II. Synopsis

Sponsor:	University of Cologne Albertus-Magnus-Platz, 50923 Cologne, Germany Represented by: Dr. med. Paula Cramer (GPI, LKP) Department I of Internal Medicine, Cologne University Hospital Kerpener Strasse 62, 50937 Cologne, Germany
Global Principal Investigator and medical contact of the sponsor:	Dr. med. Paula Cramer Department I of Internal Medicine, Cologne University Hospital Kerpener Strasse 62, 50937 Cologne, Germany
Coordinating Physician	Dr. med. Anna Fink Department I of Internal Medicine, Cologne University Hospital Kerpener Strasse 62, 50937 Cologne, Germany
Title of the clinical trial:	A prospective, open-label, multicenter phase-II trial to evaluate the efficacy and safety of a sequential regimen of bendamustine followed by obinutuzumab (GA101) and venetoclax (ABT-199) followed by ABT-199 and GA101 maintenance in CLL patients (CLL2-BAG protocol)
Indication:	Patients with untreated or relapsed/refractory CLL requiring treatment
Phase:	Phase-II clinical trial
Type of trial, trial design, methodology:	Prospective, multicenter, phase-II trial, single-arm, open-label
Number of patients:	Approximately 62 eligible patients (among them ≥21 first-line and ≥21 relapsed/refractory patients, see below)
Rationale for the trial:	When this trial was planned, several targeted agents became available for the treatment of CLL. As these agents are generally well tolerated and have different, potentially synergistic mechanisms of action, several trials evaluating different combinations and aiming at a high efficacy are under way. The German CLL Study Group designed four phase-II trials, the so called BXX-studies, each evaluating a different combination of one oral targeted drug (ibrutinib, idelalisib or venetoclax) with an anti-CD20 antibody (obinutuzumab or ofatumumab) in an all-comer population of treatment-naïve and relapsed/refractory patients, irrespective of physical fitness and high-risk genetic abnormalities[1]. In this trial, the combination of venetoclax and obinutuzumab after an optional debulking with bendamustine was tested.

Rationale for amendment 4 and 5:

The results of the primary endpoint analysis of the CLL2-BAG trial, evaluating a debulking with two cycles bendamustine (only for patients with a higher tumor load), followed by an induction and a maintenance treatment with obinutuzumab and venetoclax, were very promising: The primary endpoint of the trial was met with an overall response rate of 95% (100% in treatment naïve patients and 90% among those with relapsed/refractory CLL) and additionally, the minimal residual disease negativity rate in peripheral blood was 87%[2]. No unexpected or cumulative toxicities were observed and only one manageable, laboratory tumor lysis syndrome occurred with venetoclax. Subsequently, the combination of venetoclax and obinutuzumab was tested in several phase-III studies, including the GCLLSG frontline trials CLL13 for physically fit patients and CLL14 for elderly patients with comorbidities. Both trials demonstrated that this combination is superior to chemoimmunotherapy and the CLL14 trial led to the approval of venetoclax/ obinutuzumab for the first-line treatment of CLL.

The CLL2-BAG trial is one of the first studies evaluating the combination of venetoclax and obinutuzumab and it is scientifically very important to follow these first patients treated with this combination as long as possible. Therefore, an extended follow-up for all patients willing to continue their study participation was implemented with amendment 4 and even further extended with amendment 5. This will help to learn more about the duration of response and MRD negativity after termination of treatment, identify risk factors for early progression, e.g. genetic parameters or characteristics of prior response (e.g. residual lymph nodes/splenomegaly), as well as venetoclax resistance and clonal evolution[3].

Furthermore, offering a re-treatment with venetoclax and obinutuzumab (but without a prior bendamustine debulking) in case of a progression was also implemented with amendment 4. This will hopefully provide some insight if a re-treatment with the same targeted treatment is effective. Up to 20 patients with a clinical relapse ≥6 months after discontinuation of maintenance treatment due to a MRD negative response or completion of 24-months of maintenance treatment or because of toxicity may be re-treated with obinutuzumab and venetoclax according to the trial protocol (without a prior bendamustine debulking).

Study end points:

Primary end point:

Overall response rate (ORR) by investigator assessment at final restaging (RE) 12 weeks after the start of the last cycle of induction therapy (end of induction treatment response = EOIT) including all patients achieving:

- a (clinical) complete response ((clinical) CR),
- a (clinical) CR with incomplete recovery of the bone marrow ((clinical) CRi), or
- a partial response (PR).

