Universität zu Köln

TRIAL PROTOCOL

A PROSPECTIVE, OPEN-LABEL, MULTICENTRE **PHASE-II-TRIAL** TO EVALUATE THE EFFICACY AND SAFETY OF **ZANUBRUTINIB (BGB-3111)**, A BTK INHIBITOR, PLUS **TISLELIZUMAB (BGB-A317)**, A PD-1 INHIBITOR, **WITH AND WITHOUT SONROTOCLAX (BGB-11417), A BCL2 INHIBITOR,** FOR TREATMENT OF PATIENTS WITH **RICHTER TRANSFORMATION**

(CLL-RT1-TRIAL OF THE GCLLSG)

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II. Synopsis

Involved parties and contact information

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Participating countries:	Germany, Austria and Denmark

Information on the clinical trial

Title of the clinical trial:	A prospective, open-label, multicenter phase-II trial to evaluate the efficacy and safety of zanubrutinib (BGB-3111), a BTK inhibitor, plus tislelizumab (BGB-A317), a PD1 inhibitor, for treatment of patients with Richter transformation with or without sonrotoclax（BGB-11417), a Bcl-2 inhibitor (CLL-RT1-trial of the GCLLSG).
Indication:	Patients with previously untreated Richter Transformation or patients who responded to up to one prior line of RT therapy.
Phase:	Phase-II clinical trial
Type of trial, trial design, methodology:	Prospective, multicenter, phase-II trial, two-arm, open-label, non-randomized
Number of patients:	48 eligible patients for the double combination therapy (cohort 1), approximately 26 patients for the triple combination therapy (cohort 2).
Trial objectives:	The primary objective of the study is to evaluate the efficacy of a combinational therapy with tislelizumab and zanubrutinib in CLL patients with Richter transformation to DLBCL (cohort 1). The secondary objectives are: • To evaluate the efficacy of a combinational therapy with tislelizumab and zanubrutinib with sonrotoclax in CLL patients with Richter transformation to DLBCL (cohort 2). • To evaluate the safety of a combinational therapy with tislelizumab and zanubrutinib with or without sonrotoclax in CLL patients with Richter transformation to DLBCL (cohort 1 and cohort 2).

Rationale: Richter syndrome (RS) or Richter transformation (RT) describes the rapid development of a histologically confirmed aggressive lymphoma, in most cases a diffuse large B cell lymphoma (DLBCL), in patients with CLL. The incidence rates of RT among CLL patients range from 2 to 10% [1]. RT can occur at any time during the course of CLL. Risk factors for development of RT include intrinsic biological features like TP53 mutations or 17p deletions as well as therapy-related factors as exposure to purine analogues like fludarabine [2]. However, up to one third of patients with RT are treatment naïve CLL patients [3].

RT patients have a very poor prognosis with a median OS of 6-8 months. There is no established standard of care for RT and most patients are treated comparably to de-novo DLBCL patients with chemoimmunotherapies like R-CHOP or R-DHAP. Given the poor prognosis, fit patients are considered for allogenic transplantation once they respond to therapy. However, as CLL is a disease of the elderly with a median age of 72 years, most patients with RT are not fit enough to undergo allogenic transplantation.

The advent of a variety of novel antibodies and targeted drugs allows for new therapeutic approaches to address the unmet clinically need for a better care for RT patients.

Zanubrutinib (BGB-3111) is an orally bioavailable selective, irreversible inhibitor of Bruton's tyrosine kinase (BTK) that is currently developed in a variety of B-cell malignancies, including CLL and DLBCL. BTK is a well-established target for CLL treatment, as its inhibition by currently licensed agents like ibrutinib disrupts the BCR-dependent survival and proliferation of CLL cells. Pleiotropic effects of ibrutinib lead to distinct toxicities, particularly bleeding events and arrhythmia. Zanubrutinib is suggested to be more selective than ibrutinib and have less off target effects on other kinases like EGFR, JAK3 or ITK. Preclinical as well as early clinical data indicate that zanubrutinib has less side effects and a more favorable pharmacokinetic and pharmacodynamic profile [4].

Tislelizumab (BGB-A317) is a humanized IgG4 variant monoclonal antibody with no Fc gamma receptor binding that targets the programmed cell death-1 (PD-1) receptor. Expression of PD-1 is a mechanism by which malignant cells evade the immune system response. By blocking the interaction between PD-1 and its ligands, T-cells are allowed to recognize and kill tumor cells. So far, tislelizumab has shown clinical activity in a variety of tumors and is currently being tested in solid as well as hematological malignancies. A recent phase Ib trial has shown a manageable toxicity profile of the combination of zanubrutinib and tislelizumab in different b-cell malignancies [5].

