule the following day. If it has been greater than 8 hours, the dose should be skipped and the patient should continue treatment at the scheduled time the next day.

Venetoclax

Patients should take venetoclax tablets orally once daily (in the morning). Each dose of venetoclax will be taken with approximately 240 mL of water during breakfast or first meal of the day. Patients should avoid consumption of foods or beverages containing grapefruit or Seville oranges or starfruit, as these contain certain ingredients that inhibit CYP3A activity.
If the patient misses a dose of venetoclax within 8 hours of the time it is usually taken, the patient should take the missed dose as soon as possible on the same day and resume the normal daily dosing schedule. If a patient misses a dose by more than 8 hours, the patient should not take the missed dose and resume the usual dosing schedule the following day.
If vomiting occurs within 15 minutes of taking venetoclax and all expelled tablets are still intact, the intake may be repeated with the same dosage. Otherwise, no replacement dose is to be taken . The next dose should be taken at the usual time the following day.

9.1.3 Dose adjustments for Ibrutinib and Venetoclax

Management of toxicities with ibrutinib is described in appendix H
Management of toxicities with venetoclax is described in appendix I.
Dose adjustment of venetoclax with concomitant use of moderate CYP3A inhibitors is described in section 9.5.1

9.2 Special precautions and supportive care

9.2.1 Prophylaxis and Management of Tumor Lysis Syndrome (TLS)

Tumor lysis syndrome (TLS) is a severe and potentially fatal complication to treatment of CLL with Venetoclax. The risk can be effectively reduced by prophylactic treatment in all risk groups and identifying patients at risk and taking precautions

Clinical data suggest that the risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Tumor burden assessments, including radiographic evaluation (e.g., CT scan) to assess lymphadenopathies size and splenomegaly, and assessment of blood hematology (whole blood cell count (WBC) and ALC) and chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) should be performed in all patients and pre-existing laboratory abnormalities should be corrected prior to initiation of treatment with venetoclax. Reduced renal function (CrCl <80 mL/min) further increases the risk. The TLS risk may decrease as tumor burden decreases.
The risk of developing TLS is highest during the ramp-up period and all patients must receive the intended dose of venetoclax for 7 days before next dose-escalation is performed.
See appendix G for prophylaxis and management of TLS according to risk category.

9.2.2 Hematopoietic growth factors

Hematopoietic growth factors (e.g. G-CSF) may be administered during the entire study according to the American Society of Clinical Oncology (ASCO), EORTC, and ESMO guidelines, but are recommended in case of neutropenia CTC grade 4, even as prophylaxis for the following cycles.

9.2.3 Infections prophylaxis

For all patients
Prophylaxis of pneumocystis jirovecii-pneumonia (PCP) is recommended until least during induction treatment, e.g. with co-trimoxazole (trimethoprim/sulfamethoxazole 80/400mg or 160/800 mg, either 1 tablet 3x/week [Mo/Wed/Fr] or 2 tablets 2x/week [Mo/Thu] or according to standard institutional practice). In case of allergy or bone marrow insufficiency due to previous chemotherapy or other myelotoxicity, prophylactic use of an aerosolized formulation of pentamidine (inhalation by nebulizer once monthly) instead of cotrimoxazole should be considered.
PCP-prophylaxis as outlined above is also recommended for patients in arm B during cycle 1-12 after reinitiation of therapy.

Antiviral and antifungal prophylaxis may be given at the discretion of the investigator. Particularly in patients with history of previous HSV infection prophylaxis with aciclovir is recommended. However, caution should be made regarding possible drug-drug-interactions with ibrutinib and venetoclax. (also see 9.5)

9.2.4 Management of Decrease in Spermatogenesis

Venetoclax may cause a decrease in spermatogenesis. Male subjects should be considering preservation of fertility by banking sperm before initiating treatment with venetoclax.

9.2.5 Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animals, venetoclax may cause embryo-fetal harm when administered to a pregnant woman. In an embryo-fetal study conducted in mice, administration of venetoclax to pregnant animals at exposures equivalent to that observed in patients at the recommended dose of 400 mg daily resulted in post-implantation loss and decreased fetal weight. There are no adequate and well-controlled studies in pregnant woman using venetoclax. Advise females of reproductive potential to avoid pregnancy during treatment. If venetoclax is used during pregnancy or if the patient becomes pregnant while taking venetoclax, the patient should be apprised of the potential hazard to the fetus.
There are no adequate and well-controlled studies of ibrutinib in pregnant women. Based on findings in animals, ibrutinib may cause fetal harm when administered to pregnant women. Based on findings in animal trials, ibrutinib is teratogenic and may cause fetal harm such as postimplantation loss, increased visceral malformations, increased skeletal malformations or decreased fetal weights. No teratogenicity events have been reported from the available clinical trials. Therefore ibrutinib should not be used during pregnancy. Women of child-bearing potential must use highly effective contraceptive measures while taking ibrutinib. Those using hormonal methods of birth control must add a second barrier method. Women should avoid becoming pregnant while taking ibrutinib and for up to 3 months after ending treatment. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. The time period following treatment with ibrutinib when it is safe to become pregnant is unknown.

9.2.6 Immunization

Do not administer live attenuated vaccines prior to, during, or after treatment with venetoclax until B-cell recovery occurs. The safety and efficacy of immunization with live attenuated vaccines during or

following venetoclax therapy have not been studied. Advise patients that vaccinations may be less effective.

9.3 Ibrutinib maintenance treatment

After 15 cycles of ibruinib/venetoclax patients will be divided into three groups.

- Patients not reaching MRD negativity continue ibrutinib treatment until toxicity or progression (non-randomized patients)

Patients achieving MRD negativity after cycle 12 (PB) and at day 15 of cycle 15 (PB and BM), are randomized 1:2 between:

- Continuous ibrutinib treatment until toxicity or progression (**Arm A**)
- Treatment free observation. (**Arm B**)

Maintenance treatment (**NOT** for patients in arm B)

Agent	**Dose/day**	**Route of administration**	**Cycle**	**Days**
Ibrutinib	420 mg	Orally	1-until progression	1-28

9.4 Reinitiation of therapy for patients randomized to arm B

Patients randomized to Arm B will get reinitiation of therapy during the observation period in case of:

- progression according to IWCLL criteria or
- MRD≥10^{-3} (PB) and at least one month later MRD ≥10^{-2} (PB).

Treatment reinitiation will be as follows:

Venetoclax ramp up as outlined below for cycle 1, day 1 until day 28 after reinitiation, thereafter 400 mg daily (4 tablets. at 100 mg) until 12 cycles of 28 days (from reinitiation of ibrutinib).

Ibrutinib will be administered as a daily oral dosage of 420 mg (3 x 140mg) starting on day 1 of cycle 1 until:

1.) Progressive disease (patients not reaching any response (CR/PR/SD) according to IWCLL critera as assessed by the local investigator after 3 cycles of reinitiated therapy are considered as progressive disease and will go off protocol treatment)

or

2.) unacceptable toxicity, whatever occurs first

The continuous daily administration with a slow dose escalation of venetoclax starts on cycle 1 day 1.

Agent	Dose/day	Route of administration	Cycle	Days
Ibrutinib	420 mg	Orally	1-until progression	1-28
Venetoclax	20 mg	Orally	1	1-7
Venetoclax	50 mg	Orally	1	8-14
Venetoclax	100 mg	Orally	1	15-21
Venetoclax	200 mg	Orally	1	22-28
Venetoclax	400 mg	Orally	2-12	1-28

The same precautions regarding TLS are to be taken as described in section 9.2.1.

9.5 Co-intervention

9.5.1 Prohibited and cautionary Therapy

Patients who require the use of any of the prohibited therapies listed below will be discontinued from study treatment.

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy
- Radiotherapy
- Immunotherapy
- Any therapies intended for the treatment of leukemia whether FDA-approved or experimental (outside of this study)
- Anti-retroviral medications
- Warfarin and other vitamin K antagonists.

Please note: Patients being treated with NOACs, Ascal and NSAIDs can be included, but must be properly informed about the potential risk of bleeding under treatment with ibrutinib.

Live-virus vaccines should not be given within 28 days prior to the initiation of study treatment, at any time during study treatment, or following study treatment until B-cell levels have returned to normal.

Use of the following concomitant medications is prohibited from 7 days prior to initiation of and during study drug administration:

- Steroid therapy for anti-neoplastic intent, with the exception of inhaled steroids for asthma, topical steroids, steroids up to 25 mg of prednisolone daily to control autoimmune phenomenon's, or replacement/stress corticosteroids.
- Strong CYP3A inhibitors (see appendix K for examples).

Concomitant medications that fall into the categories below could potentially lead to adverse reaction(s) and should be considered cautionary (except where noted). If a potential study patient is taking any of the medications in the categories described below, the investigator will assess and document the use of medications known or suspected to fall in the following medication categories:

- Moderate CYP3A inhibitors. Consider alternative agents with less CYP3A inhibition. If a moderate CYP3A inhibitor must be used, reduce the ibrutinib dose to 140 mg and reduce the venetoclax dose by at least 50% for the duration of the inhibitor use. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.
- Moderate and strong CYP3A inducers. Consider alternative treatments with less CYP3A induction.
- Weak CYP3A inhibitors and inducers
- P-gp substrates
- BCRP substrates
- OATP1B1/1B3 substrates
- P-gp inhibitors
- BCRP inhibitors
- OATP1B1/B3 inhibitors
- A sample list of prohibited and cautionary medications that fall into these categories is provided in Appendix K. It is not possible to provide a complete list of medications that fall into these categories, so if in question, please refer to the appropriate product label.

Management of Potential Ibrutinib and Venetoclax Interactions with CYP3A Inhibitors

	Venetoclax		**Ibrutinib**
Inhibitors	**Initiation and Ramp-Up Phase**	**Steady Daily Dose (After Ramp-Up Phase)**	**At any time**
Strong CYP3A inhibitor	Prohibited		
Moderate CYP3A inhibitor	Avoid inhibitor use, consider alternative agent. If must be used, reduce the venetoclax dose by at least 50%		Avoid inhibitor use, consider alternative agent. If must be used, reduce ibrutinib to 140 mg

- In addition to these prohibited and cautionary medications, subjects should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruits.

9.6 Investigational Medicinal Product Ibrutinib

9.6.1 Summary of known and potential risks

- Lymphocytosis

Upon initiation of treatment, a reversible increase in lymphocyte counts (i.e., ≥ 50% increase from baseline and above absolute count 5 x10^9/l), often associated with reduction of lymphadenopathy and splenomegaly, has been observed in most patients (69% to 75%) with CLL/SLL treated with single agent ibrutinib. This observed lymphocytosis is a treatment related effect and should not be considered as progressive disease in the absence of other clinical findings of progression. Lymphocytosis typically occurs during the first weeks of ibrutinib therapy and usually resolves within a median of 19 weeks in patients with CLL, although up to 25% of patients in single therapy studies have been reported to have prevalent lymphocytosis up to one year after start of treatment.

- Leukostasis

Cases of leukostasis as a consequence of treatment related lymphocytosis have been reported in patients with CLL treated with ibrutinib. A high number of circulating lymphocytes (> 400 x10^9/l) may confer increased risk. In case of rapidly rising WBC and symptom indicating leukostasis (e.g. bleeding tendency, shortness of breath, dizziness, blurred vision) consider temporary holding of ibrutinib and suitable intervention including hydration and leukaferesis.

- Bleeding-related events

Ibrutinib inhibits thrombocyte aggregation and has been associated with a tendency of minor bleeding (petechie, ecchymosis and epistaxis) in up to 50% of patients. There have been reports of major hemorrhagic events (gastro-intestinal [GI]-bleeding, intracranial hemorrhage, hematuria) in up to 6% of patients, some fatal.
Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib. Dietary supplements such as fish oil and vitamin E preparations should be avoided. Use of ibrutinib in patients requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied.
Ibrutinib should be held at least 3 to 7 days pre- and post-surgery, depending upon the type of surgery and the risk of bleeding.

- Cardiovascular events

Atrial fibrillation and atrial flutter have been commonly (>1% and <10%) reported in patients treated with ibrutinib, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, light-headedness) or new onset of dyspnea should be evaluated clinically and if indicated have an ECG performed. For

atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the dose modification guidelines.
In a previous phase-II trial, ibrutinib was found to shorten the QTcF interval (QTc interval according to Fridericas formula) in ECG studies; the mechanism and clinical relevance of this observation is unknown. Thus, patients with other risk factors for a QTc shortening or a known short QT syndrome should only be treated with ibrutinib after careful consideration of risks and benefits.
Hypertension of mild-moderate degree, usually isolated systolic hypertension, has been reported in up to one third of patients treated with single dose ibrutinib.

- Diarrhea

Diarrhea is the most frequently reported non-hematologic adverse event (AE) with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting and constipation. These events are rarely severe and are generally managed with supportive therapies including anti-diarrheals and anti-emetics. Patients should be monitored carefully for gastrointestinal AEs and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies of diarrhea. Should symptoms be severe or prolonged, ibrutinib treatment should be modified as described in the dose modification guidelines.

- Rash

Rash has been commonly reported in patients treated with either single agent ibrutinib or in combination with chemotherapy. Most rashes were mild to moderate in severity. One case of Stevens-Johnson Syndrome (SJS), with a fatal outcome, was reported in a patient with CLL. Patients should be closely monitored for signs and symptoms suggestive of SJS. Patients receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events erythema, such as urticaria, angioedema have been reported.

9.6.2 Preparation and labeling

Ibrutinib is available in capsules of 140 mg.
Ibrutinib will be shipped to trial sites in containers labeled as an Investigational Medicinal Product.
Ibrutinib will be prepared and labeled in compliance with GMP and other applicable regulatory requirements.

9.6.3 Storage and handling

Ibrutinib should be stored and handled in accordance with the instructions in the Investigator's Brochure. The investigational medicinal product should be stored in such a manner that accidental loss or destruction or access by an unauthorized person is prevented.

9.6.4 Study drug supply

The sponsor will arrange delivery of ibrutinib to trial sites. No investigational medicinal product will be shipped until the sponsor has verified that all regulatory required documents and approvals for the site are available.

9.6.5 Drug accountability

The investigator, or a pharmacist or other appropriate individual who is designated by the investigator, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial patients (if applicable). Investigators should maintain records that document adequately that the patients were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor. The investigator should also collect and count remaining medication and empty boxes of medication to check that the patient has taken the assigned dose.

9.6.6 Study drug return and destruction

Partially used investigational medicinal product should not be redispensed to either the same or another patient after it has been returned.
The trial site should destroy used or partially used study drug containers after drug accountability records have been completed. Destruction should be documented.
At the end of study, when all patients have stopped protocol treatment, for ibrutinib, complete drug reconciliation per batch should be available at the site for verification by HOVON (as appropriate) in order to allow drug destruction or return procedure. Both the unused and expired ibrutinib must be destroyed, upon authorization of the sponsor, according to local regulations and procedures, and a copy of the destruction form must be returned to the HOVON Data Center (as appropriate).

9.7 Investigational Medicinal Product Venetoclax

Venetoclax is a bcl-2-antagonist that is specific for bcl-2 and induces death in bcl-2 dependent tumor cells. Venetoclax has been shown to be potent in cell-killing and displaying anti-tumor effects in CLL cells. It is co-developed for the treatment of hematological and immunological diseases by the pharmaceutical companies F. Hoffmann-La Roche LTD and AbbVie Inc.
For detailed information on venetoclax please see the current version of the investigator´s brochure.

