II. Synopsis

Sponsor:	University of Cologne, Albertus-Magnus-Platz, 50923 Cologne, Germany Represented by: Dr. med. Othman Al-Sawaf Department I of Internal Medicine, Cologne University Hospital, Kerpener Straße 62, 50937 Cologne, Germany
Global Principal Investigator:	Dr. med. Othman Al-Sawaf Department I of Internal Medicine, Cologne University Hospital, Kerpener Straße 62, 50937 Cologne, Germany
Title:	A phase 3 multicentre, randomized, prospective, open-label trial of ibrutinib monotherapy versus fixed-duration venetoclax plus obinutuzumab versus fixed-duration ibrutinib plus venetoclax in patients with previously untreated chronic lymphocytic leukaemia (CLL)
Indication:	Patients with previously untreated CLL
Study design, methodology:	Phase-III trial, prospective, multicentre, open-label, randomized
Number of patients:	Approximately 897 eligible patients Screening population: A failure-rate of approximately 15% by screening is assumed. 1055 patients are estimated to be screened for the study.
Countries and sites:	Approximately 180 sites in Austria, Belgium, Denmark, Finland, Germany, Ireland, Israel, Italy, Netherlands, Norway, Spain, Sweden, Switzerland
Objectives:	The primary objective of the study is to compare the efficacy of continuous ibrutinib monotherapy with fixed-duration venetoclax plus obinutuzumab and fixed-duration ibrutinib plus venetoclax by measuring progression-free survival (PFS) in patients with previously untreated CLL.
Rationale:	In the past years, the choice of frontline treatment for patients with previously untreated CLL has been based on two crucial criteria: On the one hand the age and fitness of the patient was used to evaluate whether the patient might be eligible for effective, yet potentially more toxic chemoimmunotherapies like fludarabine, cyclophosphamide and rituximab (FCR); on the other hand, the presence or absence of 17p deletion/ *TP53* mutations would indicate whether the patient should receive targeted agents like the BTK inhibitor ibrutinib, which has early proven to be more effective in patients with *TP53* aberrations than chemoimmunotherapy [1]. However, these established criteria have become less relevant as several trials indicated that chemotherapy-free regimens can yield at least similar or even higher efficacy than chemoimmunotherapy in both fit and unfit patients irrespective of *TP53*-status. Two treatment paradigms have emerged when trying to establish chemotherapy-

free regimens in CLL: *First*, the Resonate-2 trial investigated ibrutinib monotherapy in elderly patients without previous treatment [2]. Patients were randomized to receive either chlorambucil monotherapy or ibrutinib monotherapy until disease progression. In the most recent 5-year follow-up, median progression-free survival (PFS) was still not reached, despite the fact that the vast majority of patients still had detectable levels of minimal residual disease (MRD) and the PFS estimate at 5 years was 70% with ibrutinib [3].

In a 7-year follow-up of the first ibrutinib phase-1 trial (PYCC1102/1103), median PFS was also not yet reached in treatment-naïve patients and was 51 months in relapsed/ refractory (r/r) patients [1]. On the basis of these trials, ibrutinib was licensed by the FDA and EMA for treatment of all lines of therapy, including treatment-naïve patients with and without deletion 17p/ *TP53* mutations. Further studies revealed a discontinuation rate of approx. 20%, particularly due to side effects of or intolerability to ibrutinib [5]. A recent 5-year follow-up of a single-centre phase II study with ibrutinib in previously untreated CLL patients who were either elderly or who had TP53 aberrations showed a discontinuation rate due to adverse events of approx. 6% [6]. Patients with *TP53* aberrations had a 5-year PFS of 74%, whereas no disease progressions occurred in patients without adverse aberrations.

Most recently, two phase 3 trials compared ibrutinib to the most efficacious chemoimmunotherapy regimens available in CLL today, bendamustine rituximab (BR) in the ALLIANCE A041202 trial [7] and FCR in the ECOG1912 trial [2]. Although ibrutinib was combined with 6 cycles of rituximab in the ECOG 1912 trial, the ALLIANCE trial as well as the previous NCI-2014-00989 trial [9] showed in a randomized setting that the addition of rituximab does not add to the efficacy (i.e, PFS) of the single agent treatment. Both trials showed a superior PFS rate in both elderly and young patients treated with ibrutinib versus chemoimmunotherapy. Hence, these data indicate that ibrutinib monotherapy is superior to standard chemoimmunotherapy with regards to PFS, although the advantage was less pronounced in patients with IGHV mutated status and overall observation time remains relatively short.

