Protocol LOXO-BTK-20020 (J2N-OX-JZNN) Version 6.2

Study of LOXO-305 Versus Investigator's Choice (IdelaR or BR) in Patients With Previously Treated Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL) (BRUIN CLL-321)

NCT04666038

Approval Date: 14-Jun-2024

CLINICAL PROTOCOL LOXO-BTK-20020

A Phase 3 Open-Label, Randomized Study of LOXO-305 versus Investigator's Choice of Idelalisib plus Rituximab or Bendamustine plus Rituximab in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN-CLL-321)

Investigational Product:	Pirtobrutinib (LOXO-305, LY3527727)
Protocol Number:	LOXO-BTK-20020 (J2N-OX-JZNN)
Development Phase:	3
IND #:	139876
EudraCT#:	2020-004554-30
EU Trial #:	2023-507697-40-00
Sponsor:	Loxo Oncology, Inc. 281 Tresser Boulevard Stamford, CT 06901
Version:	6.2
Date:	14 June 2024

PROTOCOL APPROVAL PAGE

Protocol Title:	A Phase 3 Open-Label, Randomized Study of LOXO-305 versus Investigator's Choice of Idelalisib plus Rituximab or Bendamustine plus Rituximab in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN-CLL-321)
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The current version of the protocol has been reviewed and approved.

e-signature can be found at the end of this document

PPD

Date

I have carefully read Protocol LOXO-BTK-20020 entitled "A Phase 3 Open-Label, Randomized Study of LOXO-305 versus Investigator's Choice of Idelalisib plus Rituximab or Bendamustine plus Rituximab in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN-CLL-321)." I confirm that I have read and agree to conduct the clinical study as outlined in the protocol and in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki as amended, and all other applicable regulatory requirements. Furthermore, I understand that the Sponsor, Loxo Oncology Inc., and the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) must approve any changes to the protocol in writing before implementation.

I agree on behalf of myself and all other personnel involved in the clinical study who are employed by me, to maintain confidentiality of all information received or developed in connection with this protocol. All data pertaining to this study will be provided to Loxo Oncology and/or Eli Lilly and Company (Lilly) and any presentation or publication of study data will be reviewed by Loxo Oncology and/or Lilly before release.

Principal Investigator's Signature

Date

Print Principal Investigator's Name

PROTOCOL VERSION HISTORY

Document	Date
Version 6.2	14 June 2024
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Version 1.0	13 October 2020

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 3 Open-Label, Randomized Study of LOXO-305 versus Investigator's Choice of Idelalisib plus Rituximab or Bendamustine plus Rituximab in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN-CLL-321)

Short Title:

A Phase 3 Study Comparing LOXO-305 to Investigator's Choice of Idelalisib plus Rituximab or Bendamustine plus Rituximab

Regulatory Agency Identifier Number:

EudraCT#:	2020-004554-30
EU Trial #:	2023-507697-40-00

Rationale:

The treatment landscape for patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) has changed radically over the last 10 years, resulting in markedly improved long-term outcomes (Burger 2020). While chemoimmunotherapy combined with an anti-CD20 antibody had previously formed the foundation of therapy, more recent insights into the biologic dependence of CLL/SLL on B-cell receptor signaling as well as anti-apoptotic machinery has led to the successful development of several novel targeted therapies including agents inhibiting the Bruton's tyrosine kinase (BTK), B-cell lymphoma 2 (BCL2), and phosphoinositide 3-kinase (PI3K) delta. The introduction of these novel agents, in particular the covalent BTK inhibitors (ibrutinib and acalabrutinib) and the BCL2 inhibitor venetoclax, have substantially improved the outcome of patients with CLL and have likewise become mainstays of initial therapy for treatment-naïve patients (Fischer et al. 2019; Shanafelt et al. 2019; Woyach et al. 2018; Burger et al. 2015).

For patients who have previously received a covalent BTK inhibitor, therapeutic options include a venetoclax-based regimen (Seymour et al. 2018), a PI3K inhibitor (idelalisib or duvalesib depending on region) with or without rituximab (Furman et al. 2014; Flinn et al. 2018), chemoimmunotherapy (Fischer et al. 2008; Cuneo et al, 2018), or a clinical trial. Choice among these various options is dictated by patient characteristics, comorbid illness, CLL prognostic factors, clinical practice setting, patient preference, and region (Siegel et al. 2020). While a previous randomized study of venetoclax-containing therapy in BTK-naïve, relapsed CLL/SLL demonstrated significant improvement in outcomes, not all patients are able to receive venetoclax due to comorbid illness or logistical barrier (Seymour et al. 2018, Fischer et al. 2019). Key challenges associated with venetoclax include the risk of myelosuppression (especially in patients who received prior chemoimmunotherapy), risk of tumor lysis syndrome and its consequences including renal failure, and the need for intense monitoring and sometimes hospitalization to administer this oral regimen, which collectively can be prohibitive for some patients.

For patients previously treated with covalent BTK inhibitors and/or venetoclax, remaining available treatment options include chemoimmunotherapy and PI3K inhibitors. Of note, while these agents are widely employed in this setting, the true efficacy and safety of chemoimmunotherapy and PI3K inhibitors following exposure to either covalent BTK inhibitors or venetoclax is not well established and has not been subjected to prospective clinical studies. As such, protocol LOXO-BTK-20020 will not only establish the potential role for pirtobrutinib (LOXO-305) in patients previously treated with at least a covalent BTK inhibitor, but also help establish the efficacy of the control arm (Investigator's Choice of bendamustine plus rituximab [BR] or idelalisib plus rituximab [IdelaR]) in this patient population.

Pirtobrutinib:

Pirtobrutinib is an orally available, highly selective, adenosine triphosphate (ATP)-competitive inhibitor of BTK. Pirtobrutinib has single digit nanomolar inhibitory activity against wildtype BTK and the BTK C481S acquired resistance mutation which results from a serine substitution at position 481.

Pirtobrutinib is distinct from the approved BTK inhibitors (ibrutinib, approved globally for CLL/SLL and mantle cell lymphoma [MCL]; acalabrutinib, approved in select countries for CLL/SLL and MCL; zanubrutinib, approved in the United States [US] for MCL) on the basis of its selectivity, pharmacologic and pharmacokinetic (PK) properties, and non-covalent binding mode (Brandhuber et al. 2018). These features enable pirtobrutinib to achieve PK exposures with once daily oral dosing that exceed the BTK-wild type 90% inhibitory concentration (IC90) at trough and thus deliver tonic BTK target inhibition throughout the dosing period, regardless of the intrinsic rate of BTK turnover. Moreover, the non-covalent binding mode of pirtobrutinib is unaffected by BTK cysteine residue at position 481 (C481) substitutions, a common mechanism of drug resistance described for all available covalent inhibitors. (Byrd et al. 2013; Woyach et al. 2017; Woyach et al. 2019; Chiron et al. 2014; Xu et al. 2017). Finally, pirtobrutinib is also a highly selective molecule, with more than 300-fold more selectivity for BTK versus 370 other kinases tested and no significant inhibition of non-kinase off-targets at 1 µM, thus limiting the potential for off-target mediated toxicities.

