Universität zu Köln

TRIAL SYNOPSIS

A PROSPECTIVE, OPEN-LABEL, MULTICENTER PHASE-II-TRIALTO EVALUATE THE EFFICACY AND SAFETY OF A SEQUENTIAL REGIMEN OF **BENDAMUSTINE FOLLOWED BY GA101 (OBINUTUZUMAB), ZANUBRUTINIB (BGB-3111) AND ABT-199 (VENETOCLAX) IN PATIENTS WITH RELAPSED/REFRACTORY CLL**

(CLL2-BZAG-TRIAL OF THE GCLLSG)

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The information in this trial protocol is strictly confidential. It is for the use of the sponsor, investigator, trial personnel, ethics committee, the authorities, and trial subjects only. This trial protocol may not be passed on to third parties without the express agreement of the sponsor or the Global Principal Investigator (GPI, “Leiter der klinischen Prüfung (LKP)”)

I. Signatures

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20.08.2020

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II. Synopsis

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Coordinating Physician	Dr. med. Moritz Fürstenau Department I of Internal Medicine, Cologne University Hospital Kerpener Str. 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), zanubrutinib (BGB-3111) and venetoclax (ABT-199) in patients with relapsed/refractory CLL (CLL2-BZAG protocol)
Indication:	Patients with 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 40 eligible patients
Trial objectives:	The primary objective of the study is to evaluate the efficacy of a sequential regimen of two optional cycles of bendamustine followed by obinutuzumab (GA101), zanubrutinib (BGB-3111) and venetoclax (ABT-199) in patients with relapsed/refractory CLL. The secondary objective is to evaluate the safety of a sequential regimen of two optional cycles of bendamustine, followed by a combination therapy of obinutuzumab (GA101), zanubrutinib (BGB-3111) and venetoclax (ABT-199) in patients with relapsed/refractory CLL.

Rationale:

Several targeted agents have become available for the treatment of CLL. As these agents are tolerated well and have different, potentially synergistic mechanisms of action, several trials are currently evaluating different combinations to increase the anti-leukemic efficacy. The German CLL Study Group currently runs four phase-II trials, 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 (so called BXX-studies)1. The results of the CLL2-BAG trial, evaluating a debulking with two cycles bendamustine (only for patients with a high 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 (MRD) negativity rate in the peripheral blood was 87%.2 No unexpected or cumulative toxicities were observed and only one manageable, laboratory tumor lysis syndrome occurred with venetoclax. These promising results warrant a further evaluation and the combination of venetoclax and obinutuzumab is tested in several phase-III studies including the GCLLSG frontline trials CLL13 for physically fit patients and CLL14 for patients with comorbidities. However, in the CLL2-BAG trial only a small proportion of patients had achieved a complete remission already at final restaging at the end of induction treatment and the majority had residual lymphadenopathy and/or splenomegaly. In order to achieve faster and deeper remissions a BTK inhibitor will be added to the CLL2-BAG regimen, as these inhibitors are known to primarily act in the lymph node and spleen and redistribute the malignant cells from the homing tissue to the peripheral blood. The CLL2-BZAG trial will evaluate a debulking with two cycles bendamustine (only for patients with a high tumor load), followed by an induction and maintenance treatment with obinutuzumab, zanubrutinib and venetoclax in patients with relapsed/refractory CLL. Thus, this trial combines one established (chemotherapy) and three novel, synergistic (antibody, BTK-inhibitor and Bcl-2 antagonist) principles of action in order to achieve deep and long lasting remissions with a short duration of treatment. Additionally, this trial has an extensive accompanying scientific program aiming at a better understanding of the kinetics of response and clonal evolution of CLL.