9.7.1 Summary of known and potential risks

As of November 28, 2015 a total of 935 CLL/SLL patients have been treated in venetoclax oncology clinical program: 336 patients have received venetoclax monotherapy and 599 have received venetoclax in combination with other agents including rituximab, obinutuzumab, and bendamustine. The most common adverse events (incidence >20%) reported for all subjects in CLL/SLL monotherapy studies were diarrhea (40.2%), neutropenia (38.7%), nausea (37.8%), fatigue (27.4%), upper respiratory tract infection (26.5%), and anemia (25.3%). The most common Grade 3 and above adverse events were neutropenia (36.0%), anemia (14.6%), and thrombocytopenia (13.1%). The most common serious adverse events were pneumonia (5.7%), febrile neutropenia and malignant neoplasm progression (5.7% each). The safety profile in combination studies is consistent with that observed in monotherapy studies and with known toxicity profile of combination agents.
Additional safety and efficacy data are described in detail in the venetoclax Investigator Brochure.

- Tumor lysis syndrome

TLS is considered an important identified risk and is predominantly seen in CLL with high tumor burden. The initiation of treatment with venetoclax can cause rapid reduction in size of tumor (debulk) and may pose a risk of TLS. Prophylactic measures developed and used in previous clinical studies with venetoclax single therapy and in combination, as outlined in appendix G has been evident to greatly reduce the risk of TLS.
The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Reduced renal function (CrCl <80 mL/min) further increases the risk. Patients should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and anti-hyperuricemics. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax and at each dose increase. Monitor blood chemistries and manage abnormalities promptly. Interrupt dosing if needed. Employ more intensive measures (intravenous hydration, frequent monitoring, and hospitalization) as overall risk increases
For details regarding risk factors, prophylactic measures and handling of TLS see appendix G.

- Gastrointestinal symptoms

Diarrhea and nausea has been registered as relatively common side effects in previous studies albeit the majority of events being relatively mild (grade 2 or lower). The incidence seems to be higher in singe agent studies with reported diarrhea (all grades) in 40% and nausea in 38% of subjects. In contrast, in combination studies the incidence of all grade events to be reported, have been 13% for diarrhea and 12% for nausea.

- Neutropenia

Grade 3 or 4 neutropenia occurred in 41% (98/240) of patients treated with venetoclax in the pivotal previously treated CLL 17p deletion study. Monitor complete blood counts throughout the treatment period. Interrupt dosing or reduce dose for severe neutropenia. Consider supportive measures including antimicrobials for signs of infection and use of growth factors (e.g., G-CSF).

- Immunization

The safety and efficacy of immunization with live or attenuated viral vaccines during or following venetoclax therapy have not been studied. Immunization with live virus vaccines is not recommended during treatment and thereafter until B-cell recovery.

9.7.2 Preparation and labeling

Venetoclax is available in tablets of 10, 50 or 100 mg.
Venetoclax will be shipped to trial sites labeled as an Investigational Medicinal Product. Venetoclax will be prepared and labeled in compliance with GMP and other applicable regulatory requirements.

9.7.3 Storage and handling

Venetoclax should be stored and handled in accordance with the instructions in the Investigator's Brochure. The investigational medicinal product should be stored in such a manner that accidental loss or destruction or access by an unauthorized person is prevented.

9.7.4 Study drug supply

The sponsor will arrange delivery of venetoclax to trial sites. No investigational medicinal product will be shipped until the sponsor has verified that all regulatory required documents and approvals for the site are available. Venetoclax will be dispensed to subjects in blister packs through the dose ramp up period, and in bottles at each subsequent visit.

9.7.5 Drug accountability

The investigator, or a pharmacist or other appropriate individual who is designated by the investigator, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial patients (if applicable). Investigators should maintain records that document adequately that the patients were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor. The investigator should also collect and count remaining medication, empty boxes and blisters of medication to check that the patient has taken the assigned dose.

9.7.6 Study drug return and destruction

Partially used investigational medicinal product should not be redispensed to either the same or another patient after it has been returned.
The trial site should destroy used or partially used study drug containers after drug accountability records have been completed. Destruction should be documented.
At the end of the trial or after expiry of the product unused investigational medicinal product should be returned to AbbVie

10 Study procedures

10.1 Time of clinical evaluations

- Before enrollment: within 28 days before registration, as specified in 10.2
- After each cycle until end of cycle 15
- Weekly during venetoclax ramp up in cycle 3
- After cycle 15: every 3 months for 2 years and every 4 months for the 3rd year, whether in the maintenance or the treatment cessation group, until month 51 (15 months + 3 years)
- Thereafter every 6 months until 7 years after registration or until progression, whatever comes first.

10.1.1 Follow up

All patients will be followed until 7 years after registration.

To be able to collect long term follow up data until patient`s death after the end of this study, inclusion in a country specific registry (e.g. the Danish National CLL register or the Dutch Pharos registry or registry of the other Nordic countries) is strongly recommended. For this purpose, each patient will be informed about the importance of long term follow-up data and asked for his/her consent to the long term follow-up within an appropriate registry. For patients with a written informed consent for the registry, data for overall survival, late toxicities such as secondary malignancies, further treatments and the course of the disease will be collected after the end of the trial.

10.2 Required investigations

Table 10.2.1 Required investigations at entry, during treatment and during follow up

	At entry[1]	After each induction cycle	Extra at end of cycle 2	Cycle 3 day 8 and 15 Cycle 4 day1	Extra at end of cycle 3 and 6	Extra at end of cycle 9	Extra at end of cycle 12	Extra at day 15 of cycle 15[9]	After cycle 15: Every 3 months for 2 years, every 4 months for 3rd year (= until 51 months)	Extra at month 27	After month 51[2]	Progressive disease
Informed consent	X											
Medical history	X											
Adverse events	X	X							X		X	
Physical examination	X	X							X		X	X
CIRS / CCI	X											
Rapid Report Form					X	X	X					
Binet stage	X											
TLS risk category (appendix G)	X		X[4]									
Lab tests												
Hematology	X	X							X		X	X
Blood chemistry	X	X							X		X	
Additional chemistry	X											
Virology	X											
Bone marrow												
Bone marrow biopsy								X		X		X
(PET)-CT scan[5]	X		X[6]					X		X		X
(Clinical) response evaluation					X[7]	X	X		X	X	X	X
Quality of Life[7]	X								X[8]		X[8]	
Pregnancy test	X											

1. Laboratory tests should be performed within 2 weeks prior to registration flow and CT can be maximally 42 days old
2. Every 6 months until 7 years after registration or until progression, whatever comes first.
3. The form needs to be filled out every 3 months for as long as the patient is on ibrutinib treatment
4. In patients with high risk for TLS or CrCL 30-50 ml/min
5. PET only in case of suspected transformation.

6 CT scan after cycle 2 in patients with high risk for TLS or CrCL 30-50 ml/min

7 Only at end of cycle 3

8. Quality of life at entry, after induction cycle 15 and at 6 months, 1, 2 and 3 years after start maintenance/observation.

9. MRD and CT should be done at day 15 cycle 15 to have results available to assess SD, PR, CR, MRD negativity at end of cycle 15.

Table 10.2.2 .Collection for central lab.

	At entry	After each induction cycle	Extra at end of cycle 2	Cycle 3 day 8 and 15 Cycle 4 day1	Extra at end of cycle 3 and 6	Extra at end of cycle 9	Extra at end of cycle 12	Extra at day 15 of cycle 15[4]	After cycle 15: Every 3 months for 2 years, every 4 months for 3rd year (= until 51 months)	Extra at month 27	After month 51	Progressive disease
Mutational status[1] PB	X											
Serum parameters	X											
FISH/CGH and NGS PB	X											X
MRD (flowcytometry)												
PB	X		X			X	X	X	X[2]	X[2]		X
BM aspirate								X		X		X
Side studies												
PB	X		X	X		X	X	X	X	X		X
BM aspirate								X		X		X
Lymph node biopsy												X[3]

1 If not performed earlier

2 Patients becoming MRD pos. retest 1 month later (only during observation)

3 If accessible lymph node is present

4. MRD and CT should be done at day 15 cycle 15 to have results available to assess SD, PR, CR, MRD neg at end of cycle 15.

Table 10.2.3 Required investigations during/after reinitiation treatment[1]

	Before start of reinduction treatment	Extra at end of cycle 3	Extra at end of cycle 12	After cycle 12: Every 3 months for 2 years, every 4 months for 3rd year	Extra at 1 year after cycle 12	After month 51[2]	Progressive disease
Medical history	X			X		X	
Adverse events	X			X		X	
Physical examination	X			X		X	X
TLS risk category (appendix G)	X						
Lab tests							
Hematology	X			X		X	X
Blood chemistry	X			X		X	
Additional chemistry	X						
Bone marrow							
Bone marrow biopsy			X		X		
(PET)-CT scan	X		X		X		X
(Clinical) response evaluation		X	X		X	X	X
Quality of Life[2]	X						
CENTRAL LAB							
Flowcytometry PB (or BM if PB not done)							X
FISH/CGH and NGS PB							X
MRD (flowcytometry)							
PB			X	X	X		X
BM aspirate			X		X		X
Side studies							
PB			X		X		X
BM aspirate			X		X		X
Lymph node biopsy							X[3]

1 Note that the required investigations from month 27 as mentioned in table 10.2.1 are required for all patients

2. Follow the original schedule: quality of life at 1, 2 and 3 years after start maintenance/observation
3. If accessible lymph node is present

Medical history

Standard medical history, including:
- B symptoms
- Concomitant diseases
- Concomitant medications
- Adverse events

At entry
- Proven CLL or SLL by minimal required markers (CD19/CD20/CD5/CD23/Kappa/Lambda)
- Cumulative Illness Rating Score (see appendix F)
- Binet classification (see appendix A)
- Charlson comorbidity index (CCI)

Physical examination

Standard physical examination including body weight and height, with special attention for:
- Vital signs (Blood pressure, body temperature, pulse)
- WHO performance status (see appendix C)
- Palpable lymph nodes, spleen and liver sizes

Hematology

- Hemoglobin
- Leukocyte count
- Differential count
- Platelets count

At entry and on indication:
- DAT (direct antiglobulin test/Coombs test)
- PT
- PTT

Blood chemistry

- Creatinine clearance (calculated see appendix E)
- Bicarbonate
- Haptoglobin
- AST or ALT
- Bilirubine
- LDH

Special attention to tumor lysis lab according to appendix G. Please see appendix G for full details.

Additional blood chemistry at entry
- Glucose
- Total protein
- Albumin
- IgG
- IgM
- IgA
- Monoclonal protein
- β-2 microglobulin

Virology

- Hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc).
- Hepatitis C virus (HCV), if positive: HCV- (RNA)
- Human immunodeficiency virus (HIV) positive patients;

Bone marrow examination . Bone marrow pathology will be performed locally. Side studies will be performed centrally by bone marrow aspirate.

(PET-)CT scan

A (high resolution PET-)CT scan of neck, thorax, abdomen and pelvis and reported according to Cheson criteria. CT scan to determine lymphnode size(s) is obligatory to evaluate CR.

10.3 Storage for future studies

In addition to these investigations, all patients will be asked for informed consent to store biological material for future studies. Material for future investigations will be shipped to the central laboratory of the Academic Medical Center Amsterdam and/or Copenhagen University Hospital. More details can be found in the study lab manual. All materials are anonymized and stored for a maximum of 15 years after end of study, after which the samples will be destroyed.

10.4 Response evaluation

Response will be evaluated without CT (clinical response) at cycle 3, 9, and 12, after cycle 15 every 3 months for 2 years, and every 4 months for the 3rd year(until 51 months), and month 51 Response will be evaluated with CT at cycle 15 and month 27, and in case of suspected progressive disease. Response will be determined according to the definitions of response in the IWCLL updated NCI-WG guidelines [Hallek et al., 2008] For a tabular summary of all criteria of response definition in CLL patients see Appendix B.

10.5 Quality of Life assessment

Health related outcome parameters will be collected in this study, i.e. quality of life (QoL).
QoL will be assessed at entry, after 15 induction cycles and at 6 months, 1, 2 and 3 years after start maintenance/ observation.
The quality of life measurements will be continued after the patient is off protocol treatment, but discontinue when progression has been observed.

- EORTC QLQ-C30 questionnaire
- EORTC QLQ-CLL16

Collection of the QoL questionnaires will be performed in the following manner:
A QoL coordinator will be assigned in each participating center. The QoL questionnaire collection is left to the responsibility of the QoL coordinator. As soon as a patient is registered at the HOVON Data Center (HDC) the QoL coordinator is notified by email. Patient study number, (partial) date of birth and date of registration are mentioned in this mail.
The patient will be provided a paper print out of the questionnaire.
The baseline questionnaire will be handed or sent to the patient by the QoL coordinator. At the time points mentioned in the beginning of this section, the coordinator will hand over the questionnaire at the correct date.
The QoL coordinator will collect the questionnaire from the patient and will send them to the HOVON Data Center.

The questionnaires are described in appendix L.

10.6 Minimal Residual Disease

Minimal residual disease (MRD) levels will be examined by quantitative highly sensitive flow cytometry (MRD flow) in the peripheral blood and in the bone marrow at:

- The Department of Hematology, Rigshospitalet, Copenhagen University Hospital for the Nordic sites
- The Academic Medical Center, Amsterdam laboratory of Hematology for the HOVON sites

MRD will be quantified by six-color flow cytometry with a sensitivity of at least 10^{-4} as previously validated against ASO-primer realtime quantitative IGH-PCR X. The method utilizes an international standardized approach as mentioned Rawstron AC, Fazi C, Agathangelidis A, et al. .
MRD values will be categorized into three different MRD levels: low ($<10^{-4}$, i.e. less than 1 CLL cell per 10,000 leukocytes), intermediate ($\geq 10^{-4}$ and $<10^{-2)}$ and high ($\geq 10^{-2}$). MRD negativity is defined as $<10^{-4}$ and patients are defined as MRD negative if their disease burden is below this threshold at one executive timepoint.
MRD assessments of peripheral blood are to be performed at screening (for baseline characterization of the individual CLL clone). Further MRD assessments are to be performed:

- PB after cycle 2, 9, 12, at day 15 of cycle 15 and at month 27 for all patients;
- Every 3 months for 2 years and every 4 months for the 3rd year after cycle 15 for patients achieving MRD negativity
    - Patients becoming MRD pos. retest 1 month later
    - Bone marrow at day 15 of cycle 15 and at month 27

For assessment of MRD, a first pull sample is needed.The results of the MRD measurements will be sent to the local investigator **within 1 week**.

Further details about MRD logistics can be found in the labmanual.

10.7 Central review

10.7.1 Cytological and immunophenotype review

The diagnosis is confirmed centrally according to IWCLL criteria and the minimal requirements for diagnosis of CLL established within the ERIC collaboration.
For the final analysis of the study, the local immunophenotyping can be compared to the central flowcytometry results at baseline that are a prerequisite for subsequent MRD measurements.

10.8 Side studies

The following biomarker / side studies will be performed. These studies will provide significant insight into the effect of both intraclonal diversity and tumor microenvironmental factors on therapeutic responses:

1. Next Generation Sequencing (NGS) will be performed at baseline and at progression for recurrent mutations in CLL in alignment with the pan-European effort by ERIC. Bioinformatics, NGS platforms and statistics pipelines are present at Amsterdam Medical Center and Copenhagen University Hospital.
2. Viable frozen primary CLL cells are collected at the indicated time points in central biobanks in Amsterdam and Copenhagen along with preparations for serum/plasma, DNA, RNA etc. for translational studies that will focus on aspects that reflect the (patho)biology of the primary CLL cells and microenvironment and provide means for further tailoring of CLL treatment.

Further details about the side studies can be found in the lab manual.