Another paradigm for CLL therapy is to achieve long term disease control without need for continuous therapy. To achieve this, a more intensive treatment should be given over a defined period of time in order to reduce MRD to undetectable levels in most patients. Undetectable MRD levels are a proven surrogate parameter for response to therapy as well as progression-free survival with chemoimmunotherapy as well as targeted combination therapy. Venetoclax, an orally bioavailable inhibitor of Bcl-2, an anti-apoptotic protein that is associated with disease progression and chemotherapy resistance, has shown efficacy in heavily pre-treated CLL patients, including those with deletion 17p/ *TP53* mutations, when given until disease progression [10, 11]. It is currently licensed in the US and Europe for treatment of relapsed/ refractory (r/r) CLL patients as a single agent until progression or in combination with a CD20 antibody for a fixed duration. Recently, a phase Ib trial and a phase II trial have shown good efficacy with deep MRD responses in previously untreated as well as r/r CLL with a combination of venetoclax and obinutuzumab (VG) [12, 13]. Results of the phase III CLL14 trial showed a significantly longer PFS with fixed-duration venetoclax plus obinutuzumab (VG) compared to chlorambucil plus obinutuzumab in previously

	untreated, unfit patient with CLL [14, 15]. The HOVON 139 study, a phase II trial with a similar group of patients looking at a year maintenance of venetoclax after induction with VG also showed good tolerability and efficacy for VG in unfit patients [14, 16-18]. The FDA and EMA has approved VG for fit and unfit patients with previously untreated CLL based on the results of CLL14. Limitations are the still relatively short overall observation time, which limit analyses of smaller subgroups (initial reports did not show a PFS advantage in IGHV mutated patients, however, longer follow-up confirmed a PFS advantage also for patients with mutated IGHV when treated with VG as compared to chlorambucil-obinutuzumab [15]). Also, in CLL14 overall 22% of patients randomized to the VG arm discontinued treatment at some stage and 15% discontinued at least one compound due to adverse events [14]. It is currently unclear whether an anti-CD20 antibody, which has been the backbone of most chemotherapy-based treatment regimens in CLL for over a decade, can be replaced by ibrutinib. Thus, another approach is to combine venetoclax with ibrutinib, thereby providing a fully oral regimen without infusion of an anti- CD20 antibody. Four phase II trials have tested VI in untreated as well as previously treated CLL patients and also reported high response rates as well as deep remissions [19-22]. In all trials, high rates of undetectable MRD were observed after a treatment duration of approx. 12 cycles in the majority of patients in the first line setting. Given these two different treatment paradigms, i.e. continuous treatment with ibrutinib versus limited combinational treatment with venetoclax and obinutuzumab or venetoclax and ibrutinib, the main aim of the CLL17 trial will be to provide a randomized comparison of I versus VG and I versus VI based on the duration of progression free survival in previously untreated patients of all age and fitness levels. This will also include a comparison of drug-related toxicities, discontinuations and quality of life parameters. Ultimately, the trial will help physicians to identify the best of the currently available individual treatment options for their patients.
Endpoints:	<u>Primary endpoint:</u> • Progression-free survival (PFS) <u>Secondary endpoints:</u> • Rates of undetectable MRD (uMRD, i.e. $<10^{-4}$) in peripheral blood (PB) and bone marrow (BM) at final restaging (RE), which will be at cycle 18 after start of treatment, and additional BM assessment approx. 12 months after RE • MRD levels in PB at different time points (cycle 1 before start of therapy, start of cycle 7, start of cycle 13 [→ end of VG treatment], start of cycle 16 [→ end of VI treatment], final restaging [cycle 18], afterwards every 6 months to end of study) • Duration of undetectable MRD (uMRD) • Overall response rate (ORR; defined as rate of a response of CR, CRi, or PR) as per iwCLL guidelines [23] at final restaging • Complete response rate (CRR; defined as rate of a response of CR or CRi) at final restaging as per iwCLL guidelines [23]