Sonrotoclax (BGB-11417) is an orally available Bcl-2 inhibitor currently in development for treatment of CLL and other B-cell malignancies. Bcl-2 is almost universally overexpressed in CLL and acts as an anti-apoptotic regulator, thereby facilitating accumulation of malignant CLL cells due to dysregulated programmed cell death. Bcl-2 overexpression is also common in aggressive B-cell lymphoma, including DLBCL, and is associated with a particularly poor prognosis. Pre-clinical studies have suggested stronger Bcl-2 inhibition by sonrotoclax compared to venetoclax, the only currently approved Bcl-2 inhibitor. Pharmacokinetic models also suggested better antitumor activity of sonrotoclax compared to venetoclax at much lower drug concentrations. A current ongoing Phase 1 study identified 320 mg of sonrotoclax as the recommended dose for clinical use in patients with CLL/SLL.

Given that high PD-1 expression has been observed in patients with lymphoid malignancies, checkpoint inhibitors are promising candidates for treatment of RT. Previous data have shown that effective eradication of DLBCL cells in the bone marrow of RT patients can be achieved with single-agent PD-1 inhibitors [6]. However, persistence of CLL infiltration was observed

as well, which suggests that a combinational approach might be indicated for effective treatment.

Currently, two trials are testing combinational approaches with nivolumab, a PD-1 inhibitor, plus ibrutinib and early interim analyses showed good response rates in pre-treated patients with RT [7, 8]. Moreover, single agent BTK inhibition has shown activity in RT [9-11]. Taken together, preclinical as well as early clinical data provide a good rationale to investigate on a combination of PD-1 inhibition plus BTK inhibition in previously untreated patients with RT.

This prospective phase-II-trial will investigate a combinational regime of the PD-1 inhibitor tislelizumab and the BTK inhibitor zanubrutinib. The treatment schedule consists of 6 cycles of induction therapy (21-day cycles) during which tislelizumab will be administered once per cycle at a fixed dose, followed by 6 additional cycles of tislelizumab consolidation therapy. Zanubrutinib will be given two times daily (BID) from day 1 of cycle 1. Patients who show response to therapy after 12 cycles of therapy will continue until disease progression, unacceptable toxicities or end of trial.

An additional, exploratory cohort will explore the triple combination of tislelizumab, zanubrutinib and the Bcl-2 inhibitor sonrotoclax. The treatment schedule consists of 6 cycles of induction therapy (21-day cycles) during which tislelizumab will be administered once per cycle at a fixed dose, followed by 6 additional cycles of tislelizumab consolidation therapy. Zanubrutinib will be given two times daily (BID) from day 1 of cycle 1. Sonrotoclax will be introduced from day 1 of cycle 1 and undergo a ramp-up 3 times a week over 17 days from 2mg up to 320 mg with daily drug intake. Patients who show response to therapy after 12 cycles of therapy will continue until disease progression, unacceptable toxicities or end of trial.

Study end points:

Primary endpoint:

Overall response rate (ORR) after induction therapy (i.e. 6 cycles) according to the refined Lugano Classification (Cheson et al, 2016) [12].

- Complete response (CR)
- Partial response (PR)

Secondary endpoints:

- ORR after induction therapy (i.e. 6 cycles) according to IWCLL criteria (Hallek et al, 2018)
- ORR after consolidation therapy (i.e. 12 cycles)
- Duration of response
- Progression-free survival (PFS)
- Overall survival (OS)
- Time to next treatment (TTNT)
- Proportion of patients receiving SCT for consolidation
- Safety parameters: type, frequency, severity of adverse events (AEs), and their relationship to study treatment

Exploratory endpoints:

Evaluation of relationship between various baseline markers, including PD-1/PD-L1 expression and mutational load, and clinical outcome parameters

Criteria for evaluation:

Efficacy

- FDG-PET-CT for confirmation of CR after induction
- Computed tomography (CT) scans at screening and for each staging
- Bone marrow aspirate/biopsy at screening and for confirmation of CR
- Complete blood count (CBC)
- Peripheral blood samples for immunophenotyping for confirmation of CLL diagnosis, serum parameters (Beta-2-microglobuline and Serum-Thymidine-Kinase), genetic evaluation
- 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 with CIRS-Score
- Concomitant medications
- AEs by NCI CTCAE Version 5.0
- HBV-DNA PCR every two months in patients with positive anti-HBc (irrespective of HBsAg) at screening
- pregnancy test within 7 days before start of treatment for all women of childbearing potential

Target Population**:**

Patients must meet the following criteria:

Inclusion Criteria

1. Confirmed diagnosis of CLL according to iwCLL criteria (Hallek et al, 2018) [13]
2. Confirmed histopathological diagnosis of RT (diffuse large B-cell lymphoma or Hodgkin's lymphoma [Hodgkin's lymphoma only when not eligible for more intensive treatment])
3. Previously untreated RT or patients with objective response or non-tolerance to first-line RT treatment
4. Adequate bone marrow function as defined by:

- Absolute neutrophil count (ANC) ≥ 1000/mm^3, except for patients with bone marrow involvement in which ANC must be ≥ 500/mm^3
- Platelet ≥ 75,000/mm^3, except for patients with bone marrow involvement in which the platelet count must be ≥ 30,000/mm^3

5. Creatinine clearance ≥30ml/min calculated according to the modified formula of Cockcroft and Gault or directly measured with 24hr urine collection or an equivalent method.

6. 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/RT or to Gilbert's Syndrome, in which case a max. total bilirubin ≤ 3 x and AST/ALT ≤ 5 x the institutional ULN value are required.[1]

7. 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 two months until 2 months after last dose of zanubrutinib), negative testing for hepatitis-C RNA and negative HIV test within 6 weeks prior to registration

8. Age at least 18 years

9. ECOG performance status 0-2, ECOG 3 is only permitted if related to CLL or RT (e.g. due to anaemia or severe constitutional symptoms)

10. Life expectancy ≥ 3 months

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

Exclusion criteria

1. Patients who did not respond to previous line of RT therapy (i.e. primary progressive patients)[2]

2. Patients with more than one prior line of RT therapy

3. Allogenic stem cell transplantation within the last 100 days or signs of active GVHD after prior allogeneic stem cell transplantation within any time

1 For patients who start study treatment with elevated liver enzymes due to CLL/RT or Gilbert's syndrome, toxicity and AE reporting will follow CTCAE grading once these values further increase. E.g. if a patient starts with a bilirubin value of 2.0 mg/dl, which rises to 3.0 mg/dl after one cycle, this should be reported as grade 2 bilirubinemia (see CTCAE v5)

2 In cases with urgent need for treatment, a prephase treatment with steroids, vincristine (up to 2 mg IV) or cyclophosphamide (up to 200 mg^2 daily for max 3 days) can be administered at the discretion of the treating physician prior to enrolment or start of study medication.

4. Patients with confirmed PML
5. Uncontrolled autoimmune condition
6. Malignancies other than CLL currently requiring systemic therapies (unless the malignant disease is in a stable remission at the discretion of the treating physician)
7. Uncontrolled infection currently requiring systemic treatment
8. 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 , or any other life-threatening illness, medical condition or organ system dysfunction that – in the investigator´s opinion could comprise the patients safety or interfere with the absorption or metabolism of the study drugs
9. Requirement of therapy with strong CYP3A4 inhibitors/ inducers
10. Requirement of therapy with phenprocoumon or other vitamin K antagonists.
11. Known active infection with HIV, or serologic status reflecting active hepatitis B or C infection as follows:
    - Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Patients with presence of HBcAb, but absence of HBsAg, are eligible if hepatitis B virus (HBV) DNA is undetectable (< 20 IU), and if they are willing to undergo monitoring every 4 weeks for HBV reactivation.
    - Presence of hepatitis C virus (HCV) antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable.
12. Major surgery within 4 weeks of the first dose of study drug.
13. Any uncontrolled or clinically significant cardiovascular disease including the following:
    - Myocardial infarction within 6 months before screening
    - Unstable angina within 3 months before screening
    - New York Heart Association class III or IV congestive heart failure
    - History of clinically significant arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes)
14. History of severe bleeding disorder such as hemophilia A, hemophilia B, von Willebrand disease, or history of spontaneous bleeding requiring blood transfusion or other medical intervention
15. History of stroke or intracranial hemorrhage within 6 months before first dose of study drug

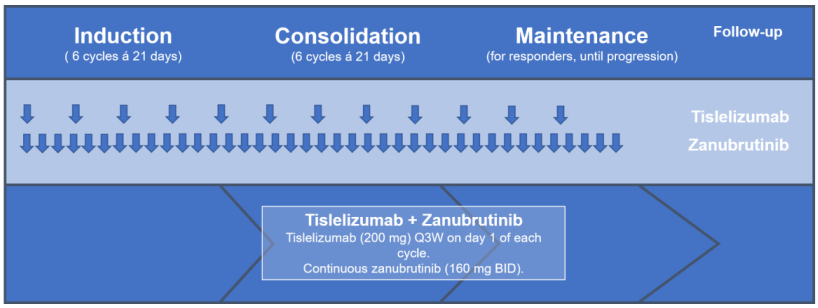
16. Severe or debilitating pulmonary disease
17. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, bariatric surgery procedures, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction
18. Use of investigational agents, e.g. monoclonal antibodies or other experimental drugs within clinical trials, which might interfere with the study drug within 28 days (or 5 times half-life [t1/2] of the compound, whichever is longer) prior to registration
19. Known hypersensitivity to tislelizumab, zanubrutinib, sonrotoclax or any of the excipients
20. Pregnant women and nursing mothers (a negative pregnancy test is required for all women of childbearing potential within 7 days before start of treatment)
21. Fertile men or women of childbearing potential unless:
    - surgically sterile or ≥ 2 years after the onset of menopause, or
22. 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 120 days after the last dose of tislelizumab, 90 days after sonrotoclax and 30 days after zanubrutinib respectively. Vaccination with a live vaccine <28 days prior to randomization
23. Legal incapacity
24. Prisoners or subjects who are institutionalized by regulatory or court order
25. Persons who are in dependence to the sponsor or an investigator