11 Withdrawal of patients or premature termination of the study

11.1 Withdrawal of individual patients from protocol treatment

Patients should be withdrawn from protocol treatment if any of the following criteria for withdrawal are met:

- Death

- Progressive disease after cycle 6 of induction treatment
  In case of suspected progressive disease according to IWCLL at or after start of cycle 6, response assessment will be performed and only patients with at least SD will continue on trial; patients with progressive disease will go off protocol treatment.
  In the case of signs of progression before start of cycle 6 i.e. Richter's, the local investigator must make a full diagnostic work up to assess whether the patient should go off protocol treatment due to progression.
- Progressive disease after at least 3 cycles of reinitiation treatment
- If, for whatever reason, one or both drugs are not given for more than 56 consecutive days
- If the patient receives systemic treatment for another malignancy during the protocol treatment

Patients can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can also decide to withdraw a patient from protocol treatment for other reasons than the criteria described above. Examples of such reasons for withdrawal from protocol treatment are:

- Excessive toxicity
- Refusal of patient to continue protocol treatment
- No compliance of the patient: patient is unable or unwilling to adhere to the treatment schedule and/or procedures required by the protocol

Patients who are withdrawn from protocol treatment will receive medical care according to local practice.

11.2 Follow up of patients withdrawn from protocol treatment

Patients who are withdrawn from treatment for other reasons than death will be followed as described in section 10.2 for follow up. SAE information will be collected as described in section 12.3.

However, for patients who are withdrawn from treatment because in hindsight they did not fulfill the eligibility criteria (see section 8.1) at time of enrolment, data will be collected until 30 days after the last protocol treatment given. SAE information will be collected as described in section 12.3

11.3 Withdrawal of informed consent

If a patient states he or she withdraws their consent to participate in the trial, the investigator should attempt to verify the patient's intent and record this in the patient's medical file:

- The patient can refuse further treatment and/or procedures according to protocol, while still consenting with further follow up data collection.
- The patient can refuse further treatment and/or procedures according to protocol, and withdraw consent for further follow up data collection.
- The patient can refuse further treatment and procedures according to protocol, withdraw consent for further follow up data collection and withdraw consent to use any data in the trial.

If the patient's intent is to withdraw consent for further data collection or to withdraw consent to use his or her data in the trial, the investigator should inform the HOVON Data Center so appropriate actions can be taken.
If the patient's intent cannot be verified, further follow up data will be collected for this patient as described in 10.2 for follow up.

11.4 Premature termination of the study

The sponsor may decide to terminate the study prematurely based on the following criteria:

- ♦ There is evidence of an unacceptable risk for study patients (i.e. safety issue);
- ♦ There is reason to conclude that continuation of the study cannot serve a scientific purpose following confirmation of the DSMB.
- ♦ The DSMB recommends to end the trial based on viable arguments other than described above.

The sponsor will promptly notify all concerned investigators, the Ethics Committee(s) and the regulatory authorities of the decision to terminate the study. The sponsor will provide information regarding the time lines of study termination and instructions regarding treatment and data collection of enrolled patients.

12 Safety

12.1 Definitions

Adverse event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Adverse event of special interest (AESI)

Atrial fibrillation and bleeding events are adverse events of special interest in this trial, and will be actively requested for.

Serious adverse event (SAE)

A serious adverse event is defined as any untoward medical occurrence or effect that at any dose:

- Results in death
- Is a life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- Requires hospitalization or prolongation of an existing hospitalization
- Results in significant or persistent disability or incapacity
- Is a congenital anomaly or birth defect
- Is an *important medical event* (i.e. important adverse events that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the above characteristics/consequences, including suspected transmission of infectious agents by a medicinal product).

Note: TLS is *an important medical event* in this trial which must be reported as SAE.

Suspected unexpected serious adverse reaction (SUSAR)

All **suspected** Adverse Reactions which occur in the trial and that are both **unexpected** and **serious**. Suspected adverse reactions (AR) are those AEs of which a reasonable causal relationship to any dose administered of the investigational medicinal product and the event is suspected. Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for an authorized medicinal product).

12.2 Adverse event

12.2.1 Reporting of adverse events

Adverse events will be reported from the first study-related procedure until 30 days following the last dose of any drug from the protocol treatment schedule or until the start of subsequent systemic therapy for the disease under study, if earlier.
Adverse events occurring after 30 days should also be reported if considered at least possibly related to the investigational medicinal product by the investigator.
Adverse events have to be reported on the Adverse Events CRF. Adverse events will be scored according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (see appendix D).
Pre-existing conditions will be collected on the baseline concomitant diseases CRF, i.e. active (symptomatic) diseases of CTCAE grade $\geq$ *2* diseases under treatment, chronic diseases and long term effects of past events as present at the time of baseline assessment.

All adverse events have to be reported, **with the exception of**:

- A pre-existing condition that does not increase in severity; the pre-existing condition should be reported on the baseline concomitant diseases CRF
- AE's of CTCAE grade 1
- Abnormal laboratory values that have been recorded as being not clinically significant by the investigator in the source documents
- Relapse/Progression of the disease under study; complications as a result of disease progression remain reportable adverse events.

AESI must be filled out on a separate CRF.

12.2.2 Follow up of adverse events

All adverse events will be followed clinically until they have been resolved, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
On the AE CRF only the incidence of adverse events is recorded. Any ongoing adverse event that increases in severity is to be reported as a new adverse event on the CRF. Other follow up information is not collected on the CRF.

12.3 Serious Adverse Events

12.3.1 Reporting of serious adverse events

Serious Adverse Events (SAEs) will be reported from the first study-related procedure until 30 days following the last dose of any drug from the protocol treatment schedule or until the start of subsequent systemic therapy for the disease under study, if earlier.
Serious adverse events occurring after 30 days should also be reported if considered at least possibly related to the investigational medicinal product by the investigator.
All cases of TLS must be reported as SAE.

SAEs must be reported to the HOVON Data Center by e-mail **within 24 hours** after the event was known to the investigator, using the SAE report form provided. This initial report should contain a minimum amount of information regarding the event, associated treatment and patient identification, as described in the detail in the instructions for the SAE report form. Complete detailed information should be provided in a follow-up report within a further 2 business days, if necessary.

The following events do not require to be reported as a serious adverse event:

- Relapse/Progression of the disease under study; **death or complications as a result of disease progression remain reportable serious adverse events**
- Hospitalization for protocol therapy administration. Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a serious adverse event.
- Hospitalization for diagnostic investigations (e.g., scans, endoscopy, sampling for laboratory tests, bone marrow sampling) that are not related to an adverse event. Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
- Prolonged hospitalization for technical, practical, or social reasons, in absence of an adverse event.
- Hospitalization for a procedure that was planned prior to study participation (i.e. prior to registration or randomization). This should be recorded in the source documents. Prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.

12.3.2 Causality assessment of Serious Adverse Events

The investigator will decide whether the serious adverse event is related to trial medication, i.e. any of the products from the protocol treatment schedule. The decision will be recorded on the serious adverse event report. The assessment of causality is made by the investigator using the following:

RELATIONSHIP	DESCRIPTION
UNRELATED	There is no evidence of any causal relationship
UNLIKELY	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
POSSIBLE	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
PROBABLE	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
DEFINITELY	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
NOT ASSESSABLE	There is insufficient or incomplete evidence to make a clinical judgment of the causal relationship.

12.3.3 Follow up of Serious Adverse Events

All serious adverse events will be followed clinically until they are resolved or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
Follow up information on SAE's should be reported monthly until recovery or until a stable situation has been reached. The final outcome of the SAE should be reported on a final SAE report.

12.3.4 Processing of serious adverse event reports

The HOVON Data Center will forward all SAE reports within 24 hours of receipt to the Principal Investigator, and the manufacturer of the investigational medicinal product(s).
The HDC safety desk will evaluate if the SAE qualifies as a suspected unexpected serious adverse reaction (SUSAR).
The Investigators Brochure will be used as a reference document for expectedness assessment.

Where reporting of SAE's to the Ethics Committee is required by national laws or regulations or by the procedures of the Ethics Committee, the HOVON Data Center will report those SAE's by means of a six-monthly SAE line listing.

12.4 Reporting Suspected Unexpected Serious Adverse Reactions

The HDC Safety Desk, on behalf of the sponsor, will ensure the reporting of any SUSARs to the Ethics Committees (EC), the Competent Authorities (CA), the manufacturer of the IMP and the investigators in compliance with applicable laws and regulations, and in accordance with any trial specific agreements between the sponsor and a co-sponsor or the manufacturer of the IMP.

Expedited reporting of SUSARs will occur no later than 15 days after the HOVON Data Center had first knowledge of the serious adverse event. For fatal or life-threatening cases this will be no later than 7 days for a preliminary report, with another 8 days for a complete report.
The manner of SUSAR reporting will be in compliance with the procedures of the Ethics Committees and Health Authorities involved.

12.5 Pregnancies

Pregnancies of a female subject or the female partner of a male subject, occurring while the subject is on protocol treatment or within 30 days following the last dose of any drug from the protocol treatment schedule, should be reported to the sponsor. Pregnancies must be reported to the HOVON Data Center by e-mail within 24 hours after the event was known to the investigator, using the pregnancy report form provided.

The investigator will follow the female subject until completion of the pregnancy, and must notify the sponsor of the outcome of the pregnancy within 5 days or as specified below. The investigator will provide this information as a follow-up to the initial pregnancy report. If the outcome of the pregnancy meets the criteria for classification as a SAE (i.e., spontaneous or therapeutic abortion, stillbirth, neonatal death, or congenital anomaly - including that in an aborted fetus), the investigator should follow the procedures for reporting SAEs. In the case of a live "normal" birth, the sponsor should be informed as soon as the information is available. All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the investigator suspects is related to the *in utero* exposure to the investigational medicinal product(s) should also be reported.

The investigator is encouraged to provide outcome information of the pregnancy of the female partner of a male subject, if this information is available to the investigator and the female partner gives her permission.

12.6 Second Primary Malignancies

Second primary malignancies (SPM) will be monitored as events of interest and must be reported as SAEs. This includes any second primary malignancy, regardless of causal relationship to any study drug, occurring at any time for the duration of the study, from the time of signing informed consent until 5 years after registration in the trial or until completion of maintenance therapy for patients who are still on maintenance at 5 years after registration.
Events of second primary malignancy are to be reported using the SAE report form and must be considered an “Important Medical Event” even if no other serious criteria apply. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (e.g. pathology report).
A SAE form should be filled out and send to HOVON Data Center as is described in section 12.3.1. SPM must also be documented in the other appropriate page(s) of the CRF (e.g. Adverse Event Form and Follow up Form).

12.7 Reporting of safety issues

The sponsor will promptly notify all concerned investigators, the Ethics Committee(s) (ECs) and the regulatory authorities of findings that could affect adversely the safety of patients, impact the conduct of the trial, increase the risk of participation or otherwise alter the ECs approval to continue the trial. In the occurrence of such an event the sponsor and the investigators will take appropriate urgent safety measures to protect the patients against any immediate hazard. The local investigator will inform the patients and local ethics or review committees according to hospital policy. The sponsor will inform any other parties that are involved in the trial.

12.8 Annual safety report

The sponsor will submit once a year a safety report to the ECs and Competent Authorities of the concerned Member States. The first report is sent one year after the first approval date of the trial. Subsequent reports are sent annually until end of trial. The content of the annual safety report will be according to the EU guidance document ‘*Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use’.*

12.9 Data Safety and Monitoring Board (DSMB)

The DSMB will advise the Principal Investigator, co-investigators and the chair of the working group in writing about the continuation of the trial. The DSMB will review the general progress and feasibility of the trial, the quality and completeness of the data, adverse events and safety, The DSMB will consider if there is any concern regarding the safety and well-being of trial subjects or regarding the scientific validity of the trial results. The DSMB will base its advice on the reports provided by the statistician. The DSMB is free to take into consideration external information, such as the (interim) results of other trials or literature reports.
The DSMB consists of at least three members, with at least one statistician and two physicians. Details of the DSMB constitution and tasks are documented in the trial specific DSMB charter.

The DSMB will receive at least the following reports from the trial statistician for review:

- Interim analysis report (as described in 14.4.4)
- Annual safety data listing the incidence of (serious) adverse events, (serious) adverse reactions and SUSARs
- Annual progress data listing the number of enrolled patients and the status of data collection

The DSMB will meet or hold a telephone conference to discuss these reports.

12.10 Safety monitoring

The first 15 patients randomized to discontinue treatment (thus first 23 patients reaching MRD negativity, based on 1:2 randomization) will be evaluated by the investigators at time of MRD test after cycle 9, 12 and 15 and at 6 and 12 months for relapse or progression of CLL. Real time monitoring of the outcome for patients randomized for stopping treatment will continue based on the MRD results.
Also, an interim analysis on safety will be performed in the first 10 patients with CrCl between 30-50 ml/min.

In the event that a patient becomes MRD positive during the observation period, thorough written advice on the significance of the finding and further steps to be taken will be provided by the physicians at the central laboratory performing the MRD testing to the treating physician. This advice will contain information about the rationale for continuing within the protocol. Contact information to the physician at the central laboratory for further advice will be provided. Patients in the observation

arm becoming MRD positive ≥10^{-3} are retested one month later, if MRD positive at this time point ≥ 10^{-2}, treatment with ibrutinib and venetoclax is reinitiated as detailed in section 9.

12.11 Product Complaints

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e., any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

- **Product complaint procedure for Ibrutinib.**
  All initial PQCs must be reported to Janssen by the study-site personnel within 24 hours after being made aware of the event. If the defect is combined with a serious adverse event, the investigational staff must report the PQC to Janssen according to the serious adverse event reporting timelines within 24 hours of their knowledge of the event. A sample of the suspected product should be maintained for further investigation if requested by Janssen.
- **Product complaint procedure for venetoclax.**
  AbbVie contact details for reporting Product Complaints:
  Productklachten.ho.nl@abbvie.com.

Please also inform the HOVON Data Center of your complaint by fax (+31 (0)10 704 1028) or email (hdc@erasmusmc.nl). Note that product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to HOVON Data Center see section 12.3.1).

13 Endpoints

13.1 Primary endpoint

(Only considered for arm B of the study)

♦ Proportion of patients fulfilling the criteria for progression free survival (PFS) at 12 months after stopping therapy (27 months after starting treatment) for patients randomized to stop treatment. In this trial, reinitiated treatment due to MRD positivity will not be considered as progression, and symptomatic CLL according to IWCLL criteria within 12 months after randomization followed by reinitiation treatment resulting in a response (at least SD) before or at 12 months after randomization will neither be considered as progression.

13.2 Secondary endpoints

Secondary endpoints (for all treatment groups: MRD positive non-randomized patients, patients MRD negative after cycle 12 and at day 15 of cycle 15 randomized for ibrutininb maintenance (arm A) or observation (arm B):

- Minimal residual disease (MRD) at 12 months after stopping treatment (month 27) for patients randomized to stop of treatment.
- PFS of all study groups.
- Time to and number of patients reinitiating treatment
- Time to treatment failure after reinitiated treatment
- Time to next CLL treatment
- MRD after cycle 12 (PB), at day 15 of cycle15 (PB and BM) and at later time points in PB
- Overall survival (OS)
- Complete response (CR)/ Partial Response (PR)/ Stable disease (SD) after cycle 3, 9, 12, 15 and month 27 and month 51 (3 years after stopping treatment)
- Duration of response
- Safety parameters: Type, frequency, and severity of
  - adverse events (AEs) and
  - adverse events of special interest (AESI) and their relationship to study treatment
- Health-related quality of life (QoL) by EORTC QLQ-C30 and QLQ-CLL16 questionnaires
- Exploratory endpoints:
- Evaluation of relationship between various baseline markers and clinical outcome parameters
- Various markers at time of progression
- Correlation between MRD in BM and PB
- Correlation between MRD in BM and PFS/OS
- Correlation between MRD in PB and PFS/OS

14 Statistical considerations

This study is designed as a phase II study with upfront registration and a late randomization for patients who are MRD-negative at 12 and 15 cycles. The primary objective of the study is to evaluate in arm B the efficacy of ibrutinib + venetoclax (VI) in terms of PFS 12 months after stopping treatment for patients achieving MRD negativity after cycle12 and at day 15 of cycle 15 in previously treated patients with CLL (arm B). The patients in arm A and the non-randomized patients are only considered for secondary and exploratory endpoints, and no formal comparison between randomized patients are made.