Study end points:

Primary endpoint:

- Negativity rate of minimal residual disease (MRD) in peripheral blood (PB) measured by multi-color flow cytometry at final restaging (RE) at the end of induction treatment (12 weeks after the start of the last induction cycle)

Secondary endpoints:

- Overall response rate (ORR) according to iwCLL criteria at

RE 12 weeks after the start of the last cycle of induction therapy including all patients achieving:

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

- CR/CRi rate at RE 12 weeks after the start of the last cycle of induction therapy
  -
- Safety parameters: Type, frequency, severity, and relationship to study treatment of
  - adverse events (AE),
  - serious adverse events (SAE) and
  - adverse events of particular/special interest (AEPI/AESI)
- MRD in PB measured by 4-color flow cytometry to guide the duration of maintenance therapy at:
  - RE 12 weeks after the start of the last cycle of induction therapy in all patients responding to study treatment and
  - every 12 weeks (= approx. 3 months) during the maintenance phase
  - every 24 weeks (= approx. 6 months) during the follow-up

and MRD in PB measured by 4-color flow cytometry for the assessment of the kinetics of response to the different treatment phases at:

- screening/baseline
- staging after debulking (if applicable)
- before start with zanubrutinib (cycle 2, d1)
- before start with venetoclax (cycle 3, d1)
- interim staging (after 3 induction cycles)
- initial response assessment (after 6 induction cycles)

- MRD in bone marrow measured by 4-color flow cytometry optionally in patients with (clin.) CR/CRi (or PR almost fulfilling CR criteria, e.g. with residual splenomegaly) 12 weeks after achievement of MRD negativity in PB
- Best response rate (BRR) until 6 months after RE
- ORR after debulking
- ORR after end of maintenance treatment
- Progression-free survival (PFS)
- Event-free survival (EFS)
- Overall survival (OS)
- Duration of response in patients with
  - a complete response (CR),

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

- Treatment-free survival (TFS) and time to next CLL treatment (TTNT)

Exploratory endpoints:

- Evaluation of relationship between various baseline markers and clinical outcome parameters

Criteria for evaluation:

Central baseline assessments (characterization of patient collective):

- immunophenotyping (for confirmation of CLL diagnosis), including CD38 and ZAP-70
- serum beta-2-microglobulin and thymidine kinase
- cytogenetics (FISH), TP53 and IGHV mutational status, karyotyping

Efficacy:

- Size of lymph nodes, spleen and liver by physical examination and ultrasound
- Magnetic resonance imaging (MRI) (or CT if available based on clinical indication) scans for confirmation of a CR at final restaging and/or before treatment termination (for confirmation of a CR) and whenever clinically indicated
- Complete blood count (CBC)
- Assessment of minimal residual disease (MRD) at several time points, including the final restaging (= primary endpoint)
- Bone marrow aspirate/biopsy for standard histopathology and MRD assessment at final restaging and/or before treatment termination
- Assessment of constitutional symptoms
- Survival status
- Survey of start and type of next treatment for CLL
- Lymph node biopsy at baseline and/or after relapse/disease progression for genome sequencing studies in patients who voluntarily agree to this procedure

Safety:

- Clinical laboratory evaluations
- ECOG Performance Status
- Assessment of comorbidity burden by CIRS-Score and concomitant medications
- AEs by NCI CTCAE Version 5
- HBV-DNA PCR every 4 weeks in patients with positive anti-HBc test at screening until approx. 12 months after last administration of obinutuzumab.
- CT scan or MRI of head/neck, chest, abdomen and pelvis/inguinal region (either at screening or during the first two treatment cycles before the start with venetoclax for evalua-

tion if bulky disease is present in mediastinum or abdomen and for risk categorization for tumor lysis syndrome with venetoclax).

- pharmacokinetic analysis for zanubrutinib and venetoclax in a subgroup of approx.10-15 patients at selected sites

Target Population:

Patients must meet the following criteria:

Inclusion Criteria:

1. Relapsed/refractory CLL in need of treatment according to iwCLL criteria[3]

In case of a recent previous treatment, patients 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-BZAG trial:

- chemotherapy ≥ 28 days
- antibody treatment ≥ 14 days
- kinase inhibitors, BCL2-antagonists or immunomodulatory agents ≥ 3 days
- corticosteroids may be applied until the start of the BZAG-regimen, these have to be reduced to an equivalent of ≤ 20mg prednisolone per day during treatment

Please note: Patients with a progression during previous treatment with venetoclax, ibrutinib or another BTK inhibitor, as well as patients with a known resistance mutation (e.g. BTK-/PLCg2) are excluded from study participation. However, patients who progressed after termination of treatment with venetoclax, ibrutinib, other BTK inhibitors and/or obinutuzumab or who stopped treatment due to intolerance to ibrutinib are eligible for participation.