Names of investigational medicinal products (IMPs):

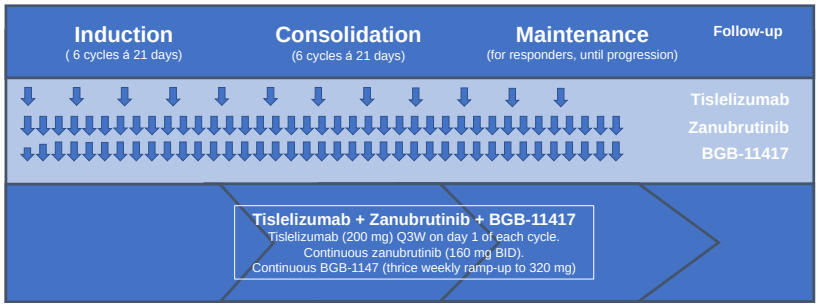
- Tislelizumab (BGB-A317)
- Zanubrutinib (BGB-3111)
- Sonrotoclax (BGB-11417)

Treatment plan:

Cohort 1



Cohort 2



Dosage and method of administration of IMP:

Induction

Cohort 1

Induction treatment consists of **6 cycles**, each with a duration of **21 days** (Q3W). Tislelizumab is administered intravenously on day 1 of each cycle. Continuous daily administration of zanubrutinib starts on day 1 of the first cycle as well.

Cycle 1-6:	Day 1:	Tislelizumab	200 mg iv
	QD:	Zanubrutinib	160 mg BID po

Cohort 2

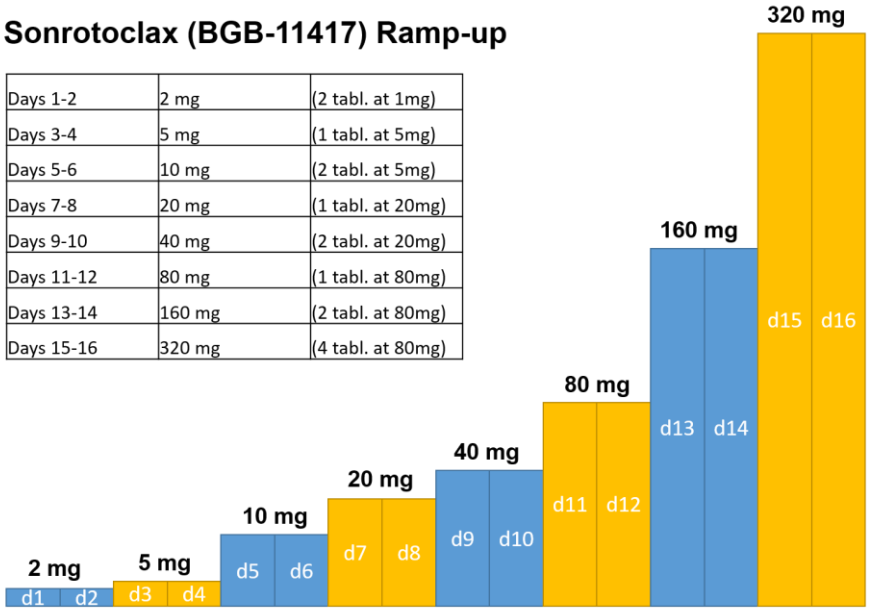
Induction treatment consists of **6 cycles**, each with a duration of **21 days** (Q3W). Tislelizumab is administered intravenously on day 1 of each cycle. Continuous daily administration of zanubrutinib starts on day 1 of the first cycle as well. The Ramp-up Phase for sonrotoclax also begins on the first day of cycle 1.