14.1 Patient numbers and power considerations

Treatment arms will be analyzed separately, only observation arm (arm B) will be considered for the primary end point. Only patients who are MRD negative after induction (i.e. MRD negative at both cycle 12 and at day 15 of cycle 15) will be randomized 1:2 for ibrutinib until progression (arm A) versus observation arm (arm B). It is expected that 45% of the registered patients will be randomized, based on the hitherto reported MRD negativity rates for venetoclax monotherapy and combination therapy with rituximab and the reported preclinical data on synergy between venetoclax and ibrutinib. The power calculation is based on the observation arm, at least equal or even better PFS is expected for the patients randomized for ibrutinib until progression. Patients who are MRD positive continuing on maintenance ibrutinib are expected to have a lower PFS than MRD negative patients.
The observation arm B is considered valuable if the PFS at 12 months after randomization is at least 75%. A success rate of less than 60% is considered not valuable for further investigation (in Phase III setting); this assumption is based on a 1-year PFS of 60% for RR CLL patients treated with FCR for the PFS endpoint (Fornecker, Am J Hem, 2015). No interim analysis on the primary endpoint is planned. An A'Hern one-stage design is used for the sample size calculation.

- Let P_0 be the largest success rate which, if true, implies that the therapeutic activity is too low and therefore does not warrant further investigation,. In the present trial, P0 has been taken as 60%.
- Let P_1 be the smallest success rate which, if true, implies that the therapeutic activity is sufficiently high and therefore warrants further investigation in clinical trials. In the present trial, P_1 has been taken as 75%.

In order to reject the null hypothesis H_0: P = P0 in favor of the alternative hypothesis H_1: P = P_1 with power 1 - β= 0.80 (1-sided significance level α= 0.05), 62 (eligible) patients are required in maintenance treatment arm with observation until progression (and at least 44 patients progression free at 12 months after randomization).
Taken into account that two parallel maintenance treatment arms will be analyzed (randomized 1:2 ibrutinib vs observation), we need 93 patient in both maintenance arms together. Given that the percentage of patients expected not to achieve MRD-neg after induction is 55% 207 patients are needed, and to overcome dropout due to ineligibility, 230 patients will be registered in the trial.

14.2 Study population definitions

All main analyses will be according the intention to treat principle i.e. patients will be analyzed according to the treatment arm they were assigned to, regardless of whether they received any of the study treatment or not. However, patients initially registered and/or randomized but considered

ineligible afterwards based on information that should have been available before registration and/or randomization, whichever applicable, will be excluded from the respective analyses.

14.3 Alerting rules

Criteria to generate a safety report for discussion of the safety results with PI and DSMB are:

- An unacceptable profile or incidence rate of AE/ AESI revealed in this or any other study in which at least one of the investigational products of this trial is administered
- Any serious adverse events or adverse events of special interest occurring with 20% or higher frequency at any time point during the study
- Significant number of cases of death associated with the study treatment

14.4 Statistical analysis

14.4.1 Efficacy analysis

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

The primary efficacy endpoint is the investigator-assessed proportion of patients with PFS at month 27 in arm B, the ITT 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], appendix A), or death from any cause, whichever occurs first. Patients in the observation arm becoming MRD positive thus restarting treatment are still considered progression free, as long as they don't progress according to IWCLL criteria after start reinitiation treatment. If patients in the observation arm have clinical progression but achieve response within three months of reinitiating treatment, they are still considered progression free. For patients reinitiating therapy before 27 months according to the rules outlined above who have progressed according to IWCLL criteria before reinitiating treatment are allowed up to 3 months after reinitiating therapy to obtain response. These patients will be considered progression free at month 27 if a response is achieved within 3 months from reinitiating therapy.

The primary objective of the study is to test the following hypothesis:

The progression free survival rate at 12 months after randomization for the observation arm (B) is more than 60% (i.e., H_0: PFS rate at 12 months post-randomization ≤ 60% versus H_1: PFS rate at 12 months post-randomization > 60%). PFS and the 95% confidence interval (CI) will be estimated using 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 randomization), and also for all patients together (from registration).

14.4.2 Toxicity analysis

The analyses of treatment toxicity will be done primarily by tabulation of the incidence of adverse effects with CTCAE grade 2 or more (appendix D). This is done for all patients together for the first 15 cycles and in the following period for all patients together and also separately for MRD positive patients, for patients randomized to arm A and for patients randomized to arm B.

14.4.3 Additional analyses

Additional analyses regarding secondary endpoints will involve progression-free survival (PFS), overall survival (OS), and overall response rate. These analyses should also be regarded as exploratory, and therefore only as hypothesis-generating. .

14.4.4 Interim analysis

No interim analysis on the primary endpoint is planned.
Draft outline of interim analyses in the study:

Analysis	**Time point**	**Analysis**	**Impact on primary endpoint**
Analysis IA	First 15 pt. after induction cycle 3	Interim analysis on safety	No, only safety
Analysis IB	First 10 pt. with low CrCl 30-50. After induction cycle 3.	Interim analysis on safety	No, only safety
Analysis II	first 23 pt. reaching MRD negativity at cycle 9 or first 51 pt. at cycle 9, which occurs first	Interim analysis on safety and efficacy	No impact, prior to randomization
Analysis III	15 pt. randomized for stopping treatment after cycle 15 or first 51 pt. at end of cycle15, which	Interim analysis on safety and efficacy	No impact, at time of randomization

	occurs first		
Analysis IV	6 months after first 15 pt. randomized for stopping treatment at cycle 15 or 6 months after first 51 pt. at cycle 15, which occurs first	Interim analysis on efficacy	Post randomization, MRD positivity and primary are dependent. No correction.
Analysis V	12 months after 15 pt. randomized for stopping treatment at cycle 15 or 12 months after first 51 pt. at cycle 15, which occurs first	Interim analysis on efficacy	Post randomization, MRD positivity and primary are dependent. No correction
Analysis VI	Last patient reaching Month 27	Primary end point analysis	
Analysis VII	Last patient reaching 7 years	Update final analysis	

In the Interim analyses on safety (IA and IB), , the incidence of (serious) adverse events, death, creatinine level, AEs of special interest (atrial fibrillation, bleeding events and TLS) and progression according to appendix B and MRD positivity, will be reported. These analyses will be before the randomization stage and patients have not been assigned to any of the arms.

In Interim analysis on safety and efficacy and In Interim analysis on efficacy, the incidence of (serious) adverse events, death, creatinine level, number of assigned patients at each treatment arm, number of progression, best response, number of reinitiated patients (if applicable), AEs of special interest (atrial fibrillation and bleeding events), TLS)and progression according to appendix B and MRD positivity, will be reported.
In Interim analyses on efficacy (IV, V), the number of assigned patients at each treatment arm, number of progression, best response, number of reinitiated patients (if applicable), AEs of special interest and progression according to appendix B and MRD positivity, will be reported.
All aforementioned analyses will be reported to the DSMB

14.4.5 Statistical analysis of the quality of life assessment (QoL)

All patients with at least the baseline QoL and one treatment or follow-up QoL questionnaire will be included in this analysis. QoL at the different time points will be summarized (median, range, number of patients); measurements during treatment and follow up will be compared to the corresponding baseline values, and the differences compared to baseline will be analyzed using a one-sample t-test. Time series analysis will be performed. To obtain estimates of the mean scores for the EORTC QLQC30 and QLQ-CLL16 subscales a linear mixed model will be used. The subscales that are based on a single item will be analyzed using (ordinal) logistic regression. More details of the analysis will be described in a statistical analysis plan (SAP) which will be made prior to the final analysis of the quality of life. Next to time, other covariates will be included in a multivariate model such as toxicity and last registered response (e.g., ≥ PR vs. < PR) prior to a certain HRQoL assessment.

14.4.6 Statistical analysis plan (SAP)

Before the final analysis, a SAP 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.

14.4.7 Data and Safety monitoring board

A data and safety monitoring board will be installed before start of the study.

15 Registration and Randomization

15.1 Regulatory Documentation

Required regulatory and administrative documents must be provided to the HOVON Data Center before shipment of study drug and before enrolment of the first patient. This will always include an Ethics Committee approval for the investigational site. The HOVON Data Center will provide each investigator with an overview of the required documents. Each investigational site will be notified when all requirements are met and enrolment can start

15.2 Registration

Eligible patients should be registered before start of treatment. Patients need to be registered at the HOVON Data Center by one of the following options:

- Trial Online Process (TOP, https://www.hdc.hovon.nl/top). A logon to TOP can be requested at the HOVON Data Center for participants.
- By faxing the completed registration/randomization CRF +31.10.7041028 Monday through Friday, from 09:00 to 17:00 CET
- By phone +31.10.7041560 Monday through Friday, from 09:00 to 17:00 CET

The following information will be requested at registration:

- Protocol number
- Institution name
- Name of caller/responsible investigator
- Local patient code (optional)
- Sex
- Year of birth
- Date written informed consent
- Specific items patient gives consent for (see ICF)
- Eligibility criteria

All eligibility criteria will be checked with a checklist.
Each patient will be given a unique patient study number (a sequence number by order of enrolment in the trial). Patient study number and result of randomization will be given immediately by TOP or phone and confirmed by fax or email.

Local Patient Code is a code that may be assigned to the patient by the investigational site for local administrative purposes. The code may be up to 8 characters long (letters and numbers allowed). The code should be in compliance with privacy regulations. It should not contain identifying data, such as patient initials or the complete hospital record number. The local code will be visible in the confirmation messages sent by TOP to local participants after registration of the patient. The key to this local patient code should only be accessible by the local investigator and the local hospital staff. Using or entering a local patient code is not obligatory.

15.3 Randomization

Patients achieving MRD negativity after cycle 12 (peripheral blood) and at day 15 of cycle 15 (peripheral blood and bone marrow), are randomized between continous ibrutinib treatment until toxicity or progression and treatment free observation. Patients not reaching MRD negativity are not randomized and continue ibrutinib treatment until toxicity or progression.

Randomization has to occur within 14 days after MRD testing after day 15 of cycle 15.
Patients need to be randomized at the HOVON Data Center as described above for registration.

The following information will be requested at randomization:

- Protocol number
- Institution name
- Name of caller/responsible investigator
- Patient study number
- Response after cycle 12 and cycle 15

Patients will be randomly assigned to maintenance ibrutinib or observation arms through 1:2 randomization process with stratification at randomization by center, comorbidity (CIRS ≤6 vs >6), and TP53 aberration (TP53 mutation and or del(17p), no vs yes) with a minimization procedure, ensuring balance within each stratum and overall balance.
Result of randomization will be given immediately by TOP or phone and confirmed by fax or email.

15.4 Late registration of MRD positive patients who will continue with ibrutinib

Eligibility to continue ibrutinib for patients who are MRD positive at cycle 12 and/or 15 should also be registered at the HOVON Data Center. If the patient appears to be MRD positive, please fill in the randomization form and e-mail it to hdc@erasmusmc.nl. It is not possible to register these patients in TOP.

16 Data collection and quality assurance

16.1 Case Report Forms

Data will be collected on *electronic* Case Report Forms (CRF) to document eligibility, safety and efficacy parameters, compliance to treatment schedules and parameters necessary to evaluate the study endpoints. Data collected on the CRF 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.

Each CRF page will be identified by a trial number, and a combination of patient study number (assigned at registration) and hospital name.
The e-CRF will be completed on site by the local investigator or sub-investigator or an authorized staff member. The CRF must be signed by the local investigator or sub-investigator upon completion by means of an electronic signature. All CRF entries must be based on source documents.
Written instructions for completing the CRF will be provided by the HOVON Data Center. Access to the e-CRF will be provided by the HOVON Data Center only to authorized site staff members who have completed a training course on the use of the e-CRF. Training materials will be provided by the HOVON Data Center.

16.1.1 Rapid reporting of events

In this trial two types of rapid request forms will be used:

- Bleeding and atrial fibrillation are events of special interest which will be actively requested for in patients treated with ibrutinib. For this purpose a short questionnaire will be generated – a Rapid Request Form -, which will be sent by email to the local investigators.
  The form needs to be filled out every 3 months for as long as the patient is on ibrutinib treatment (i.e. 15 months for patients randomized to stop treatment, until end of protocol treatment for patients who continue ibrutinib treatment).

16.2 Data quality assurance

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator before the study, and site visits by the sponsor.
Data collected on the CRF will be verified for accuracy. If necessary, queries will be sent to the investigational site to clarify the data on the CRF. The investigator should answer data queries within the specified time line.

16.3 Monitoring

This trial is part of the HOVON Site Evaluation Visit program. 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 conduct in participating sites from other countries will be organized by the 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.
Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. The sponsor expects that during site visits the relevant investigational staff will be available, the source documentation will be available and a suitable environment will be provided for review of study-related documents.

16.4 Audits and inspections

In accordance with regulatory guidelines, audits may be carried out for this study. The investigator is required to facilitate an audit by means of a site visit.
These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Patient privacy must, however, be respected.
Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

17 Ethics

17.1 Accredited ethics committee

An accredited Ethics Committee will approve the study protocol and any substantial amendment.

17.2 Ethical conduct of the study

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki, the ICH-GCP Guidelines, the EU Clinical Trial Directive (2001/20/EG), and applicable regulatory requirements. The local investigator is responsible for the proper conduct of the study at the study site.

17.3 Patient information and consent

Written informed consent of patients is required before enrolment in the trial and before any study related procedure takes place.
The investigator will follow ICH-GCP and other applicable regulations in informing the patient and obtaining consent. The investigator should take into consideration if the patient is capable of giving informed consent. Before informed consent may be obtained, the investigator should provide the patient ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the patient.
There is no set time limit for the patient to make a decision. The investigator should inform each patient if there is a specific reason why he/she must decide within a limited time frame, for example if patients condition necessitates start of treatment or if the trial is scheduled to close for enrolment.

The content of the patient information letter, informed consent form and any other written information to be provided to patients will be in compliance with ICH-GCP and other applicable regulations and should be approved by the Ethics Committee in advance of use.
The patient information letter, informed consent form and any other written information to be provided to patients will be revised whenever important new information becomes available that may be relevant to the patient's consent. Any substantially revised informed consent form and written information should be approved by the Ethics Committee in advance of use. The patient should be informed in a timely manner if new information becomes available that might be relevant to the patient's willingness to continue participation in the trial. The communication of this information should be documented.

17.4 Benefits and risks assessment.

The standard of care in treatment of patients with relapsed or refractory CLL (RR CLL) is rapidly changing. For patients with a relapse later than 1-2 years from first line therapy, repeated therapy with a first line regimen is used. This poses the risk of significant immunosuppression and infectious complications as well as a shorter event free survival than for first line treatment is expected. For patients with refractory disease, early relapse or emerging of TP53 aberrated subclones, targeted treatment with ibrutinib or idelalisib + rituximab is used. However, literature to date only supports treatment until progression or toxicity with significant impact on quality of life and significant socioeconomic implications as well as conferring the risk of clonal evolution and development of resistance with continuous exposure to treatment.