Study results from a CCI study CCI evaluating the CCI of pirtobrutinib showed that CCI

In a Phase 1/2 study (LOXO-BTK-18001, NCT03740529), pirtobrutinib has demonstrated robust and durable antitumor activity against a variety of B-cell malignancies including CLL/SLL, regardless of prior treatment, including in patients treated with covalent BTK inhibitors. Of note, this promising activity in CLL/SLL patients has been observed in patients with both wildtype BTK as well as those harboring BTK C481 mutations (Mato et al. 2021).

The purpose of this global study is to compare the efficacy and safety of pirtobrutinib administered as a continuous monotherapy versus Investigator's choice of 2 globally approved standards of care, idelalisib with rituximab (IdelaR) or bendamustine with rituximab (BR), in patients with previously treated CLL/SLL including for patients with 17p deletion (del 17p) who have received at least one prior regimen, including a BTK inhibitor.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate progression-free survival (PFS) of pirtobrutinib as monotherapy (Arm A) compared to Investigator's choice of idelalisib plus rituximab (IdelaR) or bendamustine plus rituximab (BR) (Arm B).	Assessed by Independent Review Committee (IRC): • PFS per International Workshop on Chronic Lymphocytic Leukemia (iwCLL 2018)
Secondary	
• To evaluate the effectiveness of Arm A compared to Arm B based on overall response rate (ORR) and time to event(s) outcomes	• Assessed by Investigator: – PFS per iwCLL 2018 criteria – Overall survival (OS) – Time to next treatment (TTNT), defined as time from the date of randomization to the date of the next systemic anticancer therapy for CLL/SLL (Section 9 for full definition). – Event free survival (EFS) defined as the time from date of randomization to the date of progressive disease (PD) or start of new treatment for CLL/SLL or discontinuation from treatment due to toxicity or death, whichever occurs first. • Assessed by Investigator and IRC: – ORR – Duration of response (DOR)
• To evaluate the safety and tolerability of each treatment arm	• Including, but not limited to, serious adverse events (SAEs), adverse events (AEs), deaths and clinical laboratory abnormalities per National Cancer Institute Common Terminology Criteria in Adverse Events v5.0 (NCI CTCAE v5.0)
• To evaluate the effectiveness of Arm A compared to Arm B based on patient-reported outcomes	• Patient-reported outcomes of: – Time to worsening (TTW) of CLL/SLL-related symptoms – TTW of physical functioning

Overall Design:

LOXO-BTK-20020 (BRUIN-CLL-321) is a Phase 3 global, randomized, open-label study comparing pirtobrutinib as continuous monotherapy (Arm A) to Investigator's choice of either IdelaR or BR (Arm B) in CLL/SLL patients who have been treated with a covalent BTK inhibitor, approved (ibrutinib or acalabrutinib) or investigational. Patients may have discontinued the prior covalent BTK due to PD or intolerance. The reason for prior discontinuation will be recorded. Eligible patients will be randomized in 1:1 into Arm A and Arm B based on stratification factors of deletion 17p presence (yes/no) and receipt of prior venetoclax treatment (yes/no).

BRUIN-CLL-321 will enroll adult CLL/SLL patients with an indication for treatment as defined by iwCLL 2018 criteria (Hallek et al. 2018; Cheson et al. 2012; Section 10.6, Appendix 6). During Screening, Investigator's choice therapy (IdelaR or BR) must be selected by the Investigator prior to randomization for each patient. Patients who have been previously treated with IdelaR or BR and had either documented PD as determined by the Investigator, or could not tolerate the regimen, should not be retreated with same regimen. Patients assigned to oral pirtobrutinib will receive pirtobrutinib continuously until discontinuation criteria are met

(Section 7.1). Patients assigned to BR will receive up to 6 cycles of both agents intravenously (IV) unless they experience unacceptable toxicity or progression, at which time patients will discontinue treatment. Patients who complete the full course of BR will be followed until progression, death, lost to follow-up or withdrawal of consent. Patients will be allowed to cross over from Arm B to Arm A upon confirmation of PD by IRC and if they meet the eligibility criteria for crossover (Section 5.3). Patients who have PD per the Investigators' assessment but not IRC confirmed are not eligible for crossover until they meet IRC PD criteria. Patients who progress on Arm A are not eligible for crossover but may be allowed to continue treatment beyond progression if the patient is tolerating study treatment and, in the opinion of the Investigator, is deriving ongoing clinical benefit. Continuation of treatment on Arm A post-progression must be approved by the Sponsor. Patients will need to be consented for treatment beyond progression on pirtobrutinib. Patients who progress on Arm B and decide to continue treatment are no longer eligible for crossover to Arm A (patients on idelalisib may continue while patients are undergoing Screening for crossover, but will need to meet the criteria for washout duration prior to starting pirtobrutinib if they meet all other eligibility criteria). Patients who discontinue treatment for any reason other than PD, death, lost to follow-up, or withdrawal of consent will be followed for tumor assessment until PD, regardless of whether the patient receives a new anticancer therapy. Upon PD, all patients will then be placed on Long-Term Follow-up (LTFU) every 3 months until death, lost to follow-up, or consent withdrawal.

Pirtobrutinib: Patients randomized to Arm A will receive treatment with pirtobrutinib monotherapy (refer to Treatment Groups).

Investigator's choice of idelalisib plus rituximab (IdelaR) OR bendamustine plus rituximab (BR): Patients randomized to Arm B will receive treatment at the dose and schedule appropriate for the diagnosis and according to approved prescribing instructions (refer to Treatment Groups).

On days when rituximab and bendamustine are to be administered, rituximab will be administered prior to bendamustine.

Disclosure Statement:

This is a randomized, active treatment study with 2 arms where the patient and Investigator will not be blinded.

Study Population:

The study includes patients age 18 or older (per local regulations at time of enrollment) with CLL/SLL who have been treated with an approved or investigational covalent BTK inhibitor. Patients must have confirmed diagnosis of CLL/SLL by redacted local laboratory report as defined by iwCLL 2018 criteria (see Sections 1.2.1 and 5.1).

Number of Patients:

Approximately 250 patients will be randomized 1:1, Arm A:Arm B, based on stratification factors of del 17p presence (yes/no) and receipt of prior venetoclax treatment (yes/no) (see Sections 1.2.1 and 1.2.2).