Cycle 1-6:	Day 1:	Tislelizumab	200 mg iv
	Day 1-21:	Zanubrutinib	160 mg BID po

Cycle 1:	Sonrotoclax	Start Ramp-up* to 320 mg QD po	
	Days 1-2	Sonrotoclax	2 mg (2 tabl. at 1mg)
	Days 3-4	Sonrotoclax	5 mg (1 tabl. at 5mg)
	Days 5-6	Sonrotoclax	10 mg (2 tabl. at 5mg)
	Days 7-8	Sonrotoclax	20 mg (1 tabl. at 20mg)
	Days 9-10	Sonrotoclax	40 mg (2 tabl. at 20mg)
	Days 11-12	Sonrotoclax	80 mg (1 tabl. at 80mg)

	Days 13-14	Sonrotoclax	160 mg (2 tabl. at 80mg)
	Days 15-21	Sonrotoclax	320 mg (4 tabl. at 80mg)
Cycle 2-6:	Day 1-21	Sonrotoclax	320 mg QD po

*The ramp-up schedule will be conducted over 16 days as follows:



For dose reductions please see chapter 8.7.3. Dose and schedule modifications for Sonrotoclax (BGB-11417).

Consolidation

During consolidation, patients continue to receive all agents **over 6 cycles** (Q3W).

Cohort 1:

Cycle 7-12:	Day 1:	Tislelizumab	200 mg iv
	QD:	Zanubrutinib	160 mg BID po

Cohort 2:

Cycle 7-12:	Day 1:	Tislelizumab	200 mg iv
	Day 1-21:	Zanubrutinib	160 mg BID po
	Day 1-21:	Sonrotoclax	320 mg QD po

Maintenance

Patients with response to therapy (CR, PR, and also SD) continue to take both agents (cohort 2: three agents) until disease progression, non-tolerance or when receiving allogenic SCT for consolidation.

Duration of treatment: Patients with response to therapy continue to take all agents until disease progression, non-tolerance or receiving allogenic SCT as consolidation. All patients who respond to treatment

may continue treatment until the end of trial. The end of the clinical trial is defined as Q1/2026.

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

Patients, who discontinued treatment, will be followed up until 6 months after last study drug intake. To be able to collect long-term follow up data after the end of CLL-RT1 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 participation.

Interim safety analysis:

Cohort 1

The first six patients of cohort 1 will be part of an interim safety analysis, for which a close site monitoring will be maintained in order to take into account SAEs and AESIs. Special focus will be laid on:

- 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
- laboratory syndromes,
- cardiovascular and bleeding AEs, and
- AEs with a fatal outcome.

The interim safety analysis will be performed as soon as the first six patients of cohort 1 have been treated for three cycles. 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, the coordinating physician, one statistician and the safety management team of the GCLLSG. This review will determine if the recruitment can be continued, if additional safety precautions and monitoring are needed or whether the trial will be prematurely stopped.

Cohort 2

Similar interim safety analyses will be conducted separately in cohort 2 after the first 6 patients have completed 2, 4 and 6 cycles.

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:

- An unexpectedly high rate of CTC°III/IV hematological and/or non-hematological AEs, cardiovascular and/or bleeding events in the patients from the interim safety analysis
- 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

Patients will be allocated to cohort 1 and cohort 2 in a non-randomized fashion, as recruitment

methods and study assumptions:

for cohort 2 will start after recruitment for cohort 1 is already closed.

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 one dose of study medication in the third induction cycle. This means that at least one dose of any compound of the trial medication has to be documented for the third cycle of induction treatment. The FAS is the target analysis population for the analysis of primary and secondary efficacy endpoints within cohort 1.
  Patients of cohort 1 with early discontinuation from study treatment (i.e. discontinuation prior to administration of third induction cycle) will be reported separately from the FAS.
- Intention-to-treat (ITT) population: The ITT population comprises of all enrolled patients regardless of the number of administered cycles.The ITT population is the target analysis population for the descriptive analysis of primary and secondary efficacy endpoints within cohort 2. In addition, the ITT population will be used for descriptive analyses of primary and secondary endpoints within cohort 1.
- Safety population: The safety population is defined as all subjects enrolled in 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.

All endpoints refer to both cohorts and will be reported separately for each cohort without performing any formal comparisons. But the primary objective of the study refers to cohort 1 only, thus the primary endpoint analysis (i.e. confirmatory binomial test) will be performed for patients of cohort 1 only. Patients of cohort 2 will be considered as exploratory cohort and analyzed descriptively without any formal confirmatory testing.

The primary efficacy variable (primary endpoint) is the overall response rate (ORR) at interim staging after end of induction therapy (end of induction treatment = EOIT) according to refined Lugano Classification (Cheson et al, 2016). ORR is defined as the proportion of patients having achieved a CR or PR. Patients without any documented response assessment will be kept and labeled as ‘non-responder' in the analysis.