	• Overall survival (OS) • Event-free survival (EFS) (I vs VG and I vs VI) • Time to next treatment (TTNT) • PFS2 (i.e. PFS after second-line treatment) Safety parameters: • Type, frequency, and severity of o adverse events (AEs) and o adverse events of special interest (AESI) o adverse events of particular interest (AEPI) and their relationship to study treatment • Tumour lysis syndrome (TLS) risk category after G or I lead-in (before venetoclax ramp up) Exploratory analyses: • Evaluation of relationship between various baseline markers and clinical outcome parameters (e.g. PFS, OS, ORR relative to del17p/*TP53*, IGHV, fitness, etc) • MRD by methods other than flow cytometry • Correlation between MRD in BM and PB • Correlation between MRD in BM and PFS/ EFS/ OS Correlation between MRD in PB and PFS/ EFS/ OS • Health-related quality of life by EORTC QLQC30 and QLQ-CLL17 questionnaires • Medical Resource Utilization
Evaluation criteria:	Efficacy: • Response assessment will be performed as per iwCLL guidelines 2018 [23] • Lymph nodes, spleen and liver measurements by physical examination • Computed tomography (CT) or Magnetic Resonance Imaging (MRI) scans at screening, final restaging and additionally if clinically indicated[1] • Ultrasound of abdomen for measurement of enlarged lymph nodes at any time point (if clinically indicated) • Complete blood count (CBC) • MRD levels in PB at different time points (cycle 1 before start of therapy, start of cycle 7, start of cycle 13 [→ end of VG treatment], start of cycle 16 [→ end of VI treatment], final restaging [cycle 18], afterwards every 6 months) o *Patients receiving ibrutinib monotherapy will only be assessed for MRD when lymphocyte count has normalized [i.e. <4000/µl lymphocytes]* • Bone marrow biopsy for standard histopathology and aspirate for MRD assessment at final restaging (RE, i.e. at cycle 18) by flow cytometry and additional MRD assessment of BM approx. 12 months after final

[1] For sites in Germany, see Appendix 5 “Imaging guidelines for sites in Germany”

	restaging (Staging 10 in the I-Arm; Follow up 4 in the VG/VI-Arm) o *Patients receiving ibrutinib monotherapy will only be assessed for MRD when lymphocyte count has normalized* • Survival status • Survey of date of start, type of and PFS after next treatment for CLL <u>Safety:</u> • Clinical laboratory evaluations • Concomitant medications • AEs graded by NCI CTCAE Version 5 • HBV-DNA PCR every month in patients with positive anti-HBc test at screening until at least twelve (12) months after the last treatment cycle • pregnancy testing for all women of childbearing potential <u>Accompanying research:</u> • For a randomized comparison of disease evolution, blood samples (EDTA blood) will be collected at cycle 1, start of cycle 7, start of cycle 13 (→ end of VG treatment), start of cycle 16 (→ end of VI treatment), final restaging (cycle 18), afterwards every 6 months and at disease progression
Baseline marker:	• Physical examination • Peripheral blood count/ serum chemistry • Peripheral blood samples for central testing of immunophenotyping (for confirmation of CLL diagnosis), serum parameter (beta-2-microglobulin), karyotyping, cytogenetics (FISH), CLL gene mutations including *TP53* mutations (tNGS) and IGHV mutational status and genome sequencing • CT scan or MRI of neck, thorax, abdomen and pelvis (for evaluation of bulky disease and risk assessment for tumour lysis syndrome with venetoclax)[2] o In case of relevant lymphadenopathy (high or medium TLS risk): additional re-evaluation of TLS risk before venetoclax ramp-up (VG and VI arm) via blood count/ chemistry and physical examination and/or ultrasound • ECOG Performance Status/ Disease-related symptoms • Assessment of comorbidity burden by CIRS-Score/ concomitant medications • Geriatric assessment via G8 score for patients ≥ 70 years • Medical history including infections (including antibiotics/ antivirals/vaccine usage) three years prior to baseline, emphasize on cardiac/ vascular/ metabolic morbidity, including smoking history • ECG • Health-related quality of life by EORTC QLQ-C30 and QLQ-CLL17 questionnaires

[2] For sites in Germany, see Appendix 5 “Imaging guidelines for sites in Germany”