Secondary end points:

- Safety parameters: Type, frequency, and severity of
  - adverse events (AE) and
  - adverse events of special interest (AESI)
- MRD levels (MRD negativity is defined as < 1 CLL cell in 10,000 leukocytes analyzed [0.01%], i.e. < 10^{-4}) measured in peripheral blood with four-color flow cytometry at
  - final restaging after end of induction treatment (12 weeks after last cycle of induction treatment) in all patients responding to study treatment, every 12 weeks (= 3 months) during the maintenance phase if the patient has achieved a (clinical) CR/CRi or
  - every 24 weeks (= 6 months) during the maintenance phase if the patient has achieved a PR, and
  - every 24 weeks (= 6 months) during follow up
- MRD level in bone marrow optionally in patients with (clinical) CR/CRi 3 months after achievement of MRD negativity in peripheral blood
- Best response rate (BRR) until 6 months after RE
- ORR and (clinical) CR/CRi rate assessed by the investigator at the following time points:
  - after debulking
  - at the final restaging (except for ORR by investigator assessment, which is the primary endpoint)
  - after end of maintenance treatment
- ORR in the two strata of previously untreated and relapsed / refractory patients, as well as in the fit and unfit patients for all mentioned response definitions
- ORR in biological defined risk groups
- Progression-free survival (PFS)
- Event-free survival (EFS)
- Overall survival (OS)
- Duration of response in patients with:
  - (clinical) complete response (CR),
  - (clinical) CR with incomplete recovery of the bone marrow (CRi), and
  - partial response (PR)

- Treatment-free survival and time to next CLL treatment
- Efficacy of re-treatment with venetoclax and obinutuzumab (in case of a clinical progression after termination of maintenance therapy):
    - ORR and (clinical) CR/CRi rate assessed by the investigator at the final restaging of re-treatment phase (12 weeks after the start of the last re-treatment induction cycle) and at the end of re-treatment maintenance phase
    - MRD levels measured in peripheral blood by four-color flow cytometry every 3 months during re-treatment and every 6 months during the follow-up thereafter
    - MRD levels measured in bone marrow (optionally in patients with (clinical) CR/CRi and MRD negativity in peripheral blood)
- Safety evaluation of re-treatment: Type, frequency, and severity of
    - adverse events (AE) leading to dose reductions, treatment interruption and/or discontinuation,
    - adverse events of special interest (AESI) and
    - serious adverse events (SAEs)
- Evaluation of relationship between various baseline markers and clinical outcome parameters

Criteria for evaluation:

Efficacy:

- Lymph nodes, spleen and liver measurements by physical examination
- Ultrasound of abdomen and for measurement of enlarged lymph nodes
- Computed tomography (CT) scans and/or chest X-ray if clinically indicated

- Complete blood count (CBC)
- Peripheral blood samples for immunophenotyping (for confirmation of CLL diagnosis), serum parameters (beta-2-microglobulin and thymidine kinase), cytogenetics, molecular genetics and assessment of minimal residual disease (MRD)
- Bone marrow aspirate/biopsy for standard histopathology if clinically indicated (e.g. confirmation of CR or unclear cytopenias) and for MRD assessment if the patient achieved MRD negativity in the peripheral blood and voluntarily agrees to a bone marrow aspirate
- Tissue samples of biopsies performed due to a clinical indication, e.g. lymph node tissue taken for exclusion of a Richter´s transformation in case of progression
- Assessment of constitutional symptoms
- Survival status
- Survey of start and type of next treatment for CLL

Safety:

- Clinical laboratory evaluations
- ECOG Performance Status
- Assessment of comorbidity burden by CIRS-Score and concomitant medications
- AEs by NCI CTCAE Version 4
- HBV-DNA PCR every month in patients with positive anti-HBc test at screening
- pregnancy test ≤ 7 days before start of treatment for all women of childbearing potential and every month during induction therapy and every three months during maintenance treatment respectively
- CT scan or MRI of chest and abdomen (at screening for evaluation if bulky disease is present in the mediastinum or abdomen, for risk categorization for tumor lysis syndrome with venetoclax.)

