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-Maria 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 GA101 (obinutuzumab) and CAL-101 (idelalisib) followed by CAL-101 and GA101 maintenance in CLL patients (CLL2-BCG 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:	Initially, it was planned to enrol 62 eligible patients (among them ≥ 21 first-line and ≥ 21 relapsed/refractory patients). Due to safety concerns, the first-line stratum was closed after enrolment of 16 first-line patients, and the recruitment of the relapsed/refractory stratum will be continued until approximately 41 evaluable patients with relapsed/refractory CLL have been enrolled (including relapsed/refractory patients enrolled before the second amendment and relapsed high-risk patients recruited after the second amendment).
Number of sites:	Approximately 20 sites in Germany
Trial objectives:	The primary objective of the study is to evaluate the efficacy of a sequential regimen of two cycles of bendamustine, followed by a combination therapy of GA101 (obinutuzumab) and CAL-101 (idelalisib) followed by CAL-101 and GA101 maintenance in CLL patients. The secondary objective is to evaluate the safety of a sequential regimen of two cycles of bendamustine, followed by a combination therapy of GA101 and CAL-101 followed by CAL-101 and GA101 maintenance in CLL patients.
Study endpoints:	Primary endpoint: 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 = EOT) including all patients achieving:

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

Secondary endpoints:

- Safety parameters: Type, frequency, and severity of
  - adverse events (AE) and
  - adverse events of special interest (AESI)

  and their relationship to study treatment
- 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 at
  - final restaging after end of induction treatment (12 weeks after last cycle of induction treatment) in all patients responding to study treatment and
  - every 12 weeks (= 3 months) during the maintenance phase if the patient has achieved a (clinical) CR/CRi or
  - every 24 weeks (= 6 months) in patients with a PR (with or without lymphocytosis)
- 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 (RE, see above) (except for the ORR by investigator assessment)
  - after end of maintenance treatment
- ORR in biologically 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),
  - partial response (PR) and
  - PR with lymphocytosis
- Treatment free survival and time to next CLL treatment
- 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 for measurement of enlarged lymph nodes, spleen and liver
- Computed tomography (CT) or magnetic resonance imaging (MRI) scans 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
- Assessment of constitutional symptoms
- Survival status
- Survey of start and type of next treatment for CLL

Safety:

- Clinical laboratory evaluations (every two weeks during the induction treatment with idelalisib)
- 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 until 1 year after last dosage of GA101
- CMV-PCR every two weeks in patients with positive CMV-IgG/-IgM at screening during the induction treatment with idelalisib; thereafter, the intervals may be extended to 3-monthly if no CTC°III/IV AEs occurred during the induction treatment.
- pregnancy test ≤ 7 days before start of treatment, every month during debulking and induction therapy and every three months during maintenance treatment in all women of childbearing potential

Other (exploratory) variables:

- Tissue samples of lymph node biopsies if clinically indicated (e.g. exclusion of Richter´s transformation in case of progression)
- Tissue samples of other biopsies, e.g. intestinal mucosa or liver if clinically indicated (e.g. diagnostics performed due to suspected idelalisib toxicities)
- Evaluation of leucocyte subsets, function of regulatory T- and B-cells, intracellular pathways and cytokine profiles, as well as sequencing of gut microbiota before, during and after treatment with idelalisib to characterize the immune modulation and interactions of immune system and microbiota occurring during treatment with the BCG-regimen

Target Population:

Patients must meet the following criteria:

Inclusion Criteria:

1. Relapsed/refractory CLL requiring treatment according to iwCLL criteria[1] with at least one of the following features:
   - del(17p)/TP53 mutation
   - ineligibility for ibrutinib due to refractoriness, intolerance or contraindications to receive ibrutinib (e.g. intake of vitamin k antagonists)

   Patients, must have recovered from acute toxicities of the previous treatment and pre-treatment must be stopped within the following time periods before start of the study treatment in the CLL2-BCG trial:

   - chemotherapy within ≥ 28 days
   - antibody treatment within ≥ 14 days
   - kinase inhibitors, Bcl-2-antagonists or immunmodulatory agents within ≥ 3 days
   - corticosteroids may be applied until the start of the BCG-regimen, these have to be reduced to an equivalent of ≤ 20 mg prednisolone during treatment
2. 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)
3. 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 hrs urine collection
4. Adequate liver function as indicated by a total bilirubin ≤ 1.5x, 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 GA101), negative testing for hepatitis-C RNA and negative HIV antibody 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 therapy
5. Active 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 - 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. Ongoing inflammatory bowel disease
8. Ongoing drug induced pneumonitis
9. Use of investigational agents which would interfere with the study drug ≤28 days prior to registration
10. Known hypersensitivity to GA101 (obinutuzumab), CAL-101 (idelalisib) 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
11. 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 (3-monthly))
12. Fertile men or women of childbearing potential unless:
13. surgically sterile or ≥ 2 years after the onset of menopause, or
14. 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.
15. Vaccination with a live vaccine ≤28 days prior to registration
16. Legal incapacity
17. Prisoners or subjects who are institutionalized by regulatory or court order
18. Persons who are in dependence to the sponsor or an investigator

[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.[2], 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 rated 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.