	• Bone marrow aspirate/ biopsy (if clinically indicated to prove association with CLL infiltration) • Height/ Weight/ BSA • HIV/ HBV/ HCV test • Pregnancy Test
Eligibility criteria:	Patients must meet the following criteria: <u>Inclusion criteria:</u> 1. Documented CLL requiring treatment according to iwCLL criteria [23]. 2. Age at least 18 years. 3. Life expectancy ≥ 6 months. 4. Ability and willingness to provide written informed consent and to adhere to the study visit schedule and other protocol requirements. 5. Adequate bone marrow function independent of growth factor or transfusion support within 2 weeks of screening initiation as follows, unless cytopenia is due to CLL: a. Absolute neutrophil count ≥ 1.0 × 10^9/L b. Platelet counts ≥ 30 × 10^9/L; in cases of thrombocytopenia clearly due to CLL (per the discretion of the investigator), platelet count should be ≥ 10 × 10^9/L c. Total haemoglobin ≥ 9 g/dL (without transfusion support, unless anaemia is due to CLL) 6. GFR >30ml/min directly measured with 24hr urine collection, calculated according to the modified formula of Cockcroft and Gault *(for men: GFR ≈ ((140 – age) x bodyweight)/ (72 x creatinine), for women x 0, 85)* or an equally accurate method. *a. For patients with creatinine values within the normal range the calculation of the clearance is not necessary. Dehydrated patients with an estimated creatinine clearance less than 30 ml/min may be eligible if a repeat estimate after adequate hydration is > 30 ml/min.* 7. Adequate liver function as indicated by a total bilirubin ≤ 2 x, AST/ ALT ≤ 2.5 x the institutional ULN value, unless directly attributable to the patient's CLL or to Gilbert's Syndrome. 8. Negative serological testing for hepatitis B (HbsAg negative and anti-HBc negative; patients positive for anti-HBc may be included if PCR for HBV DNA is negative and HBV-DNA PCR is performed every month until 12 months after last treatment cycle), negative testing for hepatitis C RNA within 6 weeks prior to registration for study screening (i.e. PCR only required when serology was positive). 9. Eastern Cooperative Oncology Group Performance Status (ECOG)

performance status 0-2.

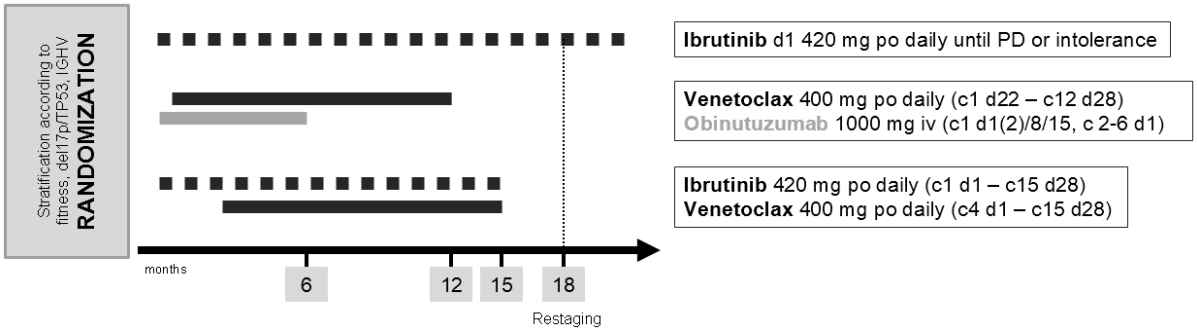
Exclusion criteria:

1. Any prior CLL-specific therapies (except corticosteroid treatment administered due to necessary immediate intervention; within the last 10 days before start of study treatment, only dose equivalents up to 20 mg prednisolone are permitted).
2. Transformation of CLL (Richter transformation). When Richter transformation is suspected, PET-CT and/or biopsy should be performed to rule out transformation.
3. Patients with a history of PML.
4. An individual organ/ system impairment score of 4 as assessed by the CIRS definition limiting the ability to receive the study treatment or any other life-threatening illness, medical condition or organ system dysfunction that, in the investigator´s opinion, could compromise the patients' safety or interfere with the absorption or metabolism of the study drugs (e.g. inability to swallow tablets or impaired resorption in the gastrointestinal tract).
5. Malignancies other than CLL currently requiring systemic therapies, not being treated with curative intent before (unless the malignant disease is in a stable remission due to the discretion of the treating physician or showing signs of progression after curative treatment.
6. Uncontrolled or active infection.
7. Patients with known infection with human immunodeficiency virus (HIV).
8. Requirement of therapy with strong CYP3A4 and CYP3A5 inhibitors/ inducers (incl. up to 7 days prior to study treatment start).
9. Anticoagulant therapy with warfarin or phenprocoumon,