Target Population:

Patients must meet the following criteria:

Inclusion Criteria:

1. Have documented CLL requiring treatment (irrespective if first- or relapse treatment) according to iwCLL criteria[4]

   In case of previously treated patients, these must have recovered from acute toxicities and treatment regimen must be stopped within the following time periods before start of the study treatment in the CLL2-BAG trial:

   - chemotherapy within ≥ 28 days
   - antibody treatment within ≥ 14 days
   - kinase inhibitors, BCL2-antagonists or immunmodulatory agents within ≥ 3 days

- corticosteroids may be applied until the start of the BAG-regimen, these have to be reduced to an equivalent of ≤ 20mg prednisolone during treatment

2. Adequate renal function, as indicated by a creatinine clearance ≥30ml/min calculated according to the modified formula of Cockcroft and Gault or directly measured with 24 hr. urine collection
3. Adequate hematologic function as indicated by a platelet count ≥ 25 x 10^9/L, a neutrophil count ≥ 1,0 x 10^9/L and a hemoglobin value ≥8.0 g/dL, unless directly attributable to the patient´s CLL (e.g. bone marrow infiltration)
4. Adequate liver function as indicated by a total bilirubin ≤ 2x, AST/ALT ≤ 2.5x the institutional ULN value, unless directly attributable to the patient's CLL or to Gilbert's Syndrome
5. 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 1 year after last dosage of obinutuzumab), negative testing for hepatitis-C RNA and negative HIV test within 6 weeks prior to registration
6. Age ≥ 18 years
7. ECOG 0 to 2, ECOG 3 is only permitted if related to CLL (e.g. due to anemia or severe constitutional symptoms)
8. Life expectancy ≥ 6 months
9. Ability and willingness to provide written informed consent and to adhere to the study visit schedule and other protocol requirements

Exclusion criteria:

1. Transformation of CLL (i.e. Richter's transformation, prolymphocytic leukemia)
2. Known central nervous system (CNS) involvement
3. Patients with confirmed PML
4. Malignancies other than CLL currently requiring systemic therapies
5. Uncontrolled infection requiring systemic treatment
6. Any comorbidity or organ system impairment rated with a CIRS (cumulative illness rating scale) score of 4, excluding the eyes/ears/nose/throat/larynx organ system[1] or any other life-threatening illness, medical condition or organ system dysfunction that – in the investigator´s opinion -

[1]) The CIRS score rates of the burden of comorbidity in each organ system with 0 to 4 points. This rating may be performed according to the guidelines by Salvi et. al.[5], which provide a point value for several different comorbidities. However, these guidelines are not binding and the treating physician´s assessment of the severity should outweigh the point value according to the Salvi guidelines. For example, a pulmonary embolism is related with 4 points according to Salvi guidelines, which means "Life threatening illness/impairment, emergency case of therapy, adverse prognosis" and would preclude trial participation, in case the pulmonary embolism occurred some time ago the treating physician may rate this history of pulmonary embolism with a lower point value and include the patient into the trial.

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)

7. Requirement of therapy with strong CYP3A4 inhibitors/inducers or anticoagulant with warfarin, phenprocoumon (marcumar) or other vitamin K-antagonists
8. Use of investigational agents ≤28 days prior to registration
9. Known hypersensitivity to obinutuzumab, venetoclax or any of the excipients

   Please note: Patients with a known hypersensitivity to bendamustine are allowed to participate but will not receive a debulking with bendamustine
10. Pregnant women and nursing mothers (a negative pregnancy test is required for all women of childbearing potential within 7 days before start of treatment, on day one of every debulking and induction cycle (monthly) and on day one of every maintenance cycle (every three months))
11. Fertile men or women of childbearing potential unless:
    - surgically sterile or ≥ 2 years after the onset of menopause, or
    - willing to use two methods of reliable contraception including one highly effective (Pearl Index <1) and one additional effective (barrier) method during study treatment and for 18 months after end of study treatment.
12. Vaccination with a live vaccine ≤28 days prior to registration
13. Legal incapacity
14. Prisoners or subjects who are institutionalized by regulatory or court order
15. Persons who are in dependence to the sponsor or an investigator

Inclusion/Exclusion criteria for extended follow-up and retreatment (Amendment 4 and 5):

1. Patients must have participated in the CLL2-BAG trial and must have benefitted from study treatment (clinical relapse ≥6 months after discontinuation of treatment due to a MRD negative response or completion of 24-months of maintenance treatment or toxicity)
2. Only patients with a confirmed progression of CLL who are in need of treatment according to iwCLL 2008 criteria[4] are eligible for retreatment with venetoclax and obinutuzumab

   Please note: Patients with a MRD conversion from negative/intermediate to positive without clinical signs of progression should not (yet) receive a retreatment in the trial

3. Patients who received any subsequent treatment for CLL outside the study are ineligible

Names of investigational medicinal products (IMPs):