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 neutrophil count ≥ 1.0 x 109/L, a hemoglobin value ≥8.0 g/dL and a platelet count ≥ 25 x 109/L, unless directly attributable to the patient´s CLL (e.g. bone marrow infiltration), in this case, platelet count should be ≥ 10 × 109/L.
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 4 weeks until one year after last dosage of GA101 (obinutuzumab) or until the last dose of zanubrutinib, whichever occurs later), 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. (Suspicion of) transformation of CLL (i.e. Richter's transformation, pro-lymphocytic leukemia) or central nervous system (CNS) involvement
2. Progression during previous treatment with venetoclax, ibrutinib or another BTK inhibitor, and/or presence of known mutations associated with resistance to therapy, e.g. Bruton´s Tyrosine Kinase and Phospholipase C Gamma 2 (PLCg2)
3. Confirmed progressive multifocal leukoencephalopathy (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 system1 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. Significantly increased risk of bleeding according to the investigator´s evaluation, e.g. due known bleeding diathesis (e.g. von-Willebrandt´s disease or hemophilia), major surgical procedure ≤ 4 weeks or stroke/intracranial hemorrhage ≤ 6 months.
8. Requirement of therapy with strong CYP3A4 inhibitors/inducers or anticoagulant with phenprocoumon (marcumar) or other vitamin K-antagonists
9. Use of investigational agents ≤ 28 days prior to start of study treatment, however, kinase inhibitors, BCL2-

[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. 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.

antagonists and antibody treatment are allowed in accordance with inclusion criterion number 1 (see above).

10. Known hypersensitivity to obinutuzumab (GA101), venetoclax (ABT-199), zanubrutinib (BGB-3111) or any of the excipients

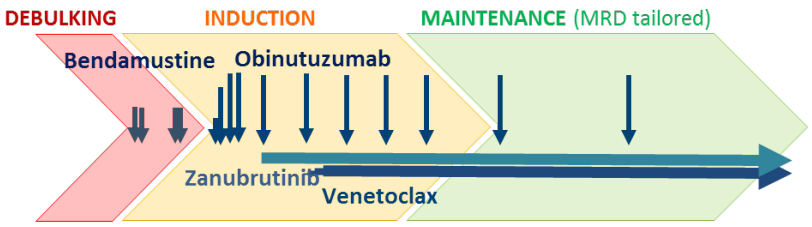
Please note: Patients with a known hypersensitivity to bendamustine are allowed to participate but will not receive a debulking with bendamustine

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)
12. 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.
13. Vaccination with a live vaccine ≤ 28 days prior to registration
14. Legal incapacity
15. Prisoners or subjects who are institutionalized by regulatory or court order
16. Persons who are in dependence to the sponsor or an investigator

Names of investigational medicinal products (IMPs):

- Bendamustine (generic medicinal products)
- Obinutuzumab (GA101, trade name: Gazyvaro®)
- Zanubrutinib (BGB-3111)
- Venetoclax (ABT-199, trade name: Venclyxto®)

Treatment overview:



Dosage and method of administration of IMP:

Debulking

Two debulking cycles of bendamustine will be administered before induction with obinutuzumab, zanubrutinib 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 109 /l and absence of bul-ky disease with no individual lymph node ≥ 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. In each of the two 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 obinutuzumab (GA101) 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 zanubrutinib (BGB-3111) starts on day 1 of cycle two and the daily intake of venetoclax (ABT-199) with a weekly dose ramp-up to final dose starting on day 1 of cycle three.

Obinutuzumab (GA101) i.v. infusion:

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

The first dosage of obinutuzumab has to be split into a 100 mg and a 900 mg infusion, which may be administered both at the full dose (1000 mg) after another on the same day if the infusion of a test-dosage of 100 mg is well tolerated by the patient. If the 100 mg test dose infusion on day 1 is not tolerated well, the remaining 900 mg have to be administered on day 2.

Zanubrutinib (BGB-3111) p.o.

Cycle 1:		--
Cycles 2-6:	Days 1-28:	zanubrutinib 160 mg p.o. twice daily

Treatment with zanubrutinib will start on day 1 of the second cycle under supervision of a study physician and before treatment with obinutuzumab. Further, patients will be instructed how to take zanubrutinib at home.