The primary efficacy analysis will be performed for patients of cohort 1 with respect to the FAS. Efficacy of the investigated regimen in cohort 1 is assessed to be not effective if the ORR is less than 40 %. The ORR will be compared with the benchmark of 40 % using a one-sided one-sample binomial test. This boundary of efficacy of 40 % ORR corresponds to response rates observed in RS patients treated with conventional chemoimmunotherapy. It is assumed to improve the ORR to at least 60 % with the investigated regimen.

Rate based endpoints (primary endpoint ORR after induction therapy according to Lugano Classification, secondary endpoints ORR after induction therapy according to IWCLL criteria and ORR after consolidation therapy) will be assessed showing frequencies and corresponding percentages including 95% Clopper-Pearson confidence intervals. Analyses of time-to-event endpoints (secondary endpoints overall survival, progression-free survival, duration of response, time to next treatment) will be performed using Kaplan-Meier methods.

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 (MedDRA) classification system. Presentations of AEs will include a case-analysis (i.e. an analysis of all reported cases of AEs without consideration of the fact that a subject might have the same event more than once) and a per-patient analysis (i.e. an analysis on patient-level, meaning that AEs will be counted once only with worst CTC grade, if a subject has the same event more than one time).

Sample size calculation:

The primary endpoint ORR at end of induction therapy according to refined Lugano Classification was used to determine the sample size of cohort 1. The following study assumptions are considered:

- As stated before the ORR for a conventional regimen is assumed to be 40 % (=P0) with corresponding null hypothesis H0: ORR ≤ 0.40 and alternative hypothesis H1: ORR > 0.40.
- The investigated regimen is considered potentially useful and worthy of further research if we can reject the null hypothesis in favor of the alternative hypothesis.
- The one-sided type I error is set to α = 2.5 % and defines the chance that the investigated regimen will be investigated further although the true ORR is lower or equal to 40 %.
- The type II error is the chance that an effective treatment will not be studied further. It is assumed to improve the ORR to at least 60 % (=P1) with the investigated regimen. The type II error should not exceed β = 20 %, so that it is aimed to achieve a power of at least (1 - β) = 80 % at the assumed ORR P1.

According to the above determined study parameters a one-sided one-sample binomial-test with an overall significance level of 2.5 % provides the sample size N=48, such that statistical significance is achieved with a power of 80 %.

The following table describes the minimum number of responders (i.e. having a CR or PR) that are required to warrant further investigation of the new regimen based on different numbers of analyzable patients:

Number of analyzable patients (cohort 1)	Minimum number of responders
51, 50	27
49, 48	26
47, 46	25
45, 44, 43	24
42, 41	23
40, 39	22
38, 37	21
36	20

For the exploratory cohort 2, the sample size is estimated by targeting a hazard ratio of 0.465 under the assumption of an improvement of median overall survival (OS) from 7.2 months (based on previous reports on RT outcomes) to 12 months with the triple combination therapy and a Weibull distributed OS with shape parameter 1.5. A one-sample log-rank test, given a projected accrual duration of 18 months, a follow-up duration of 12 months, and a two-sided significance level of 5 %, provides the sample size N=26, such that statistical significance would be achieved with a power of 90 %.

Sample size calculations were performed with R, EAST 5 software and validated with Binomial tables.

Recruitment strategy:	11 sites in Germany (9 sites for cohort 2), 1 site in Austria plus 1 site in Denmark	
Study duration:	Start of recruitment	Q1/2020 / cohort 2: Q4/2024
	End of recruitment	Q1/2023 / cohort 2: Q4/2025
	Expected End of study	Q4/2026
GCP conformance:	The present trial will be conducted in accordance with the valid versions of the trial protocol, the CTR 536/2014 and the internationally recognized Good Clinical Practice Guidelines (ICH-GCP), including archiving of essential documents.	