- Bendamustine (trade name: *Ribomustin®, Levact®*)
- GA101 (obinutuzumab, trade name: *Gazyvaro®*)
- Venetoclax (ABT-199, trade name: *Venclyxto®*)

Investigational medicinal product – dosage and method of administration:

Debulking

Two debulking cycles of bendamustine will be administered before induction with obinutuzumab and venetoclax **unless the patient has a contraindication or a debulking is not clinically indicated** based on the following criteria:

- known **hypersensitivity to bendamustine**
- **refractoriness to bendamustine** (defined as **PD within 6 months** after bendamustine-containing therapy)
- **chemotherapy-induced bone marrow damage**
- **low tumor burden** (e.g. **ALC <25 x 10^9/l** and absence of bulky disease with **lymph nodes <5 cm** in the longest diameter

Patients should receive both cycles of debulking treatment even if the patient´s tumor burden is reduced to the above-defined threshold. Debulking treatment should be stopped after the 1st cycle only if severe adverse events occur. In each of the 2 cycles bendamustine is administered intravenously on two consecutive days, the cycle is repeated after 28 days.

Bendamustine i.v. infusion:

Cycles 1-2:	Day 1:	bendamustine 70mg/m² i.v.
	Day 2:	bendamustine 70mg/m² i.v.

Induction

The induction treatment consists of **6 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 the following cycles. The continuous daily administration with a slow dose escalation of venetoclax starts in cycle two.

Obinutuzumab (GA101) i.v. infusion:

Cycles 1:	Day 1:	GA101 100mg i.v.
	Day 1 (or 2):	GA101 900mg i.v.
	Day 8:	GA101 1000mg i.v.
	Day 15:	GA101 1000mg i.v.
Cycles 2-6:	Day 1:	GA101 1000mg i.v.

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

On days with administration of both, venetoclax and obinutuzumab, oral intake of ABT-199 will be followed by intravenous administration of GA101. Patients will receive the first dosage of ABT-199 on day 1 of the second cycle in clinic/outpatient clinic/private practice after blood sampling (see below) before the administration of GA101 is started. Also the administration of the first dosage of the dose-escalations on days 8, 15 and 22 of cycle 2 and day 1 of cycle 3 will be performed in clinic or outpatient clinic/private practice. Patients will be advised how to administer all following doses at home (also on days with intravenous administration of GA101).

Venetoclax (ABT-199) p.o.:

Cycle 1:		--
Cycle 2:	Days 1-7:	ABT-199 20mg (2 tabl. at 10mg)
	Days 8-14:	ABT-199 50mg (1 tabl. at 50mg)
	Days 15-21:	ABT-199 100mg (1 tabl. at 100mg)
	Days: 22-28:	ABT-199 200mg (2 tabl. at 100mg)
Cycles 3-6:	Days 1-28:	ABT-199 400mg (4 tabl. at 100mg)

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

- **Administration of an oral uric acid reducer (e.g. allopurinol 300mg)** beginning at least 72 hours prior to the first dose of ABT-199 and continued for up to 28 days after last dose escalation
- Prophylactic administration of **rasburicase** in all patients with elevated uric acid levels and preemptively in patients with a high risk for TLS (nodal mass ≥10 cm or both an ALC ≥25.000/µl AND nodal mass of 5–10cm)
- **Overnight hospitalization** for the administration of the first dose of 20mg AND 50mg ABT-199 for patients considered to be high risk of TLS (see above) OR patients with a creatinine clearance < 80ml/min in order to allow for treatment with rasburicase and intravenous hydration
- **Outpatient intravenous hydration** is necessary for patients in the medium risk category for TLS (lymph node with the largest diameter 5-10cm OR ALC ≥25.000/µl) and for high risk patients on day 1 of the 100mg, 200mg and 400mg dose level.
- **Laboratory assessments** are required on the first day of each dose level (i.e. 20mg, 50mg, 100mg, 200mg and 400mg ABT-199) for the following time points:
  - for hospitalized patients: pre-dose, as well as 4, 8, 12 and 24 hrs post-dose
  - for ambulatory patients: pre-dose, 8 and 24 hrs post-dose

Maintenance

Before the start of the maintenance treatment, two staging assessments (initial response assessment [4 weeks after the start of the last induction cycle] and final restaging [12 weeks after the start of the last induction cycle]) will be performed to assess the response at the end of the induction treatment, which is the primary endpoint of the trial. During this **phase of staging, the intake of venetoclax is continued** and there is no interruption between induction and maintenance treatment.
In the maintenance treatment venetoclax will be continued at the same dosage, but the interval of the obinutuzumab administrations will be extended from 4 weeks in the induction phase to 12 weeks. Therefore, the duration of one cycle is 84 days (12 weeks = 3 months).
The first maintenance cycle is started after completion of the final restaging procedures for all patients who clinically benefit from study treatment.