Venetoclax (ABT-199) p.o.:

Cycles 1/2:		--
Cycle 3:	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 4-6:	Days 1-28:	venetoclax 400 mg (4 tabl. at 100 mg)

Patients will receive the first dosage of venetoclax on day 1 of the third cycle in clinic/outpatient clinic/private practice before the start of the administration of obinutuzumab. Certain safety precautions depending on the patient´s risk for a tumor lysis syndrome are necessary (see below). Afterwards, weekly dose ramp-up will be performed on days 8, 15 and 22 of cycle 3 and day 1 of cycle 4 (also with safety precautions). On the days between the dose escalations, patients take the respective dose of venetoclax at home. The oral intake of zanubrutinib is continued during the whole dose escalation period by the patients at home. On days with administration of both, zanubrutinib and venetoclax, oral intake of zanubrutinib (before breakfast) will be followed by oral intake of venetoclax (during or within 30 minutes after breakfast).

Due to the risk of tumor 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 patients must have a laboratory monitoring at baseline (pre-dose) and 6 to 8, as well as 24 hrs post-dose on the first day of each dose level (i.e. 20 mg, 50 mg, 100 mg, 200 mg and 400 mg venetoclax). Additionally, patients should receive an uric acid reducer, e.g. allopurinol and potentially also rasburicase, should have an adequate hydration of ≥2 liters per day orally and potentially also intravenously e.g. in case of an increased TLS risk and should be hospitalized in case of a significantly increased risk of a TLS [see chapter 8.5.2 Safety precautions with venetoclax for tumor lysis syndrome].

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. The MRD negativity rate at the end of the induction treatment is the primary endpoint of the trial. During this phase of staging, the intake of zanubrutinib and venetoclax is continued and there is no interruption between induction and maintenance treatment.

In the maintenance treatment zanubrutinib and 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 = approximately 3 months).

The first maintenance cycle is started after completion of the final restaging procedures for all patients who clinically benefit from study treatment.

Obinutuzumab, zanubrutinib and venetoclax:

Cycles 1-8:	Day 1:	obinutuzumab 1000mg i.v.
	Days 1-84:	zanubrutinib 160mg p.o. twice daily
	Days 1-84:	venetoclax 400mg (4 tabl. at 100mg) p.o. once daily

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

- 12 weeks (approx. 3 months) after confirmation of achievement of a CR/CRi and 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. MRD negativity must be confirmed by 2 consecutive measurements in a 12-week interval).

Please note: At the physician's discretion and after consultation with the GCLLSG study office, maintenance treatment may also be stopped in MRD-negative patients with a PR almost fulfilling CR criteria, e.g. with a residual splenomegaly or slightly enlarged lymph nodes, which are considered an inactive remainder of prior massive enlargement due to CLL infiltration.

- maintenance cycle 8 (each cycle with a duration of 84 calendar days = 12 weeks = approx. 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 [approx. 3 months], leading to a total duration of the maintenance phase of 96 weeks (approx. 2 years). Patients who still benefit from further maintenance may continue the therapy with zanubrutinib, venetoclax and obinutuzumab or one/two of the three drugs outside the trial, if the drugs are commercially available by then.

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 (GA101), zanubrutinib (BGB-3111) and venetoclax (ABT-199) will be administered (each cycle with a duration of 28 days unless administration of obinutuzumab is delayed). Thereafter, two stagings (initial response assessment and final restaging) are performed, zanubrutinib and venetoclax are continued during that phase. In the maintenance treatment with zanubrutinib, venetoclax and obinutuzumab, the duration of each cycle is 84 days (12 weeks = approx. 3 months) and up to 8 cycles of maintenance treatment are permitted, the maximum duration of the maintenance is 96 weeks (= approx. 22 months). Maintenance treatment will be continued until 12 weeks after confirmation of achievement of (clinical) CR or CRi and of MRD negativity (2 consecutive measurements 12 weeks 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 approximately 31 months (0-2 cycles debulking, 6 cycles induction, 2 months with zanubrutinib and venetoclax treatment between initial response and final restaging and