Treatment Groups:

	Arm A pirtobrutinib	**Arm B** Investigator's choice of idelalisib plus rituximab (IdelaR) or bendamustine plus rituximab (BR)			
		idelalisib plus rituximab (IdelaR)		bendamustine plus rituximab (BR)	
Treatment	pirtobrutinib	idelalisib	rituximab	bendamustine	rituximab
Dose	200 mg	150 mg	375 mg/m^2 on C1D1 and then 500 mg/m^2	70 mg/m^2	375 mg/m^2 on C1D1 and then 500 mg/m^2
Schedule	QD in 28-day continuous cycles	BID in 28-day continuous cycles	375 mg/m^2 on C1D1 and then 500 mg/m^2 Q2W for 4 infusions and Q4W for 3 infusions	70 mg/m^2 on Day 1 and Day 2 of each 28-day cycle, Cycles 1 to 6	375 mg/m^2 on C1D1 and then 500 mg/m^2 given on Day 1 of each 28-day cycle, Cycles 2 to 6
Route	Oral	Oral	IV	IV	IV
Authorized as defined by EU Clinical Trial Regulation	Not authorized in EU	Authorized and used according to EU authorization	Authorized and used according to EU authorization	Approved in the EU and used at the dose recommended by the International Consensus Panel (see Section 4.3.3)	Authorized and used according to EU authorization

Ethical Considerations of Benefit/Risk:

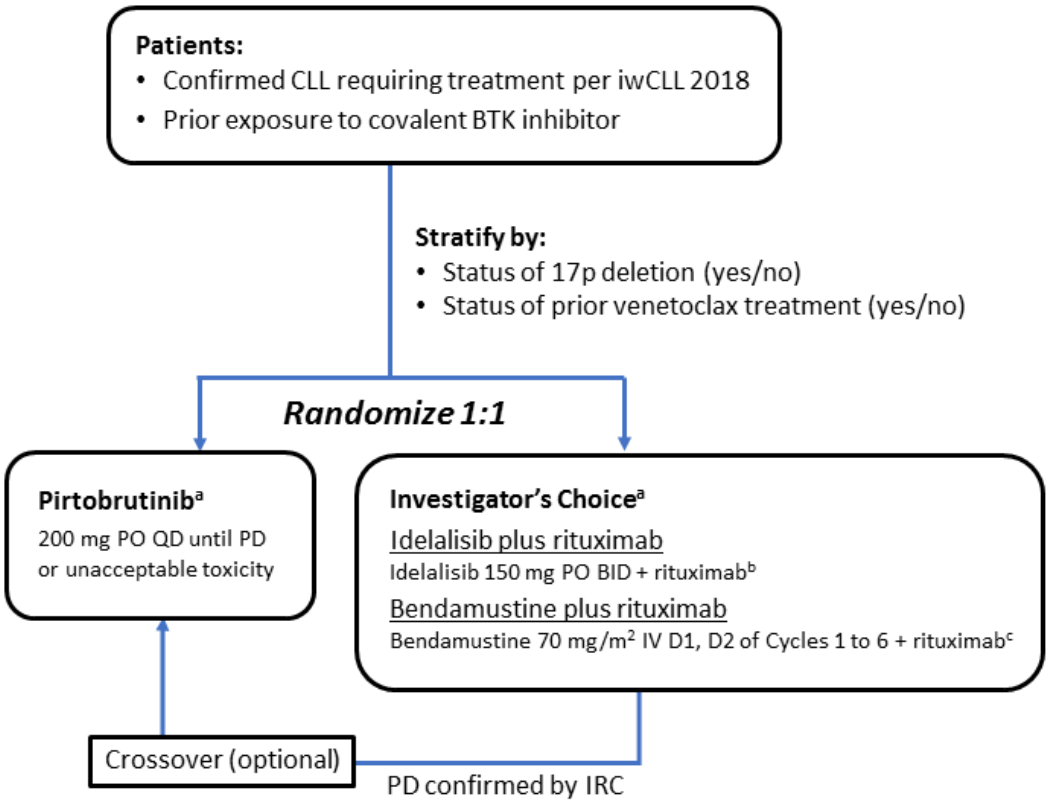
During Phase 1 and 2 studies, pirtobrutinib has demonstrated a tolerable safety profile and durable antitumor activity against a variety of B-cell malignancies, including pretreated CLL/SLL. Additionally, considering the measures taken to ensure patient safety in this study, the potential risks from taking the study interventions are outweighed by the potential benefits for individuals with CLL/SLL

Data Monitoring Committee:

A Data Monitoring Committee (DMC) will be utilized to review aggregate safety data for this study. Please refer to the DMC charter for further information.

1.2. Schema

1.2.1. Study Design Schema

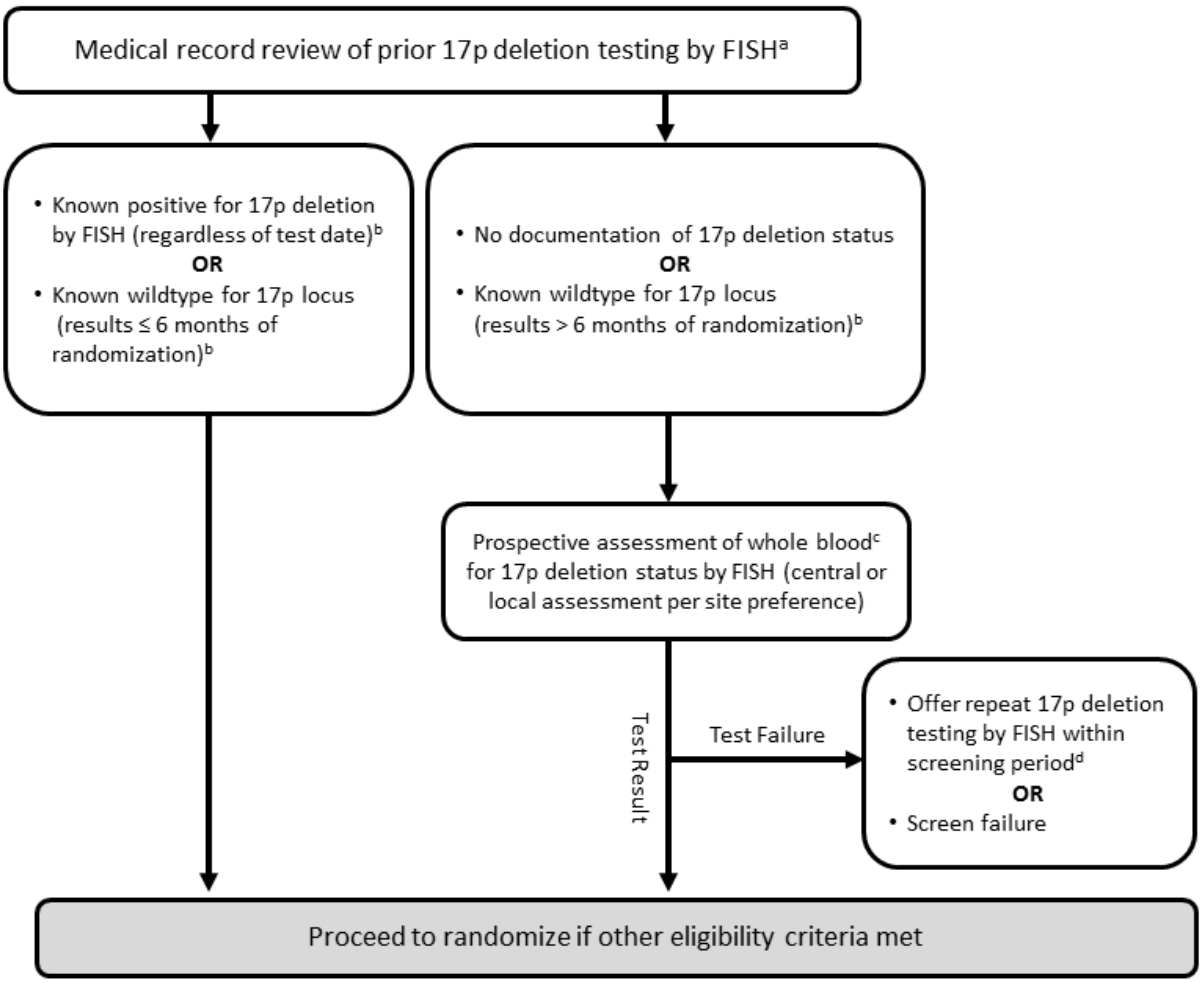


a Detailed study treatment dosing instructions are provided in Section 6.1.

b Day 1 of Cycle 1, first dose of rituximab at 375 mg/m^2, next 4 infusions at 500 mg/m^2 every 2 weeks (Q2W), next 3 infusions at 500 mg/m^2 every 4 weeks (Q4W).

c Day 1 of Cycle 1, first dose of rituximab at 375 mg/m^2, next 5 infusions Day 1 of Cycle 2 through Cycle 6 at 500 mg/m^2.