Venetoclax (ABT-199) and obinutuzumab (GA101):

Cycles 1-8:	Day 1:	GA101 1000mg i.v.
	Days 1-84:	ABT-199 400mg (4 tabl. at 100mg) p.o. once daily

The **maintenance treatment will be continued until** (whichever occurs first):

- **3 months after confirmation of achievement of MRD negativity** (MRD negativity is defined as < 1 CLL cell among 10,000 leukocytes analyzed [0.01%], i.e. < 1E-4) in the peripheral blood in patients with a **(clinical) CR/CRi** (MRD negativity must be confirmed by 2 consecutive measurements in a 3-month interval),
- **maintenance cycle 8** (each cycle with a duration of 84 calendar days = 12 weeks = 3 months),
- **progression of CLL** or start of a subsequent therapy, or
- **unacceptable toxicity.**

If neither MRD negativity, nor progression or unacceptable toxicity occur, the maintenance treatment will be continued for up to 8 cycles with a duration of 84 calendar days [3 months], leading to a total duration of the maintenance phase of 24 months. Patients are still benefitting from further maintenance may continue the therapy with ABT-199 and GA101 or one of the two outside the trial, if the drugs are commercially available by then.

Follow-up:

After termination of maintenance treatment patients will be followed three- to six-monthly until the end of the trial (Q4/2024) for certain long-term toxicities and for signs of progression. Furthermore, MRD measurements by four-color flow cytometry may be performed at these visits every 6 months in patients who achieved a remission (PR or (clinical) CR/CRi) and a MRD negative or intermediate status until they become MRD positive, progress or start a subsequent treatment for CLL [implemented after amendment 4].

Re-treatment:
Up to 20 patients with a confirmed progression of CLL in need of treatment according to IWCLL 2008 guidelines may receive a retreatment with obinutuzumab and venetoclax. However, patients with a MRD conversion from negative/intermediate to positive without clinical signs of progression and patients who received any subsequent treatment for CLL outside the study are ineligible for a retreatment in the trial. The decision upon a re-treatment should include an individual risk-benefit assessment by the treating physician together with the GCLLSG study office considering the patient´s risk factors, prior therapies, treatment-free duration after the initial BAG-therapy (at least 6 months) as well as the patient´s adverse events during BAG treatment as well as his/her wishes and expectations.
Dosing and schedule of obinutuzumab and venetoclax are the same as during the initial induction and maintenance treatment. In case of prior intolerance for obinutuzumab, the antibody may be omitted, however, the treatment with venetoclax and the criteria for discontinuation of maintenance treatment remain the same. Depending on the patient´s tumor load and risk of tumor lysis syndrome, safety precautions including hydration, uric acid reducers and laboratory assessments have to be followed during venetoclax ramp up in accordance with the current recommendations (see below). No debulking with bendamustine is to be administered ahead of the re-treatment as it is expected that the progressions are detected at an early time point.

Duration of treatment:

After a debulking treatment with 2 cycles of bendamustine (that may be omitted in case of contraindications, see above), an induction treatment with 6 cycles of obinutuzumab and venetoclax (ABT-199) will be administered (each cycle with a duration of 28 days unless administration of GA101 is delayed). Thereafter 2 stagings (initial response assessment and final restaging) are performed and ABT-199 is continued during that phase and during the maintenance treatment. In the maintenance treatment with ABT-199 and GA101, the duration of each cycle is 84 days (12 weeks = 3 months) and as up to 8 cycles of maintenance treatment are permitted, the maximum duration of the maintenance is 24 months. Maintenance treatment will be continued until 3 months after confirmation of achievement (clinical) CR or CRi and of MRD negativity (2 consecutive measurements 3 months apart), progression, start of a subsequent therapy, unacceptable toxicity or for up to 8 cycles (each with a duration of 84 days) whichever occurs first.
The maximum duration of the initial treatment is 34 months (0-2 cycles debulking, 6 cycles induction with GA101 and ABT-199, 2 months with ABT-199 treatment between initial response and final restaging and up to 24 months maintenance treatment with ABT-199 and GA101).
Previously, the duration of the follow-up phase depended on the duration of maintenance treatment; but after amendment 4 and 5 it was decided to follow all patients willing to participate in a longer follow-up until the end of the trial in Q4/2024.