Names of investigational medicinal products (IMPs):

- Bendamustine
- GA101 (obinutuzumab, trade name: *Gazyvaro*®)
- CAL-101 (idelalisib, trade name: *Zydelig*®)

Investigational medicinal product – dosage and method of administration:

Debulking

Two debulking cycles of bendamustine will be administered before induction with GA101 (obinutuzumab) and CAL-101 (idelalisib) **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 70 mg/m² i.v.
	Day 2:	bendamustine 70 mg/m² i.v.

Induction

The induction treatment consists of **6 cycles, each with a duration of 28 days**; during the first cycle GA101 (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 of CAL-101 (idelalisib) starts in cycle two.
On days with administration of both, CAL-101 and GA101, oral intake of CAL-101 will be followed by intravenous administration of GA101. Patients will receive the first dosage of CAL-101 on day 1 of the second cycle in clinic/outpatient clinic/private practice before the administration of GA101 is started. Patients will be advised how to administer all following doses at home (also on days with intravenous administration of GA101).

GA101 (obinutuzumab) i.v. infusion:

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

The first infusion of GA101 in the first cycle 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, the remaining 900 mg of the first dose should be administered on day 2.

CAL-101 (idelalisib) p.o.:

Cycle 1:		--
Cycles 2-6:	Days 1-28:	CAL-101 150 mg (1 tabl.) p.o. 1-0-1

CAL-101 tablets with a strength of 100 mg will be used in case of AEs (as described in the protocol, section *8.6.3 Dose and schedule modifications for CAL-101 (idelalisib).*

Maintenance

Before the start of 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 CAL-101 (idelalisib) is continued** and there is no interruption between induction and maintenance treatment.

In the maintenance treatment CAL-101 will be continued at the same dosage, but the interval of the GA101 (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.

CAL-101 (idelalisib) and GA101 (obinutuzumab):

Cycles 1-8:	Day 1:	GA101 1000 mg i.v.
	Days 1-84:	CAL-101 150 mg (1 tabl.) p.o. 1-0-1

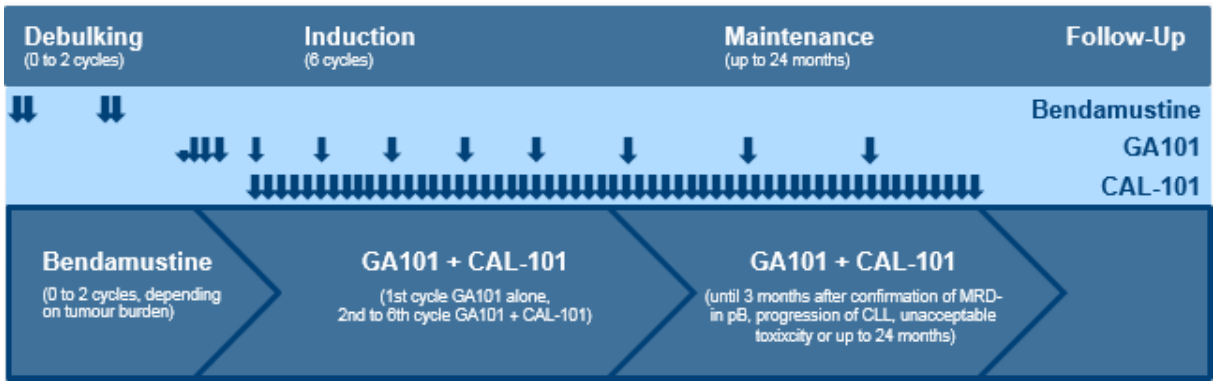
The **maintenance treatment will be continued until** (whichever occurs first):

- **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. < 10^{-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 CAL-101 (idelalisib) and GA101 (obinutuzumab) or one of the two outside the trial, if the drugs are commercially available by then.