1.2.2. Schema for 17p Deletion Stratification



[a] FISH results collected for del 17p will be used to stratify patients for randomization, with a sample collected for retrospective central confirmation.

[b] Del 17p should be documented by a redacted molecular pathology report generated from a local or central laboratory with CLIA, ISO/IEC, CAP, or other similar certification.

[c] For SLL patients, local 17p assessment on fresh lymph node biopsy is acceptable.

[d] The Sponsor should be contacted to discuss test results performed in laboratories where CLIA, ISO/IEC, CAP, or other similar certification is not clearly demonstrated to determine if retesting should be performed.

Note: 17p testing will not be repeated at the time of crossover if results were wildtype at the time of study entry regardless of the duration interval from study entry (i.e., > 6 months).

1.3. Schedule of Assessments

This section includes Schedules of Assessments (SoAs) for patients receiving the following treatments:

- ARM A: pirtobrutinib (Section 1.3.1)
- ARM B: idelalisib with rituximab (IdelaR) (Section 1.3.2)
- ARM B: bendamustine with rituximab (BR) (Section 1.3.3)
- Optional crossover treatment (for patients crossing over from Arm B to Arm A) (Section 1.3.4)

Additional SoAs include the following:

- The Response Assessment SoA is provided in Section 1.3.5.
- The Patient-Reported Outcomes (PRO) SoA is provided in Section 1.3.6.

1.3.1. Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy

Arm A: Pirtobrutinib Monotherapy									
Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**				**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1**		**Cycles 2-6**	**Cycle 7 +**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 8 (± 3 days)**	**Day 1 (± 7 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	Q12W **(± 4 weeks)** for up to 2 years after last dose, Q24W **(± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	**Instructions**
Informed consent	X								The ICF must be signed before any protocol-specified procedures are performed; refer to Section 10.1.2
Medical history	X								All ongoing conditions and relevant past surgical and medical history should be collected; refer to Section 8.2 • Malignancy history should be collected regarding disease under study, and any history of other malignancy • Prior therapy related to CLL/SLL would be collected as part of the medical history, including reason for prior covalent BTK discontinuation
Documentation of diagnosis and relevant biomarkers	X								• Anonymized/redacted pathology report(s) confirming diagnosis of CLL required for eligibility • Reports regarding status of any known CLL relevant biomarkers should be provided if available (e.g., IGHV, TP53 mutation, complex karyotype, del 11q, BTK mutation and PLCg2 mutation)

Arm A: Pirtobrutinib Monotherapy

Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**				**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1**		**Cycles 2-6**	**Cycle 7 +**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 8 (± 3 days)**	**Day 1 (± 7 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	Q12W **(± 4 weeks)** for up to 2 years after last dose, Q24W **(± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	**Instructions**
Physical examination	X	X	X	X	C7D1 and Q12W thereafter	X	X	X	• Complete PE includes height (only at Screening), weight, basic neurological examination, and review of relevant symptoms at Screening; refer to Section 8.4.2 • Symptom-directed PE should be limited to systems of primary relevance such as, cardiovascular, respiratory, and those associated with tumor assessment (lymph nodes, liver, and spleen) and may be performed at other timepoints; include weight as clinically indicated throughout the trial • Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results
ECOG PS	X	X	X	X	C7D1 and Q12W thereafter	X	X		
Vital signs	X	X	X	X	C7D1 and Q12W thereafter	X	X		• Includes systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature

Arm A: Pirtobrutinib Monotherapy

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			
Evaluation	Screening	Cycle 1		Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	
Visit Window	Up to 28 days	Day 1	Day 8 (± 3 days)	Day 1 (± 7 days)	Day 1 (± 7 days)	+ 7 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	Q12W (± 4 weeks) for up to 2 years after last dose, Q24W (± 4 weeks) beyond 2 years for patients who discontinue prior to PD	Instructions
Results of tests in the section below are required for eligibility determination and enrollment									
Deletion 17p evaluation	X								• Refer to Section 1.2.2 • Results are required for stratification
CMV	X								CMV IgG, IgM and DNA PCR at Screening only (Section 8.4.4.5)`
12-lead ECG	X	X	X	X	C7D1 and Q12W thereafter	X			• Obtain ECGs at specified visits and when patients are symptomatic; refer to Section 8.4.3 • ECGs should be collected: – At Screening, single ECG – C1D1: Predose single ECG – All other timepoints: Post dose single ECG – If an unscheduled ECG is done at any time, an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG – If a clinically significant arrhythmia is detected, details must be in EDC
Hematology	X	X	X	X	C7D1 and Q12W thereafter	X	X	X	• Includes hemoglobin, hematocrit, RBC count, WBC count, platelet count, percent or absolute differential

Arm A: Pirtobrutinib Monotherapy									
Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**				**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1**		**Cycles 2-6**	**Cycle 7 +**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 8 (± 3 days)**	**Day 1 (± 7 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	Q12W **(± 4 weeks)** for up to 2 years after last dose, Q24W **(± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	**Instructions**
									(neutrophils, lymphocytes, eosinophils, basophils, and monocytes) • Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results • Repeat testing during Screening is permitted; refer to Section 5.5 • On days when hematology is required for both safety and response assessments, samples should also be submitted to the central laboratory
Blood chemistries	X	X	X	X	C7D1 and Q12W thereafter	X	X		• Blood chemistry from serum or plasma should include assessment of: sodium, potassium, chloride, glucose, creatinine, total protein, albumin, total bilirubin, ALT and AST • Repeat testing during Screening is permitted; refer to Section 5.5 • LDH, calcium, magnesium, phosphorus and uric acid are required at Screening and Day 1 of C1 to C6 • Refer to Section 8.4.4.10 for hepatic safety monitoring • Screening results within 3 days of C1D1 are acceptable as C1D1 results

