DEUTSCHE STUDIENGRUPPE CLL

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)

SPONSOR:	UNIVERSITY OF COLOGNE ALBERTUS-MAGNUS-PLATZ 50923 COLOGNE, GERMANY
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TRIAL PROTOCOL CODE:	**CLL-RT1**
EUDRACT-NUMBER:	2018-002492-17
EUCT-NUMBER:	2023-504653-12-00
SPONSOR-NUMBER:	UNI-KOELN-3590
PROTOCOL VERSION:	NOVEMBER 7, 2025; VERSION 7.1

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), 48 eligible patients for the triple combination therapy (cohort 2).
Trial objectives:	The primary objectives of the study are: • To evaluate the efficacy of a combinational therapy with tislelizumab and zanubrutinib in CLL patients with Richter transformation to DLBCL (cohort 1). • To evaluate the efficacy of a combinational therapy with tislelizumab and zanubrutinib with sonrotoclax in CLL patients with Richter transformation to DLBCL (cohort 2). The secondary objective is 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/small lymphocytic lymphoma (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 cohort will investigate 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 (incl. SLL) 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

4. Patients with confirmed PML

5. Uncontrolled autoimmune condition

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.

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
    - 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, >7 days after sonrotoclax and 30 days after zanubrutinib respectively. Vaccination with a live vaccine <28 days prior to randomization

22. Legal incapacity

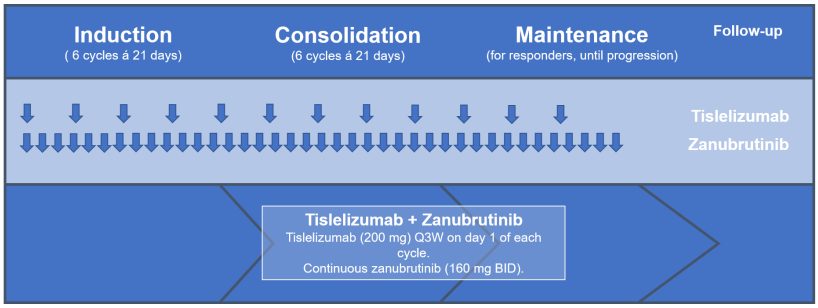
23. Prisoners or subjects who are institutionalized by regulatory or court order

24. Persons who are in dependence to the sponsor or an investigator

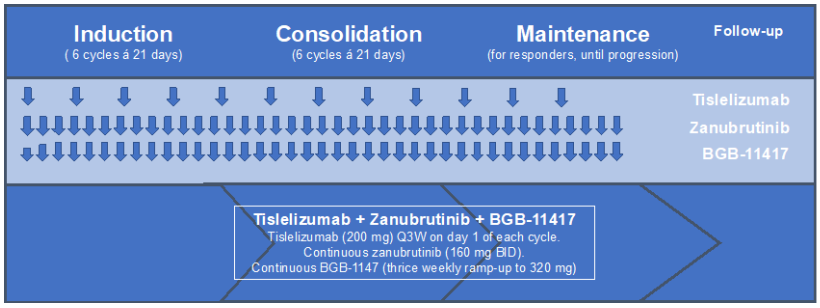
Names of investigational medicinal products (IMPs):

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

Treatment plan: Cohort 1



Cohort 2



Dosage and method of admin-istration 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