Treatment plan:



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 GA101 (obinutuzumab) and CAL-101 (idelalisib) 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 CAL-101 is continued during that phase and during the maintenance treatment. In the maintenance treatment with CAL-101 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 treatment is 34 months (0-2 cycles debulking, 6 cycles induction with GA101 and CAL-101, 2 months with CAL-101 treatment between initial response assessment and final restaging and up to 24 months maintenance treatment with CAL-101 and GA101).
The duration of the follow-up phase depends on the duration of maintenance treatment; in case of a maximum duration of the maintenance of 24 months only 2 follow-up visits (3 and 6 months after end of treatment) will be performed. On the other hand, in case of an achievement of (clinical) CR or CRi and MRD negativity after induction treatment, patients will receive the minimum number of 2 cycles of maintenance treatment and a total of 8 follow-up visits (6 follow-up visits with an interval of 3 months during the time that would have otherwise been the maintenance treatment phase and 2 regular follow-up visits). However, in a patient who discontinued treatment

during the induction phase or the first 2 cycles of maintenance treatment, the follow-up will not be extended further after the 8 follow-up visits. Afterwards the patients are considered end of study.

The end of the clinical trial is defined as the time point once the last patient has completed the maintenance phase and at least 2 follow-up visits (with an interval of 3 months) thereafter. This will take place approximately 40 months after the last patient entered the trial.

Long-term follow-up following the end of the study:

To be able to collect long-term follow-up data after the end of CLL2-BCG study, inclusion in the registry of the GCLLSG should be considered. For this purpose, 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. 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 following patient population will be defined:

- Full analysis set (FAS): comprises of all enrolled patients who received at least one dose of any study medication.

Analyses of all efficacy and safety endpoints will be based on the FAS.

The primary efficacy variable (primary endpoint) is the overall response rate (ORR) at final restaging after induction therapy (end of induction treatment response = EOT). ORR is defined as the proportion of patients having achieved a CR/CRi, clinical CR/CRi, PR or PR with lymphocytosis. Patients without any documented response assessment will be kept and labelled 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 are defined as best response achieved until and including the response assessment six months after final restaging and end of maintenance treatment.

Results of primary and secondary endpoints will be described for the two strata separately. Pairwise comparisons of the strata will be performed descriptively only.

Sample size calculation:

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

- The ORR for an uninteresting regimen was assumed to be 75 % with corresponding null hypothesis H0: ORR = 0.75. This lower boundary of efficacy corresponded to an expected ORR of a mixed CLL population and was composed of the expected ORR of relapsed/refractory as well as previously untreated (first-line) patients. For relapsed/ refractory patients (RR, stratum 1) an ORR of 64 % was expected and for first-line patients (FL, stratum 2) it was expected to achieve an ORR of 90 % approximately.
  It was aimed to improve this rate to at least 90 % with the BCG-regimen.
- The type I error was 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 was 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 % would have at least 80 % power to show an ORR of more than 75 % when the total number of patients would be 54.

To account for a mixed CLL population consisting of RR- and FL-patients and to ensure the 80 % power it was considered necessary to enrol 8 additional patients (including a 10 % drop-out rate approximately). Thus 62 patients were planned to be recruited in total. The sample size calculation was performed using EAST 5 software and Binomial tables.

Concerning different allocations of RR/FL- patients a fix lower limit of 1/3 and an upper limit of 2/3 were considered initially resulting in a flexible recruitment of 1/3 to 2/3 per stratum. Accordingly, it was planned that each stratum (first-line and relapsed/refractory) should include at least 21 patients, and that the recruitment for one stratum was planned to be closed as soon as 41 patients have been enrolled.

Due to safety concerns in the course of the study, the first-line stratum was closed after enrolment of 16 first-line patients, and the recruitment of the relapsed/ refractory stratum will be continued until approximately 41 evaluable patients with relapsed/refractory high-risk CLL have been enrolled. The goal of the study is to assess preliminary efficacy. The evaluation of efficacy will be based on the estimation of the ORR and its corresponding exact confidence interval using the Clopper-Pearson method. The 95% confidence intervals

indicating the precision for the estimations of the ORR (for a given observed ORR and sample size) are provided in the tables below. Given the small sample size (and widths of the confidence intervals) it should be acknowledged that it is not expected to get highly precise estimations.

95% confidence intervals at different ORR (FL stratum)

Sample size	Observed ORR	95% Confidence Interval using Clopper-Pearson Method
16	25%	(7%, 52%)
16	50%	(25%, 75%)
16	75%	(48%, 93%)

95% confidence intervals at different ORR (RR stratum)

Sample size	Observed ORR	95% Confidence Interval using Clopper-Pearson Method
41	~ 56%	(38%, 72%)
41	~ 61%	(45%, 76%)
41	~ 66%	(49%, 80%)
41	~ 71%	(54%, 84%)
41	~ 76%	(60%, 88%)
41	~ 80%	(65%, 91%)

Study duration:

Start of recruitment	Q2/2015 (as planned)
Expected end of recruitment	Q4/2020
End of study	Q2/2024
Final study report	Q2/2025

Statistician:

Dr. Sandra Robrecht
Department of Internal Medicine I, Study office GCLLSG, University of Cologne, Kerpener Str. 62, 50937 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.