Arm A: Pirtobrutinib Monotherapy

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			
Evaluation	Screening	Cycle 1		Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	
Visit Window	Up to 28 days	Day 1	Day 8 (± 3 days)	Day 1 (± 7 days)	Day 1 (± 7 days)	+ 7 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	Q12W (± 4 weeks) for up to 2 years after last dose, Q24W (± 4 weeks) beyond 2 years for patients who discontinue prior to PD	Instructions
									• Direct (or indirect) bilirubin should be performed any time total bilirubin is abnormal
Coagulation panel	X	As clinically indicated							• aPTT and PT (or INR)
Hepatitis B/C active disease status	X								• HBV and HCV testing to determine if patients have active infection • Refer to Section 5.2 for exclusions
Serum or urine pregnancy test (WOCBP only)	X	X		X	C7D1 and Q12W thereafter				• Perform within 24 hours of first dose of study treatment, and as indicated in table, or as required per local regulations and/or institutional guidelines • Refer to Section 10.2, Appendix 2
Urinalysis	X	X	As clinically indicated						Dipstick analysis is acceptable and should include color, specific gravity, pH, glucose, bilirubin, occult blood, protein, leukocytes, and urobilinogen
Documentation or sampling of the following are required during Screening, but results <u>not required prior to enrollment</u>									
β2 microglobulin	X								
Serum immunoglobulins	X								IgG, IgA, IgM

Arm A: Pirtobrutinib Monotherapy

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	**Screening**	**Cycle 1**		**Cycles 2-6**	**Cycle 7 +**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 8 (± 3 days)**	**Day 1 (± 7 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	Q12W **(± 4 weeks)** for up to 2 years after last dose, Q24W **(± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	
Bone marrow CCI biopsy	X			Within 4-8 weeks of confirmed CR by scan and peripheral blood assessment. Optional to confirm PD					• CCI biopsy CCI required at Screening and for confirmation of CR CCI
CT or MRI	X			C4D1	C7D1 and Q12W thereafter	X		X	• Refer to Section 8.3 for details • CT scan with IV contrast agent is the preferred method of assessment with scans of neck, chest, abdomen, and pelvis. However, MRI is acceptable if CT scan with contrast agent is contraindicated • All response assessments should occur at Q12W intervals relative to C1D1 regardless of any treatment delays or interruptions • At the EOT visit, a repeat CT/MRI does not need to be performed if done within the proceeding 2 weeks, or if PD was previously determined • A central radiology vendor will be used to collect and store images for IRC review

Arm A: Pirtobrutinib Monotherapy

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			
Evaluation	Screening	Cycle 1		Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	
Visit Window	Up to 28 days	Day 1	Day 8 (± 3 days)	Day 1 (± 7 days)	Day 1 (± 7 days)	+ 7 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	Q12W (± 4 weeks) for up to 2 years after last dose, Q24W (± 4 weeks) beyond 2 years for patients who discontinue prior to PD	Instructions
CCI									
Pirtobrutinib administration		X	X	X	X	X			• 200 mg PO administered QD (continuous) • C1D1 should occur within 3 business days after randomization • Date of last dose and date of decision for end of treatment must be recorded in EDC
Patient dosing diary		X	X	X	X	X			

Arm A: Pirtobrutinib Monotherapy

Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**				**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1**		**Cycles 2-6**	**Cycle 7 +**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 8 (± 3 days)**	**Day 1 (± 7 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	Q12W **(± 4 weeks)** for up to 2 years after last dose, Q24W **(± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	**Instructions**
Concomitant medication	X	X	X	X	X	X	X		Refer to Section 6.5
Adverse events	X	X	X	X	X	X	X		• Collect SAEs from the time of ICF signing through 28 days after the last dose (NCI CTCAE v5.0) • Collect AEs from the time of dosing through SFU; AEs that occur prior to the first dose are considered medical history unless the AE develops or worsens due to study-related procedures • All SAEs occurring from the time ICF is signed through 28 days after the last dose must be reported to Clinical Safety within 24 hours of knowledge of the event. All SAEs that the Investigator considers related to study drug occurring after the 28-day follow-up period must be reported to the Sponsor • Second primary malignancy (SPM) events are to be reported and should continue to be reported for up to 5 years from the start of study treatment, regardless of seriousness or causal attribution to treatment (Section 8.5.8)

Arm A: Pirtobrutinib Monotherapy

Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**				**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1**		**Cycles 2-6**	**Cycle 7 +**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 8 (± 3 days)**	**Day 1 (± 7 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	Q12W **(± 4 weeks)** for up to 2 years after last dose, Q24W **(± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	**Instructions**
Medical resources utilization		X	X	X	X	X	X		Hospitalizations, emergency department visits, blood product transfusions, and hematopoietic growth factor use will be collected
Patient reported outcomes		X	X	X	X	X	X		Refer to Section 1.3.6 for details
Survival status								X	• Survival information may be collected via telephone if no procedures are required; this information should be collected approximately Q12W after the SFU visit; refer to Section 6.7.5 • Subsequent anticancer therapy information should be collected Q12W after the SFU visit for the first 2 years, and approximately Q24W thereafter until death or study completion

1.3.2. Schedule of Assessments for Arm B: Idelalisib plus Rituximab

Arm B: Idelalisib plus Rituximab (IdelaR)												
Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**							**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1**		**Cycle 2**		**Cycles 3-6**		**Cycle 7+**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q12W (± 4 weeks)** for up to 2 years after last dose, Q24W **(± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	**Instructions**
Informed consent	X											• The ICF must be signed before any protocol-specified procedures are performed; refer to Section 10.1.2
Medical history	X											• All ongoing conditions and relevant past surgical and medical history should be collected; refer to Section 8.2 • Malignancy history should be collected regarding disease under study, and any history of other malignancy • Prior therapy related to CLL/SLL would be collected as part of the medical history, including reason for prior covalent BTK discontinuation

Arm B: Idelalisib plus Rituximab (IdelaR)

Study Period	Baseline	Study Treatment (Cycle = 28 days)							Post-Study Treatment Discontinuation			
Evaluation	Screening	Cycle 1		Cycle 2		Cycles 3-6		Cycle 7+	EOT	SFU	LTFU	
Visit Window	Up to 28 days	Day 1	Day 15 (± 3 days)	Day 1 (± 3 days)	Day 15 (± 3 days)	Day 1 (± 3 days)	Day 15 (± 3 days)	Day 1 (± 7 days)	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q12W (± 4 weeks)** for up to 2 years after last dose, Q24W **(± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	**Instructions**
Documentation of diagnosis and relevant biomarkers	X											• Anonymized/redacted pathology report(s) confirming diagnosis of CLL required for eligibility • Reports regarding status of any known CLL relevant biomarkers should be provided if available (e.g., IGHV, TP53 mutation, complex karyotype, del 11q, BTK mutation and PLCg2 mutation)
Physical examination	X	X	X	X	X	X	X	C7D1 and Q12W thereafter	X	X	X	• Complete PE includes height (only at Screening), weight, basic neurological examination and review of relevant symptoms at Screening; refer to Section 8.4.2 • Symptom-directed PE should be limited to systems of primary relevance such as cardiovascular, respiratory, and those associated with tumor assessment (lymph nodes, liver, and spleen) and may be performed at other timepoints; include weight as clinically

Arm B: Idelalisib plus Rituximab (IdelaR)

Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**							**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1**		**Cycle 2**		**Cycles 3-6**		**Cycle 7+**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q12W (± 4 weeks)** for up to 2 years after last dose, Q24W **(± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	**Instructions**
												indicated throughout the trial • Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results
ECOG PS	X	X	X	X	X	X	X	C7D1 and Q12W thereafter	X	X		
Vital signs	X	X	X	X	X	X	X	C7D1 and Q12W thereafter	X	X		• Includes systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature
Results of tests in the section below are <u>required for eligibility determination and enrollment</u>												
Deletion 17p evaluation	X											• Refer to Section 1.2.2 • Results are required for stratification
CMV	X					C4D1		C7D1 and Q12W thereafter				• CMV IgG, IgM and DNA PCR at Screening • CMV DNA PCR for monitoring (Section 8.4.4.5)
12-lead ECG	X											• Obtain ECGs at specified visit • Refer to Section 8.4.3 • At Screening, single ECG should be collected

Arm B: Idelalisib plus Rituximab (IdelaR)

Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**							**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1**		**Cycle 2**		**Cycles 3-6**		**Cycle 7+**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q12W (± 4 weeks)** for up to 2 years after last dose, Q24W **(± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	**Instructions**
Hematology	X	X	**X**	X	**X**	X	X	C7D1 and Q12W thereafter	X	X	X	• Includes hemoglobin, hematocrit, RBC count, WBC count, platelet count, percent or absolute differential (neutrophils, lymphocytes, eosinophils, basophils, and monocytes) • Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results • Repeat testing during Screening is permitted; refer to Section 5.5 • On days when hematology is required for both safety and response assessments, samples should also be submitted to the central laboratory

Arm B: Idelalisib plus Rituximab (IdelaR)

Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**							**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1**		**Cycle 2**		**Cycles 3-6**		**Cycle 7+**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q12W (± 4 weeks)** for up to 2 years after last dose, Q24W **(± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	**Instructions**
Blood chemistries	X	X	**X**	X	**X**	X	X	C7D1 and Q12W thereafter	X	X		• Blood chemistry from serum or plasma should include assessment of: sodium, potassium, chloride, glucose, creatinine, total protein, albumin, total bilirubin, ALT, and AST • Repeat testing during Screening is permitted; refer to Section 5.5 • LDH, calcium, magnesium, phosphorus and uric acid are required at Screening and Day 1 of C1 to C6 • Screening results within 3 days of C1D1 are acceptable as C1D1 results
Coagulation panel	X	As clinically indicated										aPTT and PT (or INR)
Hepatitis B/C active disease status	X											• HBV and HCV testing to determine if patients have active infection • Refer to Section 5.2 for exclusions

Arm B: Idelalisib plus Rituximab (IdelaR)

Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**							**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1**		**Cycle 2**		**Cycles 3-6**		**Cycle 7+**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q12W (± 4 weeks)** for up to 2 years after last dose, Q24W **(± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	**Instructions**
Serum or urine pregnancy test (WOCBP only)	X	X		X		X		C7D1 and Q12W thereafter				• Perform within 24 hours of first dose of study treatment, and as indicated in table, or as required per local regulations and/or institutional guidelines • Refer to Section 10.2, Appendix 2
Urinalysis	X	X	As clinically indicated									Dipstick analysis is acceptable and should include color, specific gravity, pH, glucose, bilirubin, occult blood, protein, leukocytes, and urobilinogen
Documentation or sampling of the following are required during Screening, but results <u>not required prior to enrollment</u>												
β2 microglobulin	X											
Serum immunoglobulins	X											IgG, IgA, IgM
Bone marrow CCI biopsy	X			Within 4-8 weeks of confirmed CR by scan and peripheral blood assessment. Optional to confirm PD.								• CCI biopsy CCI required at Screening and for confirmation of CR CCI

Arm B: Idelalisib plus Rituximab (IdelaR)

Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**							**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1**		**Cycle 2**		**Cycles 3-6**		**Cycle 7+**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q12W (± 4 weeks)** for up to 2 years after last dose, Q24W **(± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	**Instructions**
CT or MRI	X					C4D1		C7D1 and Q12W thereafter	X		X	• Refer to Section 8.3 for details • CT scan with IV contrast agent is the preferred method of assessment with scans of neck, chest, abdomen, and pelvis. However, MRI is acceptable if CT scan with contrast agent is contraindicated • All response assessments should occur at Q12W intervals relative to C1D1 regardless of any treatment delays or interruptions • At the EOT visit, a repeat CT/MRI does not need to be performed if done within the proceeding 2 weeks, or if PD was previously determined • A central radiology vendor will be used to collect and store images for IRC review
CCI												

Arm B: Idelalisib plus Rituximab (IdelaR)

Study Period	Baseline	Study Treatment (Cycle = 28 days)							Post-Study Treatment Discontinuation			
Evaluation	Screening	Cycle 1		Cycle 2		Cycles 3-6		Cycle 7+	EOT	SFU	LTFU	
Visit Window	Up to 28 days	Day 1	Day 15 (± 3 days)	Day 1 (± 3 days)	Day 15 (± 3 days)	Day 1 (± 3 days)	Day 15 (± 3 days)	Day 1 (± 7 days)	+ 7 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	Q12W (± 4 weeks) for up to 2 years after last dose, Q24W (± 4 weeks) beyond 2 years for patients who discontinue prior to PD	Instructions
CCI												
Idelalisib administration		X	X	X	X	X	X	X	X			• 150 mg PO administered BID (continuous) • C1D1 should occur within 3 business days after randomization. • Date of last dose and date of decision for end of treatment must be recorded in EDC
Rituximab administration		375 mg/m^2	500 mg/m^2 Q2W for 4 infusions (C1D15, C2D1, C2D15, C3D1) and Q4W for 3 infusions (C4D1, C5D1, C6D1)									• C1D1 should occur within 3 business days after randomization. • Date of last dose and date of decision for end of treatment must be recorded in EDC

Arm B: Idelalisib plus Rituximab (IdelaR)

Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**							**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1**		**Cycle 2**		**Cycles 3-6**		**Cycle 7+**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q12W (± 4 weeks)** for up to 2 years after last dose, Q24W **(± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	**Instructions**
Patient dosing diary		X	X	X	X	X	X	X	X			
Concomitant medication	X	X	X	X	X	X	X	X	X	X		Refer to Section 6.5
Adverse events	X	X	X	X	X	X	X	X	X	X		• Collect SAEs from the time of ICF signing through 28 days after the last dose (NCI CTCAE v5.0) • Collect AEs from the time of dosing through SFU; AEs that occur prior to the first dose are considered medical history unless the AE develops or worsens due to study-related procedures • All SAEs occurring from the time ICF is signed through 28 days after the last dose must be reported to Clinical Safety within 24 hours of knowledge of the event. All SAEs that the Investigator considers related to study drug occurring after the 28-day follow-up period must be reported to the Sponsor

Arm B: Idelalisib plus Rituximab (IdelaR)

Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**							**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1**		**Cycle 2**		**Cycles 3-6**		**Cycle 7+**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q12W (± 4 weeks)** for up to 2 years after last dose, Q24W **(± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	**Instructions**
												• Second primary malignancy (SPM) events are to be reported and should continue to be reported for up to 5 years from the start of study treatment, regardless of seriousness or causal attribution to treatment (Section 8.5.8)
Medical resources utilization		X	X	X	X	X	X	X	X	X		Hospitalizations, emergency department visits, blood product transfusions, and hematopoietic growth factor use will be collected
Patient-reported outcomes		X	X	X	X	X	X	X	X	X		Refer to Section 1.3.6 for details