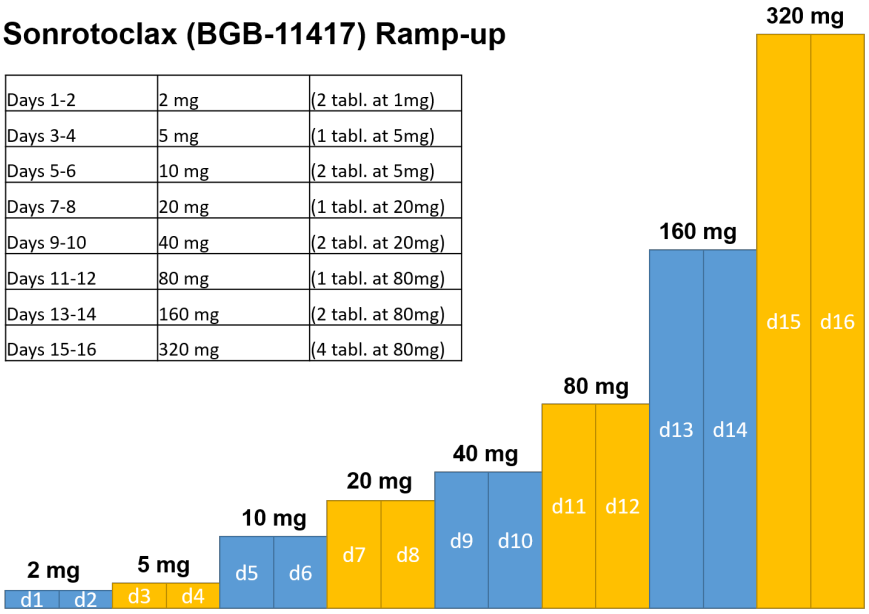
Induction treatment consists of **6 cycles**, each with a duration of **21 days** (Q3W). Tislelizumab is administered intravenously on day 1 of each cycle. Continuous daily administration of zanubrutinib starts on day 1 of the first cycle as well. The Ramp-up Phase for sonrotoclax also begins on the 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 Q3/2027.

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 methods and study	Patients will be allocated to cohort 1 and cohort 2 in a non-randomized fashion, as recruitment for cohort 2 will start after recruitment for cohort 1 is already closed.

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 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 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.

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.

For patients of cohort 1, the primary efficacy analysis will be performed 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 is based on data available at the time of study planning and corresponds to response rates observed in RT patients treated with conventional chemoimmunotherapy. It is assumed to improve the ORR to at least 60% with the combinational therapy of tislelizumab and zanubrutinb.

For patients of cohort 2, the primary efficacy analysis will be performed with respect to the ITT population. Efficacy of the investigated regimen in cohort 2 is assessed to be not effective if the ORR is less than 47.5%. The ORR will be compared with the benchmark of 47.5% using a one-sided one-sample binomial test. This boundary of efficacy of 47.5% ORR is based on the ORR observed in the ITT population of cohort 1 (Al-Sawaf et al, Nat Med 2024). It is assumed to improve the ORR to at least 67.5% with the combinational therapy of tislelizumab, zanubrutinb, and sonrotoclax.

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 counts 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 sizes of cohort 1 and cohort 2. Since patients of cohort 1 and cohort 2 will be included in different non-overlapping time periods, the respective hypotheses of both cohorts will be tested and interpreted independently from each other. Thus, the study is designed to separately draw two independent conclusions without applying a multiple testing procedure as the type I error of each conclusion will not be inflated.

The following study assumptions are considered for cohort 1:

- As stated before, the ORR for a conventional regimen is assumed to be 40% (=$P0_{cohort\ 1}$) with corresponding null hypothesis $H0_{cohort\ 1}$: ORR ≤ 0.4 and alternative hypothesis $H1_{cohort}$ 1: ORR > 0.4.
- 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% (=$P1_{cohort\ 1}$) 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 $P1_{cohort\ 1}$.

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 for cohort 1, such that statistical significance is achieved with a power of 80%.

The following study assumptions are considered for cohort 2:

- As stated before, the ORR for a conventional regimen is assumed to be 47.5% (=$P0_{cohort\ 2}$) with corresponding null hypothesis $H0_{cohort\ 2}$: ORR ≤ 0.475 and alternative hypothesis $H1_{cohort\ 2}$: ORR > 0.475.
- 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

47.5%.

- 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 67.5% (=$P1_{cohort\ 2}$) 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 $P1_{cohort\ 2}$.

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 for cohort 2, such that statistical significance is achieved with a power of 80%.

Sample size calculations were performed with EAST 5/6 software.

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: Q3/2026
	Expected End of study	Q3/2027
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.	