III. Study assessment table

Cohort 1		Informed consent, Incl. / Excl. Criteria	HIV / HBV / HCV test[2]	ECG	LVEF[3]	Urinalysis [16]	Pregnancy test[4]	G8[17]	CIRS Score / Medical history[5]	Concomitant medication (incl. premedication)[5]	ECOG / disease-related symptoms[6]	Height / Weight / BSA	Physical examination	Radiological assessment[7]	Complete blood count[8]	Serum chemistry[9]	Serum parameters (central lab Cologne)*	Immunophenotyping (central lab Cologne)*	FISH cytogenetics, TP53 and IGHV (central lab Ulm)*	Lymph node biopsy	Histopathological report (GCLLSG Central Office)	Biopsy sample [10] (Cologne)	Accompanying scientific program (Cologne)* Bone marrow aspirate/biopsy[11]		Response assessment	New treatment and survival status	Tislelizumab (BGB-A317) i.v. administration	Zanubrutinib (BGB-3111) p.o. administration	Radiation[12]	Drug accountability	(serious) adverse events
Screening/Baseline[1]		X	X	X	O	X	(X)	(X)	X	CONTINUOUS REPORTING	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)		CONTINUOUS REPORTING					CONTINUOUS REPORTING
Cycle 1-6	day 1						(X)						X		X	X											X			X	
	days 1-21														O	O												X			
Interim staging				X[15]		X	(X)	(X)			X		X	X	X	X							X	(X)	X				O		
Cycle 7-(12) (responders until PD)	day 1						(X)				X		X		X	X											X			X	
	days 1-21														O	O												X			
Final restaging (after consolidation)				X		X	(X)	(X)			X		X	X	X	X							X	(X)	X					X	
Maintenance staging [13]							(X)						X	(X)	X	X									X						
Follow-up visits [14]													X	(X)	X	X									X						
Progressive disease											X		X	X	X	X			X	X	X	X	X	(X)	X						

*) for details regarding the accompanying scientific program please see table IV
X = assessment mandatory, (x) = assessment mandatory in certain patients/certain situations
O = assessment recommended and to the investigator´s discretion, but not documented in the CRF

Cohort 2		Informed consent, Incl. / Excl. Criteria	HIV / HBV / HCV test[2]	ECG	LVEF[3]	Urinalysis [16]	**Pregnancy test[4]**	G8[17]	CIRS Score / Medical history[5]	**Concomitant medication (incl. premedication)[5]**	**ECOG / disease-related symptoms[6]**	**Height / Weight / BSA**	**Physical examination**	**Radiological assessment[7]**	**Complete blood count[8]**	**Serum chemistry[9]**	Serum parameters (central lab Cologne)*	Immunophenotyping (central lab Cologne)*	FISH cytogenetics, TP53 and IGHV (central lab Ulm)*	Lymph node biopsy	Histopathological report (GCLLSG Central Office) Biopsy sample [10] (Cologne)	**Accompanying scientific program** (Cologne)*	**Bone marrow aspirate/biopsy[11]**	**Response assessment**	**New treatment / survival status**	**Tislelizumab (BGB-A317)** i.v. administration	**Zanubrutinib (BGB-3111)** p.o. administration	**Sonrotoclax (BGB-11417)** p.o. administration	**TLS-Monitoring for Sonrotoclax**	**Drug accountability**	**Radiation[12]**	**(serious) adverse events**
Screening/Baseline[1]		X	X	X	O	X	(X)	(X)	X	CONTINUOUS REPORTING	X	X	X	X	X	X	X	X	X	X	X	X	(X)		CONTINUOUS REPORTING						CONTINUOUS REPORTING
Cycle 1 - 6	day 1						(X)						X		X	X										X				X		
	days 1-21														O	O											X	X	X	X		
Interim staging				X[15]		X	(X)	(X)			X		X	X	X	X							X	(X)	X						O	
Cycle 7 - (12) (responders until PD)	day 1						(X)				X		X		X	X										X				X		
	days 1-21														O	O											X	X		X		
Final restaging (after consolidation)				X		X	(X)	(X)			X		X	X	X	X							X	(X)	X					X		
Cycle 13 - end of trial (responders until PD)																										X	X	X		X		
Maintenance staging [13]							(X)						X	(X)	X	X									X							
Follow-up visits [14]													X	(X)	X	X									X							
Progressive disease											X		X	X	X	X			X	X	X	X	X	(X)	X							

*) for details regarding the accompanying scientific program please see table IV
X = assessment mandatory, (x) = assessment mandatory in certain patients/certain situations
O = assessment recommended and to the investigator´s discretion, but not documented in the CRF

[1]) **Screening:** once all screening CRF pages and results of the central diagnostics (immunophenotyping, serum parameters and cytogenetics) are available, these will be checked by a GCLLSG study physicain for approval of the patient; treatment should be initiated within 28 days after approval of the patient. Baseline: after approval of the patient and before start of therapy (e.g. blood sampling for accompanying scientific program).

[2]) **Exclusion of HIV, HBV and HCV** infection has to be performed ≤6 weeks prior to registration. Patients who are HBsAg negative/anti-HBc positive may be included if PCR for HBV DNA (with a lower limit of detection of the order of 10 WHO IU/mL) is negative and HBV-DNA PCR is performed every month until 1 year after last dosage of tislelizumab. If the HBV DNA assay becomes positive, patients should pre-emptively be treated with tenofovir, entecavir or la-mivudine) for at least 12 months after the last cycle of therapy or be referred to a gastroenterologist for management

[3]) **Cardiologic diagnostics** should be performed at the investigator´s discretion; in case of pathological findings, please report in the CIRS score page.

[4]) **Pregnancy test** is required for all women of childbearing potential (for definition see chapter *8.10.1.6. Teratogenicity and mutagenicity*) at baseline, every month, delayed menstruations (>1 month) and one month after last drug intake.

[5]) **Medical history** includes disease stage (Current Binet and Rai stage and Binet stage at initial diagnosis), prior therapies (treatment history) and concomitant medication 28 days prior to screening

[6]) **Disease related symptoms include B-symtpoms** like fever, weight loss, night sweat

[7])**Radiological assessment** of lymphadenopathy, liver and spleen using CT, PET-CT or MRI technique (head/neck, chest, abdomen and pelvis/inguinal region) is mandatory at screening, interim staging and final restaging. Further imaging can be performed at the investigator's discretion, e.g. in case of a suspected PD. It is recommended to perform ultrasound examinations (at least of the abdomen) at the stagings inbetween. PET-CT is mandatory at final restaging only, in which case an additional CT scan is not necessary. Written radiology reports should be provided to the study office.

[8]) including differential count: white blood cell count (WBC), hemoglobin, platelet count, absolute neutrophil and absolute lymphocyte count (ANC, ALC)

[9]) serum creatinine, total bilirubin, AST, ALT, LDH [are required at all timepoints during treatment]; sodium, potassium, calcium, phosphate, chloride and uric acid [during induction treatment]; immunoglobulins (IgA, IgM, IgG, IgE) and direct antiglobulin Coombs test [at screening and final restaging]

[10]) **Submission** of formalin-fixed paraffin embedded tumor tissue sample blocks is mandatory. If blocks are not available for shipment, 20 slides should be freshly cut and submitted to the testing laboratory within 14 days from site slide sectioning date otherwise a new specimen will be requested.

[11]) **Bone marrow** aspirate/biopsy may be performed whenever clinically indicated, e.g. it is recommended in case of uncertain cytopenia

[12]) Irradiation of nodal bulks or extranodular lesions is allowed after induction therapy at the discretion of the physician. A separate documentation for radiation and prior discussion with the PI is mandatory.

[13]) **Maintenance restaging** should be done every three cycles based on physical examination, blood count and serum chemistry. When PD is suspected, a CT scan is mandatory to assess new lesions.

[14]) **Follow-up visits** should be performed monthly for 6 months after last study drug intake to capture survival and subsequent treatments

[15]) **ECG** should be performed every six months, in particular to detect arrythmia like atrial fibrillation.

[16]) **Urine testing** strip every 6 months to check for urine glucose, occult blood and urobilinogen

[17]) **G8** questionnaire has to be performed for basic geriatric assessment in patients >65 years in Austria at time point screening and is voluntary at other indicated time points. For other participating countries the completion of the G8 questionnaire is voluntary. The G8 questionnaire will be filled in paper-based only, but not into the eCRF (see Appendix B). A copy of the completed Appendix B will be provided to the GCLLSG office.

IV. Accompanying scientific program

	TIMEPOINTS				MATERIAL	SHIPMENT DAYS	LABORATORY
	Screening[1]	Interim Staging [after induction]	Final restaging [after consolidation]	Progressive disease			
Immunophenotyping	X				10ml EDTA	Mo-Do	Kreuzer, Cologne
Serum parameters (Beta-2MG &TK)	X				5ml Serum	Mo-Do	Malchau, Cologne
FISH cytogenetics & molecular genetics[2]	X			X	30ml Heparin	Mo-Do	Stilgenbauer, Ulm
ctDNA	X	X	X	X	10 ml ctDNA tube	Mo-Do	Biobank, Cologne
Karyotyping	X				10ml Heparin	Mo-Do	Kreuzer, Cologne
Sequencing, epigenetics, immunol. assays[3]	X	X	X	X	40ml EDTA	Mo-Do	Biobank, Cologne
Formalin-fixed paraffin embedded tumor tissue [4]	X			X	FFP biopsy	Mo-Do	Biobank, Cologne

Blood sampling should always be performed before administration of study drug!

[1]) Screening: after obtaining informed consent and before administration of treatment.
[2]) Including BTK/PLCg2-Mutation in patients with prior BTK-Inhibitor treatment
[3]) Please also send bone marrow (5-10ml EDTA) together with a peripheral blood sample each time a bone marrow procedure is performed.
[4]) Submission of formalin-fixed paraffin embedded tumor tissue sample blocks is mandatory. If blocks are not available for shipment, 20 slides should be freshly cut and submitted to the testing laboratory within 14 days from site slide sectioning date otherwise a new specimen will be requested.