	Patients with re-treatment with venetoclax and obinutuzumab in the CLL2-BAG trial and who discontinue treatment (e.g. due to MRD-negative remission or toxicity), will receive at least one follow-up visit 3-months after the end of treatment and will be followed 6-monthly until end of trial in Q4/2024. The end of the clinical trial is defined as Q4/2024.
Long-term follow up following the end of the study:	Initially, it was planned to transfer all patients to the registry of the GCLLSG to be able to collect long-term follow up data after the end of CLL2-BAG study. Although the duration of the follow-up was extended with amendments 4 and 5, this seems still important as the outcome of patients has improved considerably with the novel targeted agents. Each patient will be informed about the importance of long term follow data and asked for his/her consent to the long term follow-up within the GCLLSG registry with the initial informed consent and will be asked again before his follow-up within the CLL2-BAG trial ends. 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 within the non-interventional GCLLSG registry after the end of the trial.
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. Criteria for termination of the study as a whole are: - An unacceptable profile or incidence rate of adverse events/ adverse events of special interest 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:	For the analyses, the patient population will be defined as the full analysis set (FAS) and comprises of all enrolled patients who received at least two complete cycles of induction therapy. The primary efficacy variable (primary endpoint) is the overall response rate (ORR) at final restaging after induction therapy (end of induction treatment response = EOIT). ORR is defined as the proportion of patients having achieved a CR/CRi, clinical CR/CRi or PR. Patients without any documented response assessment will be kept and labeled as 'non-responder' in the analysis. Among the secondary endpoints the best response until 6 months after final restaging (RE) and end of maintenance treatment will be assessed and is defined as best response achieved until and including the response assessment six months after final restaging and at end of maintenance treatment.

The BAG-regimen is assessed to be not effective if the ORR is less than 75% (ORR of an uninteresting regimen). It is assumed to improve the ORR after the induction treatment to at least 90% (response rate of an active regimen). The lower boundary of efficacy of 75% ORR corresponds to an expected ORR of a mixed CLL population and is composed of the expected ORR of relapsed/refractory as well as previously untreated (first-line) patients. First-line patients are defined as patients without any previous therapy; however, single agent steroids, intravenous immunoglobulins and immunosuppressive drugs will be not counted as previous therapy. For relapsed/ refractory patients (RR, stratum 1) an ORR of 64%[6] is expected and for first-line patients (FL, stratum 2) it is expected to achieve an ORR of 90%[7] approximately. Concerning different allocations of RR/FL- patients a fix lower limit of 1/3 and an upper limit of 2/3 will be considered resulting in a flexible recruitment of 1/3 to 2/3 per stratum.
Pairwise comparisons of the strata will be performed descriptively only.

Sample size calculation:

The primary endpoint (ORR) was used to determine the sample size of the study. The following study assumptions are considered:

- As stated before the ORR rate for an uninteresting regimen is assumed to be 75% with corresponding null hypothesis H0: ORR = 0.75. It is aimed to improve this rate to at least 90% with the BAG-regimen.
- The type I error is set to $\alpha = 5$.
- The type II error is the chance that an effective treatment will not be studied further. This should not exceed $\beta = 20\%$, so that it is aimed to achieve a power of at least $(1 - \beta) = 80\%$.

According to the above determined study parameters a two-sided one-sample binomial-test with an overall significance level of 5% will have at least 80% power to show an ORR of more than 75% when the total number of patients is 54.
To account for a mixed CLL population consisting of RR- and FL- patients and to ensure 80% power it will be necessary to enroll 8 additional patients (including a 10% drop-out rate approximately). Thus 62 patients have to be recruited in total.
Sample size calculation was performed using EAST 5 software and Binomial tables

Recruitment strategy:

For the initial recruitment, a fix (1/3 and 2/3) recruitment allocation for each stratum (first-line versus relapsed/refractory) was performed to include at least 21 patients in each stratum.
Up to 20 patients may receive a re-treatment in case of a progression ≥ 6 months after maintenance treatment termination.

Study duration:

Start of recruitment	Q2/2015 (planned Q1/2015)
End of recruitment	Q1/2016 (as planned)
Last patient start re-treatment	Q2/2022 (planned Q1/2022)
End of trial	Q4/2024

Statisticians:	Dr. Sandra Robrecht and Dr. Can Zhang Department of Internal Medicine I, Study office GCLLSG, University of Cologne, Kerpener Str. 62, 50924 Köln, 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.