Arm B: Idelalisib plus Rituximab (IdelaR)

Study Period	Baseline	Study Treatment (Cycle = 28 days)							Post-Study Treatment Discontinuation			
Evaluation	Screening	Cycle 1		Cycle 2		Cycles 3-6		Cycle 7+	EOT	SFU	LTFU	
Visit Window	Up to 28 days	Day 1	Day 15 (± 3 days)	Day 1 (± 3 days)	Day 15 (± 3 days)	Day 1 (± 3 days)	Day 15 (± 3 days)	Day 1 (± 7 days)	+ 7 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	Q12W (± 4 weeks) for up to 2 years after last dose, Q24W (± 4 weeks) beyond 2 years for patients who discontinue prior to PD	Instructions
Survival status											X	• Survival information may be collected via telephone if no procedures are required; this information should be collected approximately Q12W after the SFU visit; refer to Section 6.7.5 • Subsequent anticancer therapy information should be collected approximately Q12W after the SFU visit for the first 2 years and approximately Q24W thereafter until death or study completion

1.3.3. Schedule of Assessments for Arm B: Bendamustine plus Rituximab

Arm B: Bendamustine plus Rituximab (BR)									
Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**				**Post-Study Treatment Discontinuation**			**Instructions**
Evaluation	**Screening**	**Cycle 1**		**Cycles 2-6**		**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 2**	**Day 1 (± 3 days)**	**Day 2**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	Q12W **(± 4 weeks)** for up to 2 years after last dose, Q24W **(± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	
Informed consent	X								The ICF must be signed before any protocol-specified procedures are performed. Refer to Section 10.1.2
Medical history	X								• All ongoing conditions and relevant past surgical and medical history should be collected. Refer to Section 8.2 • Malignancy history should be collected regarding disease under study and any history of other malignancy • Prior therapy related to CLL/SLL would be collected as part of the medical history, including reason for prior covalent BTK discontinuation
Documentation of diagnosis and relevant biomarkers	X								• Anonymized/redacted pathology report(s) confirming diagnosis of CLL required for eligibility. • Reports regarding status of any known CLL relevant biomarkers should be provided if available (e.g., IGHV, TP53

Arm B: Bendamustine plus Rituximab (BR)

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 3 days)	Day 2	+ 7 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	Q12W (± 4 weeks) for up to 2 years after last dose, Q24W (± 4 weeks) beyond 2 years for patients who discontinue prior to PD	
									mutation, complex karyotype, del 11q, BTK mutation and PLCg2 mutation)
Physical examination	X	X		X		X	X	X	• Complete PE includes height (only at Screening), weight, basic neurological examination, and review of relevant symptoms at Screening; refer to Section 8.4.2 • Symptom-directed PE should be limited to systems of primary relevance such as cardiovascular, respiratory, and those associated with tumor assessment (lymph nodes, liver, and spleen) and may be performed at other timepoints; include weight as clinically indicated throughout the trial • Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results
ECOG PS	X	X		X		X	X		
Vital signs	X	X	X	X	X	X	X		• Includes systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature

Arm B: Bendamustine plus Rituximab (BR)

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 3 days)	Day 2	+ 7 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	Q12W (± 4 weeks) for up to 2 years after last dose, Q24W (± 4 weeks) beyond 2 years for patients who discontinue prior to PD	
Results of tests in the section below are required for eligibility determination and enrollment									
Deletion 17p evaluation	X								• Refer to Section 1.2.2 • Results are required for stratification
CMV	X								CMV IgG, IgM and DNA PCR at Screening only; Section 8.4.4.5
12-lead ECG	X								• Obtain ECGs at specified visit • Refer to Section 8.4.3 • At Screening, single ECG should be collected
Hematology	X	X		X		X	X	X	• Includes hemoglobin, hematocrit, RBC count, WBC count, platelet count, percent or absolute differential (neutrophils, lymphocytes, eosinophils, basophils, and monocytes). • Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results • Repeat testing during Screening is permitted; refer to Section 5.5 • On days when hematology is required for both safety and response assessments, samples

Arm B: Bendamustine plus Rituximab (BR)

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	**Screening**	**Cycle 1**		**Cycles 2-6**		**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 2**	**Day 1 (± 3 days)**	**Day 2**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	Q12W **(± 4 weeks)** for up to 2 years after last dose, Q24W **(± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	
									should also be submitted to the central laboratory
Blood chemistries	X	X		X		X	X		• Blood chemistry from serum or plasma should include assessment of: sodium, potassium, chloride, glucose, creatinine, total protein, albumin, total bilirubin, ALT, and AST • Repeat testing during Screening is permitted; refer to Section 5.5 • LDH, calcium, magnesium, phosphorus and uric acid are required at Screening and Day 1 of C1 to C6 • Screening results within 3 days of C1D1 are acceptable as C1D1 results
Coagulation panel	X	As clinically indicated							aPTT and PT (or INR)
Hepatitis B/C active disease status	X								• HBV and HCV testing to determine if patients have active infection • Refer to Section 5.2 for exclusions

Arm B: Bendamustine plus Rituximab (BR)

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	**Screening**	**Cycle 1**		**Cycles 2-6**		**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 2**	**Day 1 (± 3 days)**	**Day 2**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	Q12W **(± 4 weeks)** for up to 2 years after last dose, Q24W **(± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	
Serum or urine pregnancy test (WOCBP only)	X	X		X		X			• Perform within 24 hours of first dose of study treatment, and as indicated in table, or as required per local regulations and/or institutional guidelines • Refer to Section 10.2, Appendix 2
Urinalysis	X	X	As clinically indicated						Dipstick analysis is acceptable and should include color, specific gravity, pH, glucose, bilirubin, occult blood, protein, leukocytes, and urobilinogen
Documentation or sampling of the following are required during Screening, but results <u>not required prior to enrollment</u>									
β2 microglobulin	X								
Serum immunoglobulins	X								IgG, IgA, IgM
Bone marrow [redacted] biopsy	X			Within 4-8 weeks of confirmed CR by scan and peripheral blood assessment (required) and to confirm PD (optional)					• [redacted] biopsy [redacted] required at Screening and for confirmation of CR [redacted]

Arm B: Bendamustine plus Rituximab (BR)

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 3 days)	Day 2	+ 7 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	Q12W (± 4 weeks) for up to 2 years after last dose, Q24W (± 4 weeks) beyond 2 years for patients who discontinue prior to PD	
CT or MRI	X			C4D1		X		X	• Refer to Section 8.3 for details • CT scan with IV contrast agent is the preferred method of assessment with scans of neck, chest, abdomen, and pelvis. However, MRI is acceptable if CT scan with contrast agent is contraindicated. • All response assessments should occur at Q12W intervals relative to C1D1 regardless of any treatment delays or interruptions • At the EOT visit, a repeat CT/MRI does not need to be performed if done within the proceeding 2 weeks, or if PD was previously determined • A central radiology vendor will be used to collect and store images for IRC review
CCI									