   (alternative anticoagulation is allowed (e.g. DOACs), but patients must be properly informed about the potential risk of bleeding under treatment with ibrutinib).
10. History of stroke or intracranial hemorrhage within 6 months prior to registration for study screening.
11. Known bleeding disorders
12. Child B / C liver cirrhosis
13. Use of investigational agents which might interfere with the study drug within 28 days prior to registration for study screening.
14. Vaccination with live vaccines 28 days prior to registration for study screening.
15. Major surgery less than 30 days before start of study treatment.
16. History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies, known sensitivity or allergy to murine

	products. 17. Known hypersensitivity to any active substance or to any of the excipients of one of the drugs used in the trial. 18. Pregnant women and nursing mothers (a negative pregnancy test is required for all women of childbearing potential within 7 days before start of study treatment; further pregnancy testing will be performed monthly). 19. Fertile men or women of childbearing potential unless: a. surgically sterile or ≥ 2 years after the onset of menopause b. willing to use two methods of reliable contraception including one highly effective contraceptive method (Pearl Index <1) and one additional effective (barrier) method during study treatment and for 18 months after the end of study treatment. 20. Legal incapacity. 21. Prisoners or subjects who are institutionalized by regulatory or court order. 22. Persons who are in dependence to the sponsor or an investigator.
Screening and randomization:	The investigator assumes the responsibility of obtaining written informed consent for each patient before any study-specific procedures were performed. A central medical review of the screening eCRF and the results of the baseline assessments in the central laboratories will be performed by GCLLSG study physicians for verification of the eligibility of the patient, especially for confirmation of previously untreated CLL. Approval of enrolment by the GCLLSG central study office is mandatory before randomization and initiation of study treatment. Additionally, the GCLLSG study office will notify the sites if a patient is potentially at increased risk for development of TLS based on the baseline assessments. At randomization approval the tests/ assessments relevant for the screening process should not be older than 42 days (**exception:** CT/ MRI scan results are acceptable within a time frame of 56 days before randomization). Patients will be randomly assigned to treatment groups through 1:1:1 randomization process with stratification according to del(17p)/ *TP53*, IGHV and fitness (CIRS with a cut-off of 6 points and/ or GFR <70 ml/min). Treatment has to start within 14 days after randomization, but not later than 28 days after enrolment, i.e. approval of the patient by the GCLLSG study office.
Investigational medicinal products (IMPs):	- Ibrutinib (I, Imbruvica®) - Venetoclax (V, Venclyxto ®) - Obinutuzumab (G, Gazyvaro®)

Treatment schedule:



Dose and mode of administration:

Ibrutinib (I)

Ibrutinib will be administered as a daily oral dosage of 420 mg (3x 140 mg) starting on day 1 of cycle 1 until occurrence of unacceptable toxicity, progression of CLL or end of trial, whichever occurs first.

Ibrutinib p.o.:

Cycle 1 - …:	Days 1-28	ibrutinib 420 mg daily

Venetoclax plus obinutuzumab (VG)

The VG treatment consists of 12 cycles, each with a duration of 28 days. During the first cycle obinutuzumab is administered intravenously on days 1 (and 2), 8 and 15 as well as on day 1 of cycles 2-6.

Obinutuzumab i.v. infusion:

Cycle 1:	Day 1:	obinutuzumab 100 mg
	Day 1 (or 2):	obinutuzumab 900 mg
	Day 8:	obinutuzumab 1000 mg
	Day 15:	obinutuzumab 1000 mg
Cycles 2-6:	Day 1:	obinutuzumab 1000 mg

The first infusion of obinutuzumab may be administered at the full dose (1000 mg) on day 1 of the first cycle if the infusion of a test-dosage of 100 mg is well tolerated by the patient. Alternatively, if the first 100 mg infusion on day 1 is not tolerated well or as per standard practice of the participating site, the remaining 900 mg of the first dose should be administered on day 2.