	up to approx. 22 months maintenance treatment). The duration of the follow-up phase is 24 months for all patients (8 follow-up visits with an interval of 3 months). The end of the clinical trial is defined as the time point once the last patient has completed the maintenance phase and 8 follow up visits (with an interval of 3 months) thereafter.
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-BZAG 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 up 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.
Interim safety analysis:	Recruitment to the trial will be limited to six patients per month until an interim safety review. As soon as six patients have reached day 28 of the 4th induction cycle (i.e. 8 weeks of treatment with the triple combination of zanubrutinib, venetoclax and obinutuzumab), an interim safety analysis will be performed. The analysis will take into account the SAEs and AEPIs of all patients included in the trial as well as the CRF documentation of all four induction cycles of the six patients in the safety cohort. It will especially focus on the occurrence of following AEs: - CTC° III/IV infections, - CTC° III/IV hematological toxicities related to study treatment, which require an intervention (e.g. additional monitoring, administration of G-CSF or blood transfusions), - CTC° III/IV non-hematologic toxicities related to study treatment (except for alopecia and asymptomatic laboratory abnormalities not requiring a medical intervention), - laboratory and clinical tumor-lysis syndromes, - cardiovascular and bleeding AEs, and - AEs with a fatal outcome. The results from the interim safety analysis and all available data (also from other clinical trials) regarding the drugs used in this trial will be reviewed by the GPI together with the head of the GCLLSG, one statistician and other members of the protocol committee. This review will determine if the recruitment can continue without the fixed recruitment rate, if additional safety precautions and monitoring are needed or if the trial will be prematurely stopped.
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, continuous monitoring of efficacy and toxicity will be performed. Criteria for termination of the study as a whole are: - ≥4 laboratory tumor-lysis syndromes (CTC°III) and/or ≥2 clini-

cal tumor-lysis syndrome (CTC°IV) and/or an unexpectedly high rate of CTC°III/IV hematological and/or non-hematological AEs, infections, cardiovascular and/or bleeding events in the patients from the safety cohort (first 6 patients reaching day 28 of the 4th induction cycle) compared to the expected rate of these AEs based on the reference safety information of the study drugs.

- An unacceptable profile or incidence rate of (serious) 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 populations will be defined:

- Full analysis set (FAS): The FAS comprises of all enrolled patients who received at least two complete cycles of induction therapy (efficacy population). The FAS shall be used for analysis of all study endpoints except safety.
- Safety population: The safety population is defined as all subjects enrolled into the study receiving at least one dose of trial treatment, whether withdrawn prematurely or not. The safety population shall be used for evaluating the safety endpoints.

The primary efficacy variable (primary endpoint) is the negativity rate of minimal residual disease (MRD) in peripheral blood (PB) measured by 4-color flow cytometry at final restaging 12 weeks after the start of the last induction cycle.

MRD negativity is defined as less than one (1) CLL-cell among 10,000 leukocytes analyzed [0.01%], i.e. < 10-4. The MRD negativity rate is defined as the proportion of patients having achieved MRD negativity with respect to the FAS. Patients without any evaluable MRD sample at end of induction treatment will be kept and labeled as ‘MRD positive (≥10-4)' in the analysis.

The primary endpoint can be analyzed as soon as all enrolled patients who did not discontinue prematurely have achieved the landmark final restaging 12 weeks after the start of the last cycle of induction treatment.

Sample size calculation:

The primary efficacy analysis will be based on the estimation of the MRD negativity rate and its corresponding two-sided 95% Clopper Pearson confidence interval. As for the statistical analysis there will be no formal confirmatory testing. Primary and secondary endpoints will be descriptively analyzed and reported. The goal is to explore preliminary estimates.

On ground of feasibility the sample size of the study is determined at 40 patients in total. The two-sided 95% exact confidence intervals for given observed MRD negativity rates are provided in the table below.

95% confidence intervals at different MRD negativity rates at final restaging 12 weeks after last induction cycle.

Sample size N	MRD negativity rate N (%)	95% confidence interval using Clopper Pearson method
40	5 (12.5%)	(4.2%, 26.8%)
40	10 (25%)	(12.7%, 41.2%)
40	15 (37.5%)	(22.7%, 54.2%)
40	20 (50%)	(33.8%, 66.2%)
40	25 (62.5%)	(45.8%, 77.3%)
40	30 (75%)	(58.8%, 87.3%)
40	35 (87.5%)	(73.2%, 95.8%)

Study duration:

Expected start of recruitment	Q3/2020
Expected end of recruitment	Q4/2021
End of trial	Q4/2025

Statistician:

Dr. Can Zhang

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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.