Thus, there is an urgent need for alternatives, especially chemotherapy-free regimens without the need for prolonged maintenance.
As CD20 targeting agents are currently part of standard first line treatment for CLL. testing of a regimen for RR CLL without repeated CD20 targeting, thus presenting targets for treatment that have not been targeted previously for the patients, is a rational approach.
Ibrutinib is approved for treatment of patients with CLL as first line treatment and for patients with relapsed or refractory disease with a manageable safety profile. Venetoclax has been approved for treatment of patients with CLL and del(17p) by FDA, approval by EMA is awaiting, with a manageable safety profile as long as precautions concerning the risk of tumor lysis syndrome are followed as stated for this trial. Several hundreds of patients have been treated with the combination of ibrutinib and venetoclax in clinical trials, no unexpected safety signals differing from the safety profile described for each drug have been reported. However, data on long term safety and the outcome upon stopping treatment is still immature, thus the current study especially addresses these aspects in addition to the primary endpoint.
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, which may induce long lasting remissions for those patients randomized for observation after cycle 15.

17.5 Trial insurance

Prior to the start of the trial, the sponsor will ensure that adequate insurance for patients is in place covering losses due to death or injury resulting from the trial, in accordance with applicable laws and regulations in each country where the trial is conducted. The sponsor will take out an insurance policy or delegate this responsibility to a national co-sponsor. Proof of insurance will be submitted to the Ethics Committee.
In addition, the sponsor will ensure that adequate insurance is in place for both investigator(s) and sponsor to cover liability pertaining to death or injury resulting from the trial.

18 Administrative aspects and publication

18.1 Handling and storage of data and documents

18.1.1 Patient confidentiality

Each patient is assigned a unique patient study number at enrolment. In trial documents the patient's identity is coded by patient study number as assigned at enrolment. In some cases year of birth is also listed.

The local investigator will keep a subject enrolment and identification log that contains the key to the code, i.e. a record of the personal identification data linked to each patient study number. This record is filed at the investigational site and should only be accessed by the investigator and the supporting hospital staff, and by representatives of the sponsor or a regulatory agency for the purpose of monitoring visits or audits and inspections.

18.1.2 Filing of essential documents

Essential Documents are those documents that permit evaluation of the conduct of a trial and the quality of the data produced. The essential documents may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).
The investigator should file all essential documents relevant to the conduct of the trial on site. The sponsor will file all essential documents relevant to the overall conduct of the trial. Essential documents should be filed in such a manner that they are protected from accidental loss and can be easily retrieved for review.

18.1.3 Record retention

Essential documents should be retained for 15 years after the end of the trial. They should be destroyed after this time, unless a longer record retention period is required by site specific regulations.
Source documents (i.e. medical records) of patients should be retained for at least 15 years after the end of the trial described in section 18.4. Record retention and destruction after this time is subject to the site's guidelines regarding medical records.

18.1.4 Storage of samples

Biological samples should only be stored for the purpose of additional research if the patient has given consent. If no informed consent was obtained, samples should be destroyed after the patient has completed all protocol treatment and procedures.
Storage of biological samples on site is subject to the site's guidelines; samples may be labeled with the patients identifying information (e.g. name, hospital record number).
Samples that are shipped to another facility (e.g. a central laboratory) for a purpose as described in this protocol or for additional scientific research, should be stripped from any identifying information and labeled with a code (trial name or number and patient study number as assigned at enrolment).

18.2 Amendments

A ‘substantial amendment’ is defined as an amendment to the terms of the Ethics Committee application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the patients of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be submitted to the Ethics Committee and to the Competent Authority.

Non-substantial amendments will not be submitted, but will be recorded and filed by the sponsor.

18.3 Annual progress report

The sponsor will submit a summary of the progress of the trial to the accredited Ethics Committee once a year. The first report is sent one year after the first approval date of the trial. The last report is sent one year after the last patient has completed protocol treatment. Information will be provided on the date of inclusion of the first patient, numbers of patients included and numbers of patients that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

18.4 End of trial report

The sponsor will notify the accredited Ethics Committee and the Competent Authority of the end of the trial within a period of 90 days. The end of the study is defined as the last patient’s last visit.

In case the study is ended prematurely, the sponsor will notify the accredited Ethics Committee and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the primary endpoint analysis of the trial, the sponsor will submit an end of study report with the results of the study, including any publications/abstracts of the study, to the accredited Ethics Committee and the Competent Authority. Upon request of the accredited Ethics Committee or the Competent Authority the sponsor will submit an updated version of the end of study report within one year after the last patient’s last visit.

18.5 Publication policy

Trial results will always 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 a publication.

All and any publications of (interim) trial results are subject to the HOVON Publication Policy, according to the version of this policy that is effective at the time of publication. The HOVON Publication Policy is available on the HOVON website and a copy can be requested from the HOVON Data Center.

Glossary of abbreviations

(in alphabetical order)

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALC	Absolute lymphocyte count
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AST	Aspartate Transaminase
BM	Bone Marrow
Ca	Calcium
CA	Competent Authority
CBC	Complete Blood Count
CCI	Charlson Comorbidity Index
CIRS	Cumulative Illness Rating Scale
CLL	Chronic Lymphocytic Leukemia
CR	Complete Remission
CRi	Complete Remission with incomplete blood count recovery
CRF	Case Report Form
CRP	C-Reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
DAT	Direct Antiglobulin Test
DSMB	Data Safety and Monitoring Board
ECG	Electrocardiogram
EORTC	European Organisation for Research and Treatment of Cancer
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GI	Gastro-intestinal
Hb	Hemoglobin
anti-HBc	Hepatitis B core Antibody
HBsAG	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HOVON	Dutch-Belgian Hematology-Oncology Cooperative Group
ICH	International Conference on Harmonization of technical requirements for registration of

	pharmaceuticals for human use
IGHV	immunoglobulin variable heavy-chain
IMP	Investigational Medicinal Product
ITT	Intention To Treat
IU	International Units
LDH	Lactate Dehydrogenase
IWCLL	International Workshop on Chronic Lymphocytic Leukaemia
METC	Medical Ethical Review Committee
MRD	Minimal Residual Disease
NCI	National Cancer Institute
NYHA	New York Heart Association
OS	Overall Survival
PB	Peripheral Blood
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QoL	Quality of Life
SAE	Serious Adverse Event
SD	Stable Disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
TLS	Tumor Lysis Syndrome
ULN	Upper Limit of Normal
WBC	White blood Cell
WHO	World Health Organization
WMO	Wet Medisch-Wetenschappelijk Onderzoek met mensen

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A. Criteria for diagnosis

A. IWCLL criteria for symptomatic CLL

For active CLL at least one of the following criteria should be met:

- At least one of the following disease-related (constitutional) symptoms must be present:
  - weight loss ≥ 10% within the previous 6 months
  - Extreme fatigue (i.e., WHO performance status ≥2)
  - Fevers ≥ 38.6 °C for ≥ 2 weeks without evidence of infection
  - Night sweats without evidence of infection
- Evidence of progressive marrow failure as manifested by the development of, or worsening of anemia and/or thrombocytopenia
- Autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroid therapy
- Massive (i.e., > 6 cm below the left costal margin) or progressive splenomegaly
- Massive nodes or clusters (i.e., > 10 cm in longest diameter) or progressive lymphadenopathy
- Progressive lymphocytosis with an increase of > 50% over a 2-month period, or an anticipated doubling time of less than 6 months

NB: Marked hypogammaglobulinemia or the development of a monoclonal protein in the absence of any of the above criteria is not sufficient for protocol therapy.

B. Binet classification system

Stage A: Lymphocytosis and lympadenopathy/organomegaly involving < 3 areas*

Stage B: Lymphocytosis and lympadenopathy/organomegaly involving ≥ 3 areas*

Stage C: Lymphocytosis and Hb < 6.2 mmol/l (< 10 g/dl) or platelet count < 100 x 10^9/l

* An involved area is either:

- cervical (head and neck, including Waldeyers ring, involvement of more than one group of nodes counts as one area)
- axillary (involvement of both axillae counts as one area)
- inguinal lymphadenopathy (including superficial femorals, involvement of both groins counts as one area)
- splenomegaly
- hepatomegaly

B. Response criteria

(Halek et al, 2008)

Response assessment will be based on the revised guidelines of the international workshop on CLL (IWCLL); these are as follows (see table on the next page) – a separate manual will be supplied to indicate the exact response assessment guidelines.

Complete remission (CR)[1] :
All below listed criteria must be fulfilled and no disease related symptoms should be present.

Complete remission with incomplete recovery of the bone marrow (CRi)[1]:
All below listed criteria must be fulfilled, except for an incomplete recovery of the bone marrow with persisting anemia, thrombocytopenia and/or neutropenia (related to toxicity of treatment and not due to CLL) and no disease related symptoms should be present.

Partial response (PR):
Among the below listed criteria at least 2 from group A and 1 from group B must be fulfilled.

PR lymphocytosis:
PR without a 50% decrease in blood lymphocytes

Stable disease (SD):
Failure to achieve a PR and absence of PD.

Progressive disease (PD):
Presence of at least 1 of the below enlisted criteria or appearance of new lymph nodes >1.5cm, hepato- or splenomegaly or organ infiltration by CLL.

Relapse:
progressive disease more than 6 months after PR/CR was reached.

[1] A clinical CR/CRi fulfills the same criteria as a CR or CRi but was not (yet) confirmed with a bone marrow examination.

Parameter	CR	Cri	PR	PD
Group A (indicating tumor load)				
Lymphadenopathy[1]	none >1.5cm		decrease ≥50%	increase by ≥50% or new lymph nodes ≥1.5cm
Hepatomegaly	None		decrease ≥50%	increase by ≥50%
Splenomegaly	None		decrease ≥50%	increase by ≥50%
Blood lymphocytes	<4000/µl		decrease of ≥50% from baseline	increase by ≥50% over baseline to ≥5000/µl
Bone marrow	normocellular	hypocellular	50% reduction in BM infiltrates[2]	irrelevant
	<30% lymphocytes, no B-lymphoid nodules			
Group B (indicating function of the hematopoietic system)				
Platelet count	≥100000/µl	Irrelevant	≥100000/µl or increase by ≥50% from baseline	decrease by ≥50% due to CLL
Hemoglobin	>11g/dl (6.8 mmol/L)	Irrelevant	>11g/dl or increase by ≥50% from baseline	decrease by > 2g/dl (1.2 mmol/L)
Neutrophil count	>1500/ml	Irrelevant	>1500/ml or increase by ≥50% from baseline	

[1] Assessed as sum of the products of multiple lymph nodes, if available an indicator lymph node (the largest palpable) from every region should be compared in every staging.

[2] In case of B-lymphoid nodules a 4-colour-flow cytometry is recommended to clarify if this is related to CLL, if flow cytometry is negative these patients can be rated as CR/CRi, if all other criteria are fulfilled

C. ZUBROD-ECOG-WHO Performance Status Scale

0 Normal activity

1 Symptoms, but nearly ambulatory

2 Some bed time, but to be in bed less than 50% of normal daytime

3 Needs to be in bed more than 50% of normal daytime

4 Unable to get out of bed

5 Death

D. Common Terminology Criteria for Adverse Events

The grading of adverse events will be done using the NCI Common Terminology Criteria for Adverse Events, CTCAE version 4.0. A complete document may be downloaded from the HOVON website:

http://www.hovon.nl (under Trials > General information about studies)

E. Modified Cockcroft Gault Formula for Calculated Creatinine Clearance (CrCl)

For Serum creatinine concentration in mg/dl:

$$\text{CrCl} \quad \frac{(140-\text{age(yr)}) \times (\text{IBM}) \times (0.85 \text{ if female, or } \times 1.0 \text{ if male})}{72 \times \text{serum creatinine (mg/dL)}} = \text{(ml/min)}$$

For Serum creatinine concentration in µmol/L:

$$\text{CrCl} \quad \frac{(140-\text{age (yr)}) \times (\text{IBM}) \times (1.23 \text{ if male, or } 1.04 \text{ if female})}{\text{serum creatinine (µmol/l)}} = \text{(ml/min)}$$

IBM (kg) = [(height in cm−154) × 0.9] + (50 if male, 45.5 if female)

F. Cumulative illness rating scale (CIRS)

The Modified Cumulative Illness Rating Scale (CIRS)

Please take into account that CLL induced illness or organ damage are not included in this rating scale.

Body system	Score				
1. Cardiac (heart only)	0	1	2	3	4
2. Hypertension (rating is based on severity; organ damage is rated separately)	0	1	2	3	4
3. Vascular (blood, blood vessels and cells, bone marrow, spleen, lymphatics)	0	1	2	3	4
4. Respiratory (lungs, bronchi, trachea below the larynx)	0	1	2	3	4
5. EENT (eye, ear, nose, throat, larynx)	0	1	2	3	4
6. Upper GI (esophagus, stomach, and duodenum; pancreas; do not include diabetes)	0	1	2	3	4
7. Lower GI (intestines, hernias)	0	1	2	3	4
8. Hepatic (liver and biliary tree)	0	1	2	3	4
9. Renal (kidneys only)	0	1	2	3	4
10. Other GU (ureters, bladder, urethra, prostate, genitals)	0	1	2	3	4
11. Muscular-skeletal-integumentary (muscle, bone, skin)	0	1	2	3	4
12. Neurological (brain, spinal cord, nerves, do not include dementia)	0	1	2	3	4
13. Endocrine-Metabolic (includes diabetes, thyroid; breast; systemic infections; toxicity)	0	1	2	3	4
14. Psychiatric/Behavioral (includes dementia, depression, anxiety, agitation/delirium, psychosis)	0	1	2	3	4

RATING SUGGESTIONS (GENERAL PRINCIPLES)

Every single disease must be classified in the appropriate system. If there are several problems in the same system, only the most severe is rated. Example: for a patient suffering from a well-controlled angina (Rated 2) and terminal heart failure (Rated 4), only the higher rated condition would be scored in the Cardiac system (e.g., rating is 4).

The spread of a cancer may lead to rate the condition in more than one category. For example, a lung cancer with bone metastases treated with nonsteroidal anti-inflammatory drugs (NSAIDs) is Rated 4 in Respiratory and 2 in Musculoskeletal.

General rules for severity rating:

0 No problem affecting that system or past problem without clinical relevance.

1 Current mild problem or past significant problem.

2 Moderate disability or morbidity and/or requires first line therapy.

3 Severe problem and/or constant and significant disability and/or hard to control chronic problems (complex therapeutic regimen).

4 Extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment.

LEVEL 0

No problem or healed minor injuries; past childhood illnesses (chickenpox); minor surgery (carpal tunnel completely healed, caesarean); uncomplicated healed fractures; other past problems healed without sequel, residual or complication (pneumonia).

LEVEL 1

Any current medical problem that causes mild discomfort or disability, or has occasional exacerbations, having only minor impact on morbidity (asthma controlled with bronchodilators, occasional heartburn relieved with antiacids). Medical problems that are not currently active but were significant problems in the past (passage of a kidney stone) or required major surgery (hysterectomy, cholecystectomy, appendectomy).

LEVEL 2

Medical conditions that require daily treatment or first line therapy (asthma controlled with inhaled steroids, gastro-esophageal reflux treated with daily medication, osteoarthritis requiring daily NSAID, etc.) and/or have moderate disability or morbidity.

LEVEL 3

Chronic conditions that are not controlled with first line therapy (asthma needing continuous corticosteroid therapy, symptomatic angina despite medical regimes, heart failure with symptoms or uncontrolled hypertension despite complex therapeutic regimen) and/or constant significant disability, but not severe disability.

LEVEL 4

Any acute condition that requires immediate treatment or hospitalization (unstable angina, acute myocardial infarction, stroke, but also bladder outlet obstruction) and/or extremely severe problems; organ failure (end-stage renal disease needing dialysis, oxygen-dependent chronic obstructive pulmonary disease, terminal heart failure); severe sensory impairment (almost complete blindness or deafness, being wheelchair bound) and/or severely affected quality of life, severe impairment in function; delirium by medical (organic) conditions.

RATING MALIGNANCIES

Consistent scoring of severity ratings for various malignancies is a difficult problem. Each malignancy has its own rating system and prognostic indicators, the complexity of which would quickly exceed the aim of the intended simplicity and ease of use of CIRS.
The following general guidelines are intended to provide a reasonably accurate delineation of medical burden for cancer without excessive complexity.

Level 1: Cancer diagnosed in the remote past without evidence of recurrence or sequel in the past 10 years or skin cancer excised in the past without major sequel (other than melanoma).

Level 2: No evidence of recurrence or sequel in the past 5 years.

Level 3: Required chemotherapy, radiation, hormonal therapy or surgical procedure for cancer in the past 5 years.

Level 4: Recurrent malignancy or metastasis (other than to lymph glands) or palliative treatment stage.

These ratings are to be made in the appropriate organ category for a given malignancy.

ORGAN-SPECIFIC CATEGORIES

The following organ-specific categories will attempt to provide guidelines for consistent rating of comparable severity. Common conditions will be stressed with the focus on the "judgment strategy" that can be applied to other problems not listed.
If there are several problems in the same system, only the most severe is rated.

HEART

In this category, only heart and coronary disease have to be considered (not vascular): coronary arteries disease, heart failure, valvular heart diseases, heart disease secondary to hypertension, endocarditis, myocarditis, pericarditis, arrhythmias (extrasystoles, bundle-branch blocks, atrial fibrillation, pacemaker placement), heart malignancies. Functional impact must be considered too (e.g., NYHA II heart failure has different value between dependent and independent persons).

0 No problems

1 Remote myocard infarction (MI) (> 5 years ago); occasional [exertion] angina; asymptomatic valvular disease

2 Chronic heart failure (CHF) compensated with meds (NYHA I-II); daily anti-angina meds; left ventricular hypertrophy; atrial fibrillation, bundle branch block, daily anti-arrhythmic drugs (even for prophylaxis); PMK placement for asymptomatic bradycardia (relieved by Holter ECG monitoring); valvular disease requiring medical treatment

3 Previous MI (< 5 years ago); abnormal stress test; status post (previous) percutaneous coronary angioplasty, coronary artery bypass graft surgery or other cardiac

surgery (valve replacement); moderate CHF (NYHA II–III) or complex medical treatment; bifascicular block; PMK placement for cardiogenic syncope; pericardial effusion or pericarditis

4 Acute coronary syndrome, unstable angina or acute MI; intractable CHF (NYHA III–IV acute or chronic); marked restriction to the normal activity of daily living secondary to cardiac status

HYPERTENSION

Consider only hypertension severity; organ damage (complications) should be considered into the respective categories.

0 Normotension

1 Borderline hypertension; hypertension compensated with salt restriction and weight loss, drug free (when drug therapy is indicated, but the patient does not take meds, the score is at least 2)

2 Daily antihypertensive meds: hypertension controlled by 1 pill therapy (even fixed doses combinations)

3 Hypertension requiring two or more pills for control

4 Malignant hypertension, or hypertension non-controlled by complex therapeutic regimen

VASCULAR-HEMATOPOIETIC

Artery disease: carotid atherosclerosis, peripheral arteries disease (PAD), aneurysms (every site);
Venous disease: venous insufficiency, varices, deep venous thrombosis (DVT), pulmonary embolism, primary pulmonary hypertension;
Immunologic disease: systemic lupus erythematosus, systemic sclerosis (scleroderma), sarcoidosis, hypersensitivity

0 No problem

1 Venous insufficiency, varices, lymphedema; carotid stenosis $< 70\%$; hemoglobin 10–12 g/dL (in females), 12–14 g/dL (in males); anemia of chronic “inflammatory” disease

2 Previous DVT; one symptom of atherosclerosis disease (claudication, bruit, amaurosis fugax, absent pedal pulses) or daily meds (e.g., anti-platelets drugs); PAD IIa–IIb by Fontaine; carotid stenosis $> 70\%$; aortic aneurysm < 4 cm; hemoglobin 8–10 g/dL (in females), 10–12 g/dL (in males); anemia secondary to iron, B12 vitamin or folate deficiency, or to chronic renal failure; total white blood cell (WBC) 2000–4000/mmc; mild thrombocytopenia (50000–150000/mmc)

3 DVT or recent DVT ($<$ 6 months ago); two or more symptoms of atherosclerosis (see above); PAD Fontaine III or recent/previous angioplasty (with or without stenting); hemoglobin $<$ 8g/dL (in females), $<$10 g/dL (in males); dyserythropoietic anemia; WBC $<$ 2000/mmc; severe thrombocytopenia ($<$ 50000/mmc)

4 Pulmonary embolism (acute or recent/previous); atherosclerosis requiring surgical intervention (e.g., aortic aneurysm > 4 cm, symptomatic carotid stenosis > 70%, PAD Fontaine IV or amputation for vascular causes, etc.); recent/previous vascular surgery; any hematological or vascular malignancy (including multiple myeloma)

In case of immunological disease, score should be assigned by considering blood abnormalities, stadium of organ damage and/or functional disability (2: symptoms controlled by daily meds; 3: symptoms not well controlled; 4: symptoms impossible to be controlled or short time poor prognosis).

RESPIRATORY

In this category COPD, asthma, emphysema, restrictive pulmonary interstitial lung diseases, malignancies of lung and pleura, pneumonia, and smoking status are considered.

0 No problem

1 Recurrent episodes of acute bronchitis; currently treated asthma with prn inhalers when required; cigarette smoker > 10 but < 20 pack years

2 Instrumental diagnosis of COPD or pulmonary interstitial disease (X-ray, CT, spirometry); daily prn inhalers (≤ 2 pharmacological classes); two or more episodes of pneumonia in the last 5 years; cigarette smoker > 20 but < 40 pack-years

3 Exertion dyspnea secondary to limited respiratory capacity, not well controlled by daily meds; required oral steroids for lung disease; daily prn inhalers (3 pharmacological classes); acute pneumonia treated as an outpatient

4 Chronic supplementation of oxygen; respiratory failure requiring assisted ventilation, or previous (at least one episode); any lung or pleural neoplasm; acute pneumonia requiring hospitalization

Smoking is an important respiratory and cardiovascular risk, so it is considered as a disease, and it is rated according to *lifetime pack-years*:

Number of cigarette packs smoked per day × Number of years smoked in their lifetime

e.g., 1 pack-year = 20 cigarettes/day (1 pack) × 1 year

Ex-smokers should be rated too, but those who have been smoke-free for the most recent 20 years would merit a lower rating than those who are currently smoking.

Examples:

a) Patient smoking 20 cig/day (1 pack) for 25 years = 25 pack-years – CIRS score: 2

b) Patient smoking 40 cig/day (2 packs) for 25 years = 50 pack-years – CIRS score: 3

c) Ex-smoker of 20 cig/day (1 pack) for 25 years, he stopped 5 years ago – CIRS score: 2

d) Ex-smoker of 20 cig/day (1 pack) for 25 years, he stopped 20 years ago – CIRS score: 1

Classification of COPD could be more specific when instrumental data (objective evidence) are available: blood gases, forced expiratory volume in 1 second (FEV1), etc.

EYES, EARS, NOSE & THROAT, and LARYNX

To simplify the potential complexity of this category it was decided to score according to the severity of the disability created by sensory diseases (degree of limited autonomy and communication), and avoid rating each type of pathology. Sensory impairments should be rated after instrumental correction (corrective lenses, hearing aid, etc.).

Eyes: glaucoma, cataracts, macular degeneration (diabetic/hypertensive retinopathy), any other pathology

Ears: otitis, dizziness, any cause of hearing impairment

Nose & Throat: rhinitis, pharyngitis, nasal polyps, sinusitis, malignancies

Larynx: dysphonia, acute and chronic laryngitis, malignancies

0 No problems

1 Corrected vision with glasses; mild hearing loss; chronic sinusitis

2 Difficulty in reading newspaper or drive although glasses; required hearing aid; chronic sinonasal complaints requiring medication; vertigo/dizziness requiring daily meds

3 Severe low vision, partially blind (required an escort to venture out, unable to read newspaper); severe ear impairment (conversational heading still impaired with hearing aid); laryngeal dysphonia (not neurological dysarthria)

4 Functional blindness/deafness: unable to read, recognize a familiar face, unable to conversational hearing, even if “organically” he is not completely blind or deaf; laryngectomy (every cause, especially malignancies); required surgical intervention for vertigo; aphonia secondary to laryngeal impairment.

UPPER GASTROINTESTINAL SYSTEM

This category is comprehensive of the intestinal tract from esophagus to duodenum, and pancreatic trees: dysphagia, gastroesophageal reflux disease (GERD), hiatal hernia, esophageal diverticula, any type of gastritis (consider also *H. Pylori* eradication or not), gastric/duodenal ulcer, acute or chronic pancreatitis, malignancies (comprehensive of gastric lymphoma).

Ensure that type 1 diabetes is rated under “metabolic.”

0 No problem

1 Hiatal hernia, GERD or gastritis requiring meds; previous ulcer (> 5 years ago); previous *H. Pylori* eradication therapy (> 5 years ago)

2 Daily proton pump inhibitor/anti-acid meds; documented gastric or duodenal ulcer or *H. Pylori* eradication therapy within 5 years

3 Active gastric or duodenal ulcer; positive fecal occult blood test; any swallowing disorder or dysphagia; chronic pancreatitis requiring supplemental pancreatic enzymes for digestion; previous episode of acute pancreatitis

4 Any type of malignancies (see "Rating Malignancies"); previous gastric surgery because of cancer; history of perforated ulcer (gastric surgery not because of cancer, ulcorrhaphy); melena/heavy bleeding from upper GI source; acute pancreatitis

LOWER GASTROINTESTINAL SYSTEM

Comprehensive of the rest of the GI system, from small bowel to anus: Whipple's disease, diverticulosis, irritable bowel, malignancies. Constipation is rated, too, by type and frequency of laxatives required, or by history of impaction.

0 No problems, previous appendectomy, previous hernia repair (without complications)

1 Constipation managed with meds; active hemorrhoids; intestinal hernia requiring surgery; previous hernia repair with complications (intestinal adherences, laparocele, etc.); irritable bowel syndrome (few symptoms)

2 Constipation requiring daily bulk laxatives (psyllium, policarbophil, sterculia, guar gum, etc.), or stool softeners; diverticulosis (previous diverticulitis); inflammatory bowel disease in remission with meds (> 5 years ago)

3 Bowel impaction/diverticulitis within the last year; daily use of stimulant (irritant) or osmotic laxatives (bisacodyl, senna, glycerol, sodium docusate; lactulose, polyethylene glycol) or enemas; chronic bowel inflammation in remission with meds (< 5 years ago)

4 Diverticulitis flare up; active inflammatory disease; current impaction; hematochezia/active bleeding from lower GI source; bowel carcinoma

LIVER AND BILIARY TREES

Comprehensive of liver, gallbladder, biliary trees, portal system: acute and chronic hepatitis (viral, alcoholic, toxic, autoimmune, idiopathic), cirrhosis, portal hypertension, hemochromatosis, primary biliary cirrhosis, cholelithiasis, cholangitis, primary malignancies. As the hepato-biliary system is difficult to assess through the physical examination, therefore, laboratory results must be used.

0 No problem

1 History of hepatitis (actually normal values of transaminases); cholecystectomy

2 Cholelithiasis; chronic hepatitis or previous hepatitis (< 5 years ago) or any other liver disease (hemochromatosis, primary biliary cirrhosis) with mildly elevated transaminases (within 3-times normal values); heavy alcohol use within 5 years (to rate in "psychiatric", too)

3 Chronic hepatitis or any other liver disease with marked elevation of transaminases (> 3-times normal values); elevated bilirubin

4 Acute cholecystitis; any biliary obstruction; active hepatitis/liver cirrhosis; any liver or biliary tree carcinoma

RENAL

This category is exclusive of kidney: kidney stones, acute/chronic renal failure, glomerulonephritis; nephrosic/nephritic syndrome; active/chronic pyelonephritis, diabetic or hypertensive nephropathy (albuminuria/proteinuria), renal carcinoma. Bence-Jones proteinuria in multiple myeloma should not be considered.

0 No problem

1 Asymptomatic kidney stone; kidney stone passage within the last ten years; pyelonephritis within 5 years; kidney cysts without hematuria

2 Serum creatinine > 1.5 but < 3 mg/dL without diuretic or antihypertensive medication (particularly ACE-inhibitors or SRAA blockers); kidney calculi requiring daily meds

3 Serum creatinine > 3 mg/dL or < 1.5 mg/dL in conjunction with diuretics, antihypertensive, or bicarbonate therapy; active pyelonephritis; nephrosic syndrome; colic symptoms treated as an outpatient

4 Required dialysis; renal carcinoma; colic symptoms requiring hospitalization

GENITO-URINARY

Ureters, bladder, urethra. Genitals, prostate, testicles, penis, seminal vesicles.
Uterus, ovaries. *Mammary gland is rated under "metabolic".*
This category is comprehensive of all GU tract impairments: ureteral or bladder stones, benign prostate hypertrophy (BPH), urinary tract infections (UTI's), prolapses, etc. Urinary incontinence and indwelling catheter should also be considered.

0 No problem

1 Stress incontinence; BPH without urinary symptoms; hysterectomy or ovariectomy (uterine fibroma, benign neoplasm)

2 Pathological pap smear (or 2 consecutives abnormal); frequent UTIs (3 or more in the past year) in female or current UTIs; urinary incontinence (not stress) in females; BPH with urinary symptoms (frequency, urgency, hesitancy); status post TURP; any urinary diversion procedure; indwelling catheter; bladder calculi

3 Prostatic cancer in situ (e.g., incidentally found during TURP); vaginal bleeding; cervical carcinoma in situ; hematuria (any cause); urinary incontinence (not stress) in males; bladder polyps

4 Acute urinary retention; current urosepsis; any GU malignancies except as above

MUSCULOSKELETAL/INTEGUMENT

This is a very broad category, including: osteoarthritis, osteoporosis, any bone fracture; primary neoplasm (bone, muscle, connective tissue, skin), distinguishing melanoma from other localized skin cancers; rheumatoid arthritis and polymyalgia rheumatica; muscular injuries (rotator cuff, long head of the biceps); pressure sores; any dermatological disease.

The scores of this category are strictly correlated to the disability they cause; for the evaluation of the level of disability, refer to basic activities of daily living (BADL) and instrumental activities of daily living (IADL).

NOTICE: Score the severity of each illness according to the level of disability caused by the same illness in this category, without considering the disability caused by other diseases. For example: a patient affected both by osteoarthritis and hemiplegia from a previous stroke has a high level of disability, but you have to score 2 for disability by osteoarthritis (in this category) and 4 for disability by stroke (in the neurological category); for a patient with both a deforming rheumatoid arthritis and a previous stroke without remaining outcomes you have to score 4 for disability from arthritis (in this category) and 2 for disability from stroke (in the neurological category).

0 No problem

1 Requires meds for osteoarthritis (NSAID) or has mildly limited IADL from joint pathology; excised skin cancers (except melanoma); skin infections requiring antibiotics within a year

2 Daily anti-osteoarthritis meds (NSAID) or use of assistive devices or little limitation in ADL (previous arthroprosthesis or treated fracture with a low level of remaining disability); osteoporosis without vertebral fractures; daily meds for chronic skin diseases (even local, as psoriasis or pressure sores); non-metastatic melanoma; daily meds for rheumatoid arthritis (except steroids) with a low level of disability

3 Osteoarthritis with a moderate level of disability in ADL; requires chronic treatment with steroids for arthritic conditions or joints' deformities or severely impaired; osteoporosis with vertebral compression fractures

4 Wheelchair bound for osteomuscular disease; severe joint deformities or severely impaired usage; osteomyelitis; any bone or muscle or connective tissue neoplasm (see "Rating Malignancies"); metastatic melanoma.

Fractures and/or arthroprosthesis (both recent and old) have to be scored according to the level of disability they cause (considering outcomes too), in order to avoid confusion about possible classifications of different fractures or joints. The same is true for muscular diseases.

CENTRAL AND PERIPHERAL NERVOUS SYSTEM

This category includes the "somatic" pathologies of the central and peripheral nervous system: any kind of stroke, neurodegenerative diseases (Parkinson's disease and parkinsonism, multiple sclerosis, amyotrophic lateral sclerosis, etc.), myelopathies, traumas with neurological outcomes, primary or secondary epilepsy, neuropathies (diabetic, alcoholic, any other etiology), primary tumors, chronic headaches (migraine), insomnia, etc. It must carefully estimate the severity and prognosis of the illness but also the functional impairment that the illness causes.

0 No problem (or fewer convulsions in childhood)

1 Frequent headaches requiring meds without impairment in Advanced ADL; previous TIA (one event); previous epilepsy, actually not treated, without crisis since more than 10 years ago.

2 Chronic headache requiring daily meds (even for prophylaxis) or with regularly functional impairment in Advanced ADL (bed rest, job withdrawal, etc.); actual TIA or more than one previous TIA; previous stroke without significant residual; mild severity neurodegenerative diseases (see above), treated and well controlled; epilepsy controlled with drugs.

3 Previous stroke with mild residual dysfunction (hemiparesis, dysarthria); any neurosurgical procedure; moderate severity neurodegenerative diseases (see above), not well controlled by meds; epilepsy in treatment but with periodic crisis.

4 Acute stroke or previous stroke with severe residual dysfunction (hemiplegia, aphasia, severe vascular dementia) or more than one previous stroke (multi-infarct encephalopathy); severe neurodegenerative diseases (see above) causing disability in ADL; neurological coma.

Alzheimer's disease and dementia should not be rated into this category (Psychiatric and behavioral diseases): Alzheimer's disease should be listed only under psychiatric disorders; if dementia stems from vascular and/or mixed dementia and/or other neurological condition (e.g., Parkinson's Disease), both "neurologic" and "psychiatric" categories should be endorsed at the appropriate level for severity, considering in this category the stroke and the multi-infarct encephalopathy responsible for the cognitive impairment (score 3 for stroke with remaining outcomes, score 4 for multi-infarct encephalopathy).

ENDOCRINE-METABOLIC SYSTEM AND BREAST (systemic infections and poisonings)

Type 1 and Type 2 diabetes (organ damage should be considered into the respective categories, like for hypertension), obesity and dyslipidemia (hypercholesterolemia) represent the core of this category; it includes also hypo- and hyper-thyroidism, hypo- and hyper-parathyroidism, adrenal pathologies (Cushing' or Addison' disease), hypogonadism, hypopituitarism, etc. Malignancies of these glands, both benignant (like thyroid nodules) and malignant (like thyroid or adrenal cancer, vipoma, etc.) are included too.

Even if it is an exocrine gland, breast was included in this category because the authors did not find a more appropriate one; so it also includes breast cancer.
Moreover, it includes: electrolyte disorders, sepsis, systemic infections (like tuberculosis, syphilis, AIDS) scored according to their severity and the functional impairment they cause (see general indications) and poisonings (chronic by metals or acute by pesticides or carbon monoxide).

0 No problem

1 Diabetes and/or dyslipidemia compensated with diet; mild obesity (BMI 30-35 kg/m2); hypothyroidism in replacement therapy (L-thyroxin); hyperthyroidism caused by Plummer' adenoma surgically treated.

2 Diabetes compensated with oral hypoglycemic drugs or insulin (hemoglobin $A_{1c} < 7\%$); dyslipidemia well controlled by daily meds (c-LDL lower than the recommended target according to the individual global cardiovascular risk); moderate obesity (BMI 35–45 kg/m^2); hyperthyroidism in pharmacologic treatment; asymptomatic or surgically treated hyperparathyroidism; fibrocystic breast disease.

3 Diabetes not well compensated by therapy (hemoglobin A_{1c} 7–8.5%, presence of complications); dyslipidemia not well controlled (c-LDL higher than the recommended target according to the individual global cardiovascular risk; for instance, c-LDL > 100 mg/dL in patients with previous myocardial infarction or stroke); severe obesity (BMI > 45 kg/m^2); symptomatic hyperparathyroidism (e.g., hypercalcaemia); replacement therapy for adrenal failure; any electrolytes disorder requiring hospitalization.

4 Uncontrolled diabetes (hemoglobin $A_{1c} > 8.5\%$) or one diabetic ketoacidosis or nonketotic hyperosmolar coma during the past year; genetic uncontrolled dyslipidemia; acute adrenal failure during hormonal replacement therapy; any neoplasm of thyroid, breast, adrenal gland (see "Rating Malignancies").

NOTICE: when the patient is not treated with drug therapy for diabetes or dyslipidemia but he should be for the optimal control of the pathology (for instance, hemoglobin $A_{1c} > 7\%$, total cholesterol > 250 mg/dL), score the pathology according to the laboratory values, which really define its severity.

PSYCHIATRIC AND BEHAVIORAL DISEASES

This category includes both dementia and related behavioral disorders (psychosis, anxiety, depression, agitation) and all the pre-existing and/or not related to dementia psychiatric disorders. Since this is the only item analyzing patient's mental status (all the others refer to physical status), it is very important to evaluate it carefully considering further information derived from the Comprehensive Geriatric Assessment (MMSE; Geriatric Depression Scale, Neuro-Psychiatric Inventory if available).

0 No psychiatric problem or history thereof

1 Minor psychiatric condition or history thereof: previous (occasional) psychiatric treatment without hospitalization; major depressive event and/or use of antidepressants more than 10 years ago without hospitalization; occasional use of minor tranquilizers (e.g., BDZ; even if as hypnotherapy for insomnia); mild cognitive impairment (MMSE 25-28).

2 A history of major depression (according to DSM-IV criteria) within the last 10 years (treated or untreated); mild dementia (MMSE 20-25); previous admission to Psychiatric Department for any reason; history of substance abuse (more than ten years ago, including alcoholism).

3 Current major depression (according to DSM-IV criteria) or more than two previous major depression episodes in the past 10 years; moderate dementia (MMSE 15–20); current and usual usage of daily anti-anxiety meds (even as hypnotherapy for insomnia); current or within the past ten years substance abuse or dependence (according to DSM-IV criteria); requires daily antipsychotic medication; previous attempt at suicide.

4 Current mental illness requiring psychiatric hospitalization, institutionalization, or intensive outpatient management (psychiatric emergency, as attempt at suicide or severe depression with suicide purpose, acute psychosis or acute decompensation of chronic psychosis, severe substance abuse; severe agitation from dementia); severe dementia (MMSE $<$ 15); delirium (acute confusion or altered mental status for medical (organic) reasons: in this case you have to codify also the medical cause in its own category with the appropriate level of severity).

A psychiatric consult could be requested for this category; dementia and depression, the most frequent diseases in the elderly, can be scored in details using the MMSE and GDS. The severity of any mental disorder (dementia, depression, anxiety, psychosis, substance abuse and all the others) has to be scored according to the level of functional impairment or disability they cause.

CHECKLIST

Medical history

- Timing of events and/or interventions (how long ago underwent surgery for…; how long ago had myocardial infarction or stroke, etc.) and evaluation of functional impairment
- Drugs list (fundamental), including laxatives and tranquilizers (even hypnoinducent)
- Symptoms of atherosclerotic disease (TIA, angina, claudication, amaurosis)
- Etiological diagnosis (reasonably reliable) of anemia
- Degree of vascular stenosis or aneurism dimension (by Doppler and/or ultrasound and/or TC data, when available)
- Information about smoking status (how many cigarettes per day for how many years, when stopped)

- Use of glasses? With this aid, the patient is able to read a newspaper? Requires an escort to venture out?
- Any hearing aid? (you should evaluate possibility to communicate with patient)
- "Peptic history" of the patient (including previous eradication therapy for H. Pylori)
- Urinary symptoms, incontinence, presence of bladder catheter (even from BADL)

Physical examination

- Height (m^2) and weight (kg) (measured, not reported, if possible) to calculate BMI
- Blood pressure, heart rate, cardiac murmurs, peripheral arterial pulses
- Joint pain or passive stiffness limitation (non–X-ray-based diagnosis of osteoarthritis)
- Residual neurological deficits (dysarthria/aphasia, hemiparesis/hemiplegia)

Baseline laboratory samples

- Blood count: hemoglobin, WBC and platelet count
- Creatinine, electrolytes
- AST, ALT, fractioned bilirubin
- Thyroid function and serum B12 (when indicated)
- Hemoglobin A_{1c} (for diabetic patients)

From: Miller MD, Paradi

Miller MD1, Paradis CF, et al Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. Psychiatry Res. 1992 Mar;41(3):237-48.

G. Tumor Lysis prophylaxis

Risk categories for development of tumor lysis syndrome (TLS)

Based on review of all currently available data, three risk categories for developing TLS were defined including the size of the enlarged lymph nodes and the absolute lymphocyte count (ALC). In addition, the creatinine-clearance (CrCl) of the patient needs to be taken into account by the investigator (see below).

The following risk categories were defined:

	Low Risk	**Medium Risk**	**High Risk**	
Lymph Nodes	All measurable lymph nodes with the largest diameter <5 cm by radiographic assessment	Presence of any single measurable lymph node with the largest diameter ≥5 cm and <10 cm by radiologic assessment	A single measurable lymph node with the largest diameter ≥5 cm by radiologic assessment.	Any single measurable lymph node with the largest diameter ≥10 cm by radiologic assessment
	AND	**OR**	**AND**	
Absolute lymphocyte Count (ALC)	$< 25 \times 10^9$/L	$\geq 25 \times 10^9$/L	$\geq 25 \times 10^9$/L	

All patients enrolled in the trial will be assessed at screening and categorized based on their tumor burden, as described above. A repetition of imaging for evaluation of lymph node size before the administration of the first dosage of venetoclax is required for patients with high risk or CrCL 30-50ml/min. Patients can be restaged into a lower TLS risk group at any time according to their ALC or repetition of imaging. Imaging is due to the investigator´s discretion; ultrasound may be accepted in case of clear results.

Please note: Patients with **CrCl < 80 ml/min** should be monitored very closely for signs of TLS, especially if they are in the intermediate or high risk TLS risk category (lymph node ≥ 5 and/or ALC ≥ 25×10^9/L). Patients with **CrCl 30-50 ml/min** should be handled as high risk patients.

Initial dosing and monitoring

Low and medium risk patients -

- Administration of an oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to first dose and continued until at least 28 days after last dose escalation.
- Laboratory assessment of clinical chemistries (see under 'laboratory monitoring') and assessment of vital signs (blood pressure, body temperature, pulse) are required pre-dose, 6-8 and 24 hours post-dose at first dose of 20 mg and 50 mg. Pre-dose and 24 hours post-dose are required at subsequent ramp-up doses. The pre-dose laboratory samples are to be reviewed prior to dosing and should not demonstrate any clinically significant abnormalities prior to the first dose of venetoclax, or the patient should receive additional prophylactic treatment and hydration prior to the initiation of dosing. The 6-8 hour post-dose laboratory values must be reviewed for evidence of TLS prior to a patient leaving the clinical and electrolyte abnormalities should be corrected promptly.
- Serum chemistries must be re-assessed before administering the second dose of each ramp-up (i.e., at 24 hours).
- Any patient who, at any dose, develops clinically significant electrolyte abnormalities must have his or her subsequent venetoclax dose withheld until the electrolyte abnormalities resolve.
- Patients who develop electrolyte abnormalities should undergo aggressive management and further monitoring as outlined below (see under 'further actions')'.
- Oral hydration consisting of fluid intake of >2 L/day should be maintained during the whole ramp-up period of venetoclax.

High risk patients -

- Administration of an oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to first dose and continued until at least 28 days after last dose escalation.
- Laboratory assessment of clinical chemistries (see in the table below) and assessment of vital signs (blood pressure, body temperature, pulse) are required pre-dose, 6-8 and 24 hours post-dose on the first day of each dose level, The pre-dose laboratory samples are to be reviewed prior to dosing and should not demonstrate any clinically significant abnormalities prior to the first dose of venetoclax, or the patient should receive additional prophylactic treatment and hydration prior to the initiation of dosing. For subsequent ramp-up doses the 6-8 hour post-dose laboratory values must be reviewed for evidenice of TLS prior to a patient leaving the clinic and electrolyte abnormalities should be corrected promptly.
- Serum chemistries must be re-assessed before administering the second dose of each ramp-up (i.e., at 24 hours).
- Any patient who, at any dose, develops clinically significant electrolyte abnormalities must have his or her subsequent venetoclax dose withheld until the electrolyte abnormalities resolve.

- Patients who develop electrolyte abnormalities should undergo aggressive management and further monitoring as outlined below (see under ‘further actions’)’.
- Oral hydration consisting of fluid intake of >2 L/day should be maintained during the whole ramp-up period of venetoclax.

The following table summarizes the safety precautions for mitigation of TLS depending on different risk categories:

Recommended TLS Prophylaxis Based on Tumor Burden from Clinical Trial Data (consider all patient co-morbidities before final determination of prophylaxis and monitoring schedule)

Tumor Burden		**Prophylaxis**		**Blood Chemistry Monitoring[c,d]**
		Hydration[a]	**Anti-hyperuricemics**	**Setting and Frequency of Assessments**
Low	All LN <5 cm AND ALC <25 x10^9/L	Oral (1.5-2 L)	Allopurinol[b]	Outpatient 1. Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg 2. Pre-dose and 24 hours at at subsequent ramp-up doses
Medium	Any LN 5 cm to <10 cm OR ALC ≥25 x10^9/L	Oral (1.5-2 L) and consider additional intravenous	Allopurinol	Outpatient 3. Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg 4. Pre-dose and 24 hours at subsequent ramp-up doses 5. Consider hospitalization for subjects with CrCl <80mL/min at first dose of 20 mg and 50 mg; see below for monitoring in hospital
High	Any LN ≥10 cm OR ALC ≥25 x10^9/L AND any LN ≥5 cm	Oral (1.5-2 L) and intravenous (150-200 mL/hr as tolerated)	Allopurinol; rasburicase is recommended if baseline uric acid is elevated **(ALLOPURINOL SHOULD NOT BE GIVEN AT SAME DAY AS RASBURICASE)**	In hospital (recommended) at first dose of 20 mg and 50 mg 6. Pre-dose, 6 to 8, and 24 hours Outpatient at subsequent ramp-up doses 7. Pre-dose, 6 to 8 hours, 24 hours

ALC = absolute lymphocyte count; LN = lymph node.

a. Administer intravenous hydration for any patient who cannot tolerate oral hydration.

b. Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of venetoclax.

c. Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.

d. For subjects at low/medium risk of TLS, monitor blood chemistries pre-dose and 24 hours at each subsequent ramp-up dose. For subjects at high risk of TLS, monitor blood chemistries pre-dose, at 6-8 hours and at 24 hours at each dose level.

Hydration: Ensure adequate hydration prior to initiating therapy with venetoclax and throughout the ramp-up phase, especially the first day of each ramp-up dose. Administer intravenous (IV) fluids as indicated based on overall risk of TLS or for those who cannot maintain adequate oral hydration.

Anti-hyperuricemic agents: Administer uric acid reducing agents (e.g., allopurinol). Start 2-3 days prior to initiation of venetoclax; consider continuing through the ramp-up phase.

Laboratory Assessments:

Pre-dose (within 24 hours prior to ramp-up dose) :

- Sodium, potassium, calcium, phosphate, chloride
- uric acid, urea, total bilirubin, serum creatinine
- LDH
- complete blood count (CBC), including hemoglobin, platelets and white blood cell count with differentials
- liver enzymes (AST, ALT, alkaline phosphatase)

Assess blood chemistries mentioned above prior to initiating venetoclax to evaluate kidney function and correct pre-existing hyperuricemia, hyperkalemia, hyperphosphatemia, or hypocalcemia to normal levels. Reassess blood chemistries before starting each subsequent ramp-up dose of venetoclax.

Post-dose: For subjects at low or medium risk of TLS, monitor blood chemistries at 6-8 hours and at 24 hours after initiating venetoclax at the 20 mg and 50 mg doses. For subjects at high risk of TLS, monitor blood chemistries in the hospital at 4, 8, 12 and 24 hours after initiating venetoclax at the 20 mg and 50 mg doses; subsequent ramp-up doses can be administered in the outpatient setting with monitoring of blood chemistries at 6-8 hours and at 24 hours after initiating venetoclax. Electrolyte abnormalities should be corrected promptly. The next dose of venetoclax should not be administered until the 24 hour blood chemistry results have been evaluated.

Hospitalization:

Based on physician assessment, some patients, especially those at greater risk of TLS and patients with CrCl 30-50 ml/min, may require hospitalisation on the day of the first dose of venetoclax for more intensive prophylaxis and monitoring during the first 24 hours. Hospitalisation should be considered for subsequent dose increases based on reassessment of risk.

Scoring of tumor lysis syndrome and further actions

The below listed criteria defined by Cairo and Bishop should be used to diagnose a laboratory or clinical TLS.

Laboratory Tumor Lysis Syndrome (LTLS):

Laboratory Parameter	Laboratory Result
Uric Acid	≥ 476 µmol/L(≥ 8.0 mg/dL) or 25% increase from baseline
Potassium	≥ 6.0 mmol/L (≥ 6.0 mEq/L) or 25% increase from baseline
Phosphorous	≥1.45 mmol/L (≥ 4.5 mg/dL) or 25 % increase from baseline
Calcium	≤ 1.75 mmol/L(≤ 7.0 mg/dL) or 25% decrease from baseline

Laboratory tumor lysis syndrome (LTLS) is defined as either a 25% change or level above or below normal, as defined above, **for any two or more serum values** of uric acid, potassium, phosphate, and calcium within 3 days before or 7 days after the initiation of chemotherapy. This assessment assumes that a patient has or will receive adequate hydration (± alkalinization) and a hypouricaemic agent(s) (Cairo, 2004).

Clinical Tumor Lysis Syndrome (CTLS):

Clinical tumor lysis syndrome (CTLS) assumes the laboratory evidence of metabolic changes and significant clinical toxicity that requires clinical intervention

The presence of LTLS and one or more of the following criteria:
Creatinine: ≥ 1.5 ULN *
Cardiac arrhythmia / sudden death*
Seizure*

*) Not directly or probably attributable to a therapeutic agent (e.g. rise in creatinine after amphotericin administration). (Cairo, 2004)

Cairo-Bishop Tumor Lysis Syndrome Grading

#	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
LTLS	-*	+	+	+	+	+
Creatinine#	≤ 1.5 x ULN	1.5 x ULN	> 1.5-3.0 x ULN	> 3.0-6.0 x ULN	> 6.0 x ULN	Death$
Cardiac arrythmia#	None	Intervention not indicated	Nonurgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock	Death$
Seizure#	None	-	One brief, generalized seizure; seizures(s) well controlled by anticonsulvants; or infrequent focal motor seizures not interfering with ADL	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizure despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death$

CTLS requires one or more clinical manifestations along with criteria for LTLS

Maximal CTLS manifestation (renal, cardiac, neuro) defines the grade

* No LTLS

\# Not directly or probably related to a therapeutic agent

$ Attributive probably or definitely to CTLS

Further actions need to be taken in case of:

- potassium increase by ≥0.5mmol/l from baseline and/or any potassium value >5.0 mmol/l
- phosphorus increase of >0.5 mg/dl 0.16 mmol/l and >4.5 mg/dl 1,45 mmol/l
- any other significant laboratory change, especially electrolyte imbalances

These actions should be according to the institutional practice and include but are not limited to:

- discontinuation of administration of venetoclax, no further dosage should be taken until resolution
- hospitalization for more aggressive monitoring (especially regular laboratory assessments, telemetry/ECG monitoring, observation for signs/symptoms of TLS (e.g. fever, chills, tachycardia, nausea/vomiting, diarrhea, sweating, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, and seizures)
- administration of intravenous fluids at a rate of ≥1 ml/kg/h (≥50 ml/hr., target 150 to 200 ml/hr.; as clinically appropriate)
- in case the diagnosis of TLS is established, further measures, such as urine alkalization with intravenous sodium bicarbonate or administration of rasburicase as per institutional practice should be considered
- consultation of nephrology (or acute dialysis service) to ensure emergency dialysis is available

Please note: A rapidly rising serum potassium level is a medical emergency.

Reassessment of risk category

Patients classified as high risk for developing TLS who presented at screening with BOTH an ALC≥ 25 × 10^9/L AND a measurable lymph node with the largest diameter ≥ 5 cm by radiologic assessment may have their TLS risk category reassessed.

Prior to dose increases above 50 mg of venetoclax, patients may have a reassessment of their disease status based on their most recent ALC. Based on those results, one of the following two options may be implemented:

– If the patient's ALC decreases to < 25 × 10^9/L, patients may be re-categorized as medium risk and follow the management guidelines for the medium-risk category for the subsequent increases in dose during the dose ramp-up period.

– If the patient's ALC remains ≥ 25 × 10^9/L, they will remain in the high-risk category and continue to follow management guidelines for high-risk patients for subsequent dose increases of venetoclax during the dose ramp-up period.

Reassessment of the patient's risk category can occur prior to each subsequent dose increase.

H. Dose adjustments for Ibrutinib according to toxicity

Dose levels for ibrutinib

Dose level	Dose
0	420
-1	280
-2	140

The below actions should be taken for the following toxicities unless they are directly attributable to the underlying CLL by the judgment of the investigator:

- Grade 4 neutropenia (ANC <0.5 x 10^9/L) for >14 days
- Grade 3 thrombocytopenia (platelets <50 x 10^9/L) in the presence of ≥ Grade 2 bleeding
- Grade 4 thrombocytopenia (platelets <25 x 10^9/L)
- Grade 3 or 4 nausea, vomiting, or diarrhea (if persistent despite optimal antiemetic or anti-diarrhea therapy)
- any Grade 3 toxicity that is not resolving with medical management
- any other Grade 4 toxicity

Occurrence of the same event	Action
First	hold ibrutinib until recovery to Grade ≤1 or baseline; restart at original dose level
Second	hold ibrutinib until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (280 mg daily)
Third	hold ibrutinib until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (140 mg daily)
Fourth	discontinue ibrutinib

Ibrutinib may be held for a maximum of 28 consecutive days.

No reescalation of ibrutinib in case of dose reductions and especially no dose escalation to more than 3 capsules/day (= above 420 mg) is permitted in this study.

Dose adjustment of ibrutinib with concomitant use of moderate CYP3A inhibitors is described in section 9.5.1.

Ibrutinib may be held for a maximum of 28 consecutive days. If ibrutinib is discontinued for maximum 28 days, the patient will return to the original treatment schedule (missed doses will be skipped). If ibrutinib is to be discontinued for more than 28 days the investigator may decide to continue treatment after consultation of HOVON Data Center.

I. Dose adjustments for venetoclax according to toxicity

Dose levels for venetoclax

Dose level	Dose
0	400
-1	200
-2	100
-3	50
-4	20

Dosing interruption and/or dose reduction may be required. See Table I1 below for dose modifications for hematologic and other toxicities related to venetoclax. For subjects who have had a dosing interruption greater than 1 week during the first 5 weeks of ramp-up phase or greater than 4 weeks when at the daily dose of 400 mg, reassess for risk of TLS to determine if reinitiation with a reduced dose is necessary (e.g., all or some levels of the dose ramp-up schedule)

I1 Venetoclax Recommended Dose Modifications for Toxicities[a]

Event	Occurrence	Action
Tumor Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS (Cairo-Bishop grading in Appendix G)	Any	Withhold the next day's dose. If resolved within 24-48 hours of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at one dose level reduction
		For any events of clinical TLS, resume at one dose level reduction following resolution
Non-Hematologic Toxicities		
Grade 3 or 4 non-hematologic toxicities	1st occurrence	Interrupt venetoclax Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose. No dose modification is required.
	2nd and subsequent occurrences	Interrupt venetoclax. Restart at one dose level reduction when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at

Event	Occurrence	Action
		the discretion of the investigator.
Hematologic Toxicities		
Grade 3 or 4 neutropenia with infection or fever; or Grade 4 hematologic toxicities (except lymphopenia)	1st occurrence	Interrupt venetoclax. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with venetoclax if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose.
	2nd and subsequent occurrence	Interrupt venetoclax. Consider using G-CSF as clinically indicated. Restart at one dose level reduction when resuming treatment with venetoclax after resolution. Additional dose reductions may occur at the discretion of the physician.

Patients who require dose reductions to less than 100 mg for more than 4 weeks should stop treatment.

Management of Neutropenia

Nonclinical and clinical experience indicates that venetoclax may cause neutropenia. Subjects with a history of neutropenia who have received multiple prior therapies and/or have significant bone marrow involvement may be at a particularly high risk.

Grade 3 or 4 neutropenia has been reported in patients treated with venetoclax. Complete blood counts should be monitored throughout the treatment period. Dose interruptions or dose reductions are recommended for patients with severe neutropenia. Supportive measures including antimicrobials for any signs of infection and prophylactic use of growth factors(e.g. G-CSF) should be considered.

Management of Hematologic Toxicities Other Than Neutropenia or Lymphopenia

Venetoclax treatment should be withheld for any Grade 4 hematologic toxicity. Once the toxicity has resolved to Grade 1 or baseline level (recovery), venetoclax may be re-started at the same dose. If the toxicity recurs, the dose reduction guidelines in table I1 should be followed when resuming study treatment following resolution. Additional dose reductions may occur at the discretion of the physician.

Management of Non-Hematologic Toxicity

Venetoclax treatment should be withheld for any clinically relevant ≥ Grade 3 non-hematologic toxicity. Once the toxicity has resolved to Grade 1 or baseline level (recovery), venetoclax may be re-started at the same dose. If the toxicity recurs, the dose reduction guidelines in table I1 should be followed when resuming study treatment following resolution. Additional dose reductions may occur at the discretion of the physician.

J. Charlson comorbidity index

Clinical Condition	Weight
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Dementia	1
Cerebrovascular disease	1
Chronic pulmonary disease	1
Connective tissue disease	1
Ulcer disease	1
Mild liver disease	1
Slight diabetes without complications	1
Hemiplegia	2
Moderate or severe renal disease	2
Diabetes with end organ damage	2
Tumors	2
Leukemia	2
Lymphoma	2
Moderate or severe liver disease	3
Metastatis solid tumor	6
Acquired immunodeficiency syndrome	6

M. Charlson, T.P. Szatrowski, J. Peterson, et al. Validation of a combined comorbidity index
J Clin Epidemiol, 47 (1994), pp. 1245–1251

K. Sample List of Prohibited and Cautionary Medications

Prohibited (strong CYP3A inhibitors and warfarin/vitamin K antagonists) and cautionary medications are defined as follows. Refer to section 9.5.1 on instructions for concomitant use of moderate CYP3A inhibitors, and moderate and strong CYP3A inducers, with ibrutinib and venetoclax.

INHIBITORS AND INDUCERS		**SUBSTRATES**
Inhibitors of CYP3A (Ibrutinib and Venetoclax)	**Inducers of CYP3A (Ibrutinib and Venetoclax)**	
Strong CYP3A inhibitors - PROHIBITED:	**Strong CYP3A inducers:**	**Substrates of P-gp (Ibrutinib and Venetoclax)**
boceprevir	avasimibe	aliskiren
clarithromycin	carbamazepine	ambrisentan
cobicistat	phenytoin	colchicines
conivaptan	rifabutin	dabigatran etexilate
indinavir	rifampin	digoxin
itraconazole	St. John's Wort	everolimus
ketoconazole	phenobarbital	fexofenadine
lopinavir		lapatinib
mibefradil	**Moderate CYP3A inducers:**	loperamide
nefazodone	bosentan	maraviroc
nelfinavir	efavirenz	nilotinib
posaconazole	etravirine	ranolazine
ritonavir	modafinil	saxagliptin
saquinavir	nafcillin	sirolimus
telaprevir	troglitazone	sitagliptin
telithromycin	oxcarbazepine	talinolol
troleandomycin		tolvaptan
voriconazole*		topotecan
Moderate CYP3A inhibitors:	**Weak inducers:**	**Substrates of BCRP (Venetoclax only)**
aprepitant	glucocorticoids (e.g. prednisone)	methotrexate

amprenavir	pioglitazone	mitoxantrone
atazanavir	amprenavir	irrinotecan
ciprofloxacin	aprepitant,	lapatinib
crizotinib	armodafinil	rosuvastatin
darunavir/ritonavir	clobazamechinacea	sulfasalazine
dronedarone	nevirapine	topotecan
erythromycin	rufinamide	
diltiazem	vemurafenib	**Substrates of OATP1B1/B3 (Venetoclax only)**
fluconazole		atrasentan
fosamprenavir	**Inhibitors of OATP1B1/B3 (Venetoclax only)**	atorvastatin
imatinib	gemfibrozil,	ezetimibe
verapamil	eltrombopag	fluvastatin
	cyclosporine	glyburide
Weak CYP3A inhibitors:	tipranavir	rosuvastatin
alprazolam		simvastatin acid
amiodarone	**Inhibitors of BCRP (Venetoclax only)**	pitavastatin
amlodipine	cyclosporine	pravastatin
atorvastatin	geftinib	repaglinide
bicalutamide		telmisartan
cilostazol	**Inhibitors of P-gp (Venetoclax only)**	valsartan
cimetidine	amiodarone	olmesartan
cyclosporine	azithromycin	
fluvoxamine	captopril	**OTHER**
fluoxetine	carvedilol	**Vitamin K antagonists - PROHIBITED (Ibrutinib only)**
ginkgo	cyclosporine	warfarin
goldenseal	dronedarone	phenoprocoumon
isoniazid	felodipine	

nilotinib	quercetin	
oral contraceptives	quinidine	
pazopanib	ranolazine	
ranitidine	ticagrelor	
ranolazine		
Suboxone		
tipranavir/ritonavir		
ticagrelor		
zileuton		

Note that this is not an exhaustive list. Further information can be found at the following websites: http://medicine.iupui.edu/clinpharm/ddis/main-table/ and http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm.

In addition to the medications listed in this table, subjects should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruits.

L. Questionnaires

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH

EORTC QLQ – CLL16

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you lost weight?	1	2	3	4
32. Have you had a dry mouth?	1	2	3	4
33. Did you bruise?	1	2	3	4
34. Did you have abdominal discomfort?	1	2	3	4
35. Has your temperature been going up and down?	1	2	3	4
36. Did you have night sweats?	1	2	3	4
37. Have you had skin problems (e.g. itchy, dry)?	1	2	3	4
38. Did you feel ill or unwell?	1	2	3	4
39. Did you feel lethargic?	1	2	3	4
40. Have you felt "slowed down"?	1	2	3	4
41. Were you limited in planning activities, for example meeting friends, in advance?	1	2	3	4
42. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:	Not at All	A Little	Quite a Bit	Very Much
43. Have you had trouble with chest infections?	1	2	3	4
44. Have you had trouble with other infections?	1	2	3	4
45. Have you needed repeated courses of antibiotics?	1	2	3	4
46. Have you worried about picking up an infection?	1	2	3	4