The continuous daily administration with a slow dose escalation of venetoclax starts on day 22 in cycle 1.

Venetoclax p.o.:

Cycle 1:	Days 22-28:	venetoclax 20 mg (2 tabl. at 10 mg)
Cycle 2	Days 1-7:	venetoclax 50 mg (1 tabl. at 50 mg)
	Days 8-14:	venetoclax 100 mg (1 tabl. at 100 mg)
	Days: 15-21:	venetoclax 200 mg (2 tabl. at 100 mg)
	Days 22-28:	venetoclax 400 mg (4 tabl. at 100 mg)

Cycles 3-12: Days 1-28: venetoclax 400 mg (4 tabl. at 100 mg)

Due to the risk of adverse events, especially tumour lysis syndromes (TLS), the dose of venetoclax will be increased slowly every week until the final dose of 400 mg is reached (ramp-up). In order to diagnose a TLS at an early stage certain safety measures (see *X Venetoclax ramp-up*) must be followed.

On days with administration of both, venetoclax and obinutuzumab, oral intake of venetoclax will be followed by intravenous administration of obinutuzumab. Patients will be advised how to administer venetoclax at home (also on days with intravenous administration of obinutuzumab).

Venetoclax plus ibrutinib (VI)

The VI treatment consists of 15 cycles, each with a duration of 28 days. Oral intake of daily ibrutinib monotherapy will begin over the first three months and venetoclax ramp-up will be initiated at day 1 of cycle 4 for 12 cycles.

Ibrutinib p.o.:

Cycles 1-15: Days 1-28 ibrutinib 420 mg daily

The continuous daily administration with a slow dose escalation of venetoclax starts on day 1 of cycle 4.

Venetoclax p.o.:

Cycle 4:	Days 1-7	venetoclax 20 mg (2 tabl. at 10 mg)
	Days 8-14	venetoclax 50 mg (1 tabl. at 50 mg)
	Days 15-21	venetoclax 100 mg (1 tabl. at 100 mg)
	Days: 22-28	venetoclax 200 mg (2 tabl. at 100 mg)
Cycles 5-15	Days 1-28	venetoclax 400 mg (4 tabl. at 100 mg)

Due to the risk of adverse events, especially tumour lysis syndromes (TLS), the dose of venetoclax will be increased slowly every week until the final dose of 400 mg is reached (ramp-up). In order to diagnose a TLS at an early stage certain safety measures (see *X Venetoclax ramp-up, 8.3.2 Safety precautions with venetoclax*) must be followed.
On days with administration of more than one study drug, oral intake of ibrutinib (before breakfast) will be followed by oral intake of venetoclax (during breakfast). Patients will be advised how to administer the study drugs at home.

Safety measures for TLS prophylaxis during venetoclax ramp-up:

1. Oral hydration (>2 l over 24 hours) should be performed during the ramp up period; hydration should be increased at the initiation of venetoclax and maintained during every ramp-up dose in all patients.
2. Prophylaxis with uric acid reducing agents (e.g. rasburicase or allopurinol) should be additionally administered to all patients. Allopurinol should be started 2-3 days prior to the first dose of venetoclax and continued through the ramp-up phase as clinically indicated.

   Patients with high TLS risk should additionally receive IV hydration in addition to uric acid reducing agents.
3. Laboratory assessments are required on the first day of each dose level (i.e. 20

	mg, 50 mg, 100 mg, 200 mg and 400 mg venetoclax) pre-dose as well as 6-8 and 24 hours post-dose. Pre-existing as well as new electrolyte abnormalities should be corrected before and after initiation of treatment
Treatment duration:	Daily ibrutinib intake will be continued until disease progression or unacceptable toxicity. Obinutuzumab in combination with venetoclax will be administered for 6 cycles, followed by 6 additional cycles venetoclax alone (each cycle with a duration of 28 days). Ibrutinib in combination with venetoclax will be administered for a total of 12 cycles with a prior ibrutinib monotherapy lead-in of 3 cycles. After the end of therapy and the appropriate staging procedures of final restaging all patients will be followed until end of study. This will take place latest at end of the clinical trial, that may take place approximately 80 months after first patient has been randomized (FPI).
Patient registry:	To be able to collect long term follow up data until patient`s death after the end of the CLL17 study, inclusion in a country specific registry (e.g. the registry of the German CLL study group (GCLLSG), the Dutch Pharos registry or registry of the 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 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. Patients from countries where no country-specific registry is available can be followed within the ERIC registry following appropriate informed consent and/or the HARMONY registry.
Stopping rules:	Any decision to prematurely terminate the study as a whole will be made by the sponsor in accordance with the regulatory and ethical principles. During the study, continual monitoring of efficacy and toxicity will be performed by an independent data safety monitoring board (DSMB). Criteria for termination of the study as a whole are: • An unacceptable profile or incidence rate of adverse events revealed in this or any other study in which at least one of the investigational products of this trial is administered. • Demonstration that the study treatment is ineffective or only insufficiently active. • Significant number of cases of death associated with the study treatment. • Any other factor that in the view of the sponsor constitutes an adequate reason for terminating the study as a whole.
Statistical methods and study assumptions:	**Overview** This study is designed as non-inferiority trial aiming to assess • the non-inferiority of VG compared to I and • the non-inferiority of VI compared to I with regard to the primary endpoint progression-free survival (PFS). Randomization:

A centralized 1:1:1 randomization stratified by fitness status according to del17p/*TP53* and IGHV and fitness (CIRS with a cut-off of 6 points and/ or GFR <70 ml/min), using an electronic system (IXRS) will be performed.

Study population definitions

Intention-to-Treat (ITT) population:

The ITT population is defined as all randomized subjects regardless of whether they received any of the study treatment or not. Subjects will be assigned to treatment groups and analysed as randomized. The ITT population shall be used for analysis of all study endpoints except safety.

Safety population:

The safety population is defined as all subjects enrolled in the study receiving at least one dose of any component of the treatment. The safety population shall be used for evaluating the safety endpoints. Subjects in this population will be analyzed by what they have received (not as originally randomized).

Study assumptions

PFS is set as primary endpoint using a one-sided significance level of 2.5% per each non-inferiority hypothesis of fixed-duration treatment compared to continuous I (i.e. one-sided 2.5% for the comparison of VG versus I and one-sided 2.5% for the comparison of VI versus I). Both non-inferiority hypotheses will be considered as equal and the interpretation of both analyses will be made independently from each other.

The primary endpoint is investigator-assessed PFS, defined as the time from randomization to the first occurrence of progression or relapse (determined using standard *iwCLL* guidelines [23]), or death from any cause, whichever occurs first. For patients who have not progressed, relapsed, or died at the time of analysis, PFS will be censored on the date of the last tumour assessment. If no tumour assessments were performed after the baseline visit, PFS will be censored at the time of randomization + 1 day. All patients, including patients who discontinue all components of study therapy prior to disease progression (e.g., for toxicity), will continue on study and will be followed for progressive disease and survival regardless of whether or not they subsequently receive new anti-leukemic therapy.

Based on results from the Resonate 2 (patients >65 years, including fit patients, without *TP53* aberrations), ALLIANCE A041202 (patients >65 years, including fit patients, including *TP53* aberrations) and ECOG1912 trial (fit patients, excluding *TP53* aberrations) it is assumed that estimated 85% of patients treated with I would be event-free after 3 years.

Similarly, according to the results of the CLL14 study, which only included unfit patients, and according to further data from the CLL2-BAG trial, the expected 3-year PFS rate for VG is estimated also at 85%.

PFS data on VI are very limited, but based on available MRD after 12 months reported in several phase II trials, including VISION and CAPTIVATE trial, a similar PFS rate of 85% at 3 years is estimated for VI [20-22]

Any difference of ≤8% in the PFS rates would be considered clinically not meaningful. In particular, given that this study compares continuous monotherapy to limited duration combination therapy, differences of up to 8% PFS rate could be one clinical factor considered in the context of others such as reduced non-hematologic toxicity and time off treatment.

Sample size calculation:	The primary endpoint PFS is used to determine the sample size of the study. The following requirements are given for each hypothesis test for non-inferiority (VG compared to I respectively VI compared to I): • One-sided 2.5% significance level, 80% power. • Exponential distribution of PFS. • 3-year PFS rate for I = 85% and 3-year PFS rate for fixed-duration treatment (VG respectively VI) is not less than 77%, which corresponds to a non-inferiority margin of the hazard ratio (HR) = 1.608. This translates into the following null and alternative hypotheses: H_0: HR > 1.608 versus H_1: HR ≤ 1.608. • One interim analysis for non-inferiority after 65% of PFS events and a minimum study follow-up of 24 months since last patient enrolled (significance level determined via Lan-DeMets alpha spending function with an O'Brien-Fleming boundary so that the overall one-sided type I error rate will be maintained at the 2.5% level). Based on these assumptions 142 PFS events (71 per treatment group) and 598 patients (299 per treatment group) are required for each final non-inferiority testing of fixed-duration treatments (VG respectively VI) compared to I to achieve 80% power. Taken together (i.e. considering all three treatment groups), a total of 213 PFS events (71 per treatment group) and a total of 897 eligible patients (299 per treatment group) are needed to test both non-inferiority hypotheses (each with regard to a one-sided 2.5% significance level). Assuming non-linear accrual of 897 patients over approximately 36 months, the 213 PFS events will be reached approximately 80 months after the first patient has been randomized. A failure-rate of approximately 15% by screening is assumed. Therefore, 1055 patients are estimated to be screened for the study. Sample size calculations were performed with EAST 6 software.
Statistical analysis:	**Description of study population** Background and demographic characteristics: Patient`s age and other continuous baseline characteristics will be summarized using descriptive statistics, while gender and other categorical variables will be provided using frequency tabulations. Subject disposition: Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency tabulations. **Primary efficacy analysis** The primary objective of the study is to compare the following hypotheses for fixed-duration treatment (VG respectively VI) versus I: H_0: HR >1.608 versus H_1: HR ≤ 1. 608, with 1.608 being the predefined non-inferiority margin. For the primary endpoint analysis, (VG versus I and VI versus I) the HR including an adjusted 95% confidence interval (CI) (at one-sided 2.5% significance level and additionally

	adjusted for the interim analysis) will be calculated according to Cox regression analysis under the assumption of proportional hazards and adjusted for the stratification factors fitness, 17p/ *TP53* and IGHV. The non-inferiority hypothesis of fixed-duration treatment (VG respectively VI) compared to I will then be tested by comparing the adjusted 95% CI of the HR with the predefined non-inferiority margin of 1.608. The null hypothesis can be rejected if the upper limit of the adjusted 95% CI is less or equal 1.608 [i.e. ≤ 1.608]). Then it will be concluded that the fixed-duration treatment (VG respectively VI) is non-inferior as compared to I. The adjustment of confidence intervals will be based on information used for each comparison separately (i.e. VG versus I and VI versus I). Time-to-event analyses using Kaplan-Meier methods will be performed to support the primary analysis including calculation of median PFS and PFS rates for 1, 2, and 3 years etc. after randomization. The Kaplan-Meier curve will be presented to provide a visual description. **Statistical analysis of other efficacy endpoints** Rate based endpoints will be assessed showing frequencies and corresponding percentages including 95% Clopper Pearson confidence intervals. Analyses of time-to-event endpoints will be performed using Kaplan-Meier methods. **Safety analysis** Safety parameters will be analyzed on the safety population. The recent updated version of NCI Common Terminology Criteria for AEs (NCI-CTCAE v 5.0) will be used for assessing the severity of AEs (Grading). Classifications will be performed using the Medical Dictionary for Regulatory Activities classification system (MedDRA preferred term). Presentations of AEs will include a complete-case and a per-patient analysis.
Study duration:	Start of recruitment Q4/2020 Expected end of recruitment Q4/2023 End of trial Q3/2027
Statisticians:	Dr. Can Zhang Department of Internal Medicine I, Study office GCLLSG, University of Cologne, Kerpener Straße 62, 50924 Cologne, Germany
GCP conformance:	The present trial will be conducted in accordance with the valid versions of the trial protocol and the internationally recognized Good Clinical Practice Guidelines (ICH-GCP), including archiving of essential documents.