Arm B: Bendamustine plus Rituximab (BR)

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 3 days)	Day 2	+ 7 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	Q12W (± 4 weeks) for up to 2 years after last dose, Q24W (± 4 weeks) beyond 2 years for patients who discontinue prior to PD	
CCI									
Bendamustine administration - IV		70 mg/m^2	70 mg/m^2	70 mg/m^2	70 mg/m^2				• C1D1 should occur within 3 business days after randomization • Date of last dose and date of decision for end of treatment must be recorded in EDC
Rituximab administration - IV		375 mg/m^2		500 mg/m^2 Day 1 of Cycles 2-6					• C1D1 should occur within 3 business days after randomization • Date of last dose and date of decision for end of treatment must be recorded in EDC
Concomitant medication	X	X	X	X	X	X	X		Refer to Section 6.5
Adverse events	X	X	X	X	X	X	X		• Collect SAEs from the time of ICF signing through 28 days after the last dose (NCI CTCAE v5.0)

Arm B: Bendamustine plus Rituximab (BR)

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 3 days)	Day 2	+ 7 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	Q12W (± 4 weeks) for up to 2 years after last dose, Q24W (± 4 weeks) beyond 2 years for patients who discontinue prior to PD	
									• Collect AEs from the time of dosing through SFU; AEs that occur prior to the first dose are considered medical history unless the AE develops or worsens due to study-related procedures • All SAEs occurring from the time ICF is signed through 28 days after the last dose must be reported to Clinical Safety within 24 hours of knowledge of the event. All SAEs that the Investigator considers related to study drug occurring after the 28-day follow-up period must be reported to the Sponsor • Second primary malignancy (SPM) events are to be reported and should continue to be reported for up to 5 years from the start of study treatment, regardless of seriousness or causal attribution to treatment (Section 8.5.8)

Arm B: Bendamustine plus Rituximab (BR)

Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**				**Post-Study Treatment Discontinuation**			**Instructions**
Evaluation	**Screening**	**Cycle 1**		**Cycles 2-6**		**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 2**	**Day 1 (± 3 days)**	**Day 2**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	Q12W **(± 4 weeks)** for up to 2 years after last dose, Q24W **(± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	
Medical resources utilization		X	X	X	X	X	X		Hospitalizations, emergency department visits, blood product transfusions, and hematopoietic growth factor use will be collected
Patient-reported outcomes		X	X	X	X	X	X		Refer to Section 1.3.6 for details
Survival								X	• Survival information may be collected via telephone if no procedures are required; this information should be collected approximately Q12W after the SFU visit; refer to Section 6.7.5 • Subsequent anticancer therapy information should be collected approximately Q12W after the SFU visit for the first 2 years and approximately Q24W thereafter until death or study completion

1.3.4. Schedule of Assessments for Optional Crossover Treatment (for Patients Crossing Over from Arm B to Arm A)

NOTES:

This SoA is applicable only for patients who were initially randomly assigned to Arm B (Investigator's choice), who have PD that is confirmed by the IRC, who are eligible for crossover (CO) treatment (refer to Section 5.3 Eligibility Criteria for Crossover Treatment), and have elected for optional crossover.

Patients who cross over will complete the Arm B End of Treatment (EOT) before crossing over to Arm A. Testing and assessments that are performed as part of Arm B, and that are within the Screening window of up to 42 days, do not need to be repeated as a part of the Screening evaluation for crossover.

Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)

Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**		**Post-Study Treatment Discontinuation**			**Instructions**
Evaluation	**CO-Screening**	**CO-Cycle 1**	**CO-Cycle 4 and higher**	**CO-EOT**	**CO-SFU**	**CO-LTFU**	
Visit Window	**Up to 42 days**	**Day 1**	**± 14 Days**	**+14 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q24W (± 4 weeks)**	
Informed consent	X						• The ICF for crossover must be signed before any protocol-specified procedures are performed. Refer to Section 10.1.2 • Crossover screening procedures must be completed within 42 days of IRC-confirmed PD
Physical examination	X	X	CO-C7D1 and Q24W thereafter	X	X	X	• Complete PE includes height (only at Screening), weight, basic neurological examination and review of relevant symptoms at Screening (refer to Section 8.4.2) • Symptom-directed PE should be limited to systems of primary relevance such as cardiovascular, respiratory, and those associated with tumor assessment (lymph nodes, liver, and spleen) and may be performed at other timepoints; include weight as clinically indicated throughout the trial • Screening results obtained within 3 days of CO-C1D1 are acceptable as CO-C1D1 results

Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)							
Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**		**Post-Study Treatment Discontinuation**			
Evaluation	**CO-Screening**	**CO-Cycle 1**	**CO-Cycle 4 and higher**	**CO-EOT**	**CO-SFU**	**CO-LTFU**	
Visit Window	**Up to 42 days**	**Day 1**	**± 14 Days**	**+14 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q24W (± 4 weeks)**	**Instructions**
ECOG PS	X	X	CO-C7D1 and Q24W thereafter	X	X		
Vital signs	X	X	CO-C7D1 and Q24W thereafter	X	X		• Includes systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature
Results of tests in the section below are required for crossover eligibility determination							
12-lead ECG	X						• Obtain ECGs at specified visits and when patients are symptomatic. Refer to Section 8.4.3 • ECGs should be collected: – At Screening, single ECG – If an unscheduled ECG is done at any time, an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG – If a clinically significant arrhythmia is detected, details must be in EDC
Hematology	X	X	CO-C7D1 and Q24W thereafter	X	X	X	• Includes hemoglobin, hematocrit, RBC count, WBC count, platelet count, percent or absolute differential (neutrophils, lymphocytes, eosinophils, basophils, and monocytes) • Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results • Repeat testing during Screening is permitted; refer to Section 5.5

Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)							
Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**		**Post-Study Treatment Discontinuation**			
Evaluation	**CO-Screening**	**CO-Cycle 1**	**CO-Cycle 4 and higher**	**CO-EOT**	**CO-SFU**	**CO-LTFU**	
Visit Window	**Up to 42 days**	**Day 1**	**± 14 Days**	**+14 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q24W (± 4 weeks)**	**Instructions**
Blood chemistries	X	X	CO-C7D1 and Q24W thereafter	X	X		• Blood chemistry from serum or plasma should include assessment of: Sodium, potassium, chloride, glucose, creatinine, total protein, albumin, total bilirubin, ALT, and AST • Repeat testing during Screening is permitted; refer to Section 5.5 • Tests for LDH, calcium, magnesium, phosphorus and uric acid are only required on Day 1 of CO-C1 • Screening results within 3 days of CO-C1D1 are acceptable as CO-C1D1 results • Direct (or indirect) bilirubin should be performed any time total bilirubin is abnormal
Coagulation panel	X	As clinically indicted					aPTT and PT (or INR)
Serum or urine pregnancy test (WOCBP only)	X	X	CO-C7D1 and Q24W thereafter				Perform within 24 hours of first dose of study treatment, and as indicated in table, or as required per local regulations and/or institutional guidelines. Refer to Section 10.2
Urinalysis	X	As clinically indicated					Dipstick analysis is acceptable and should include color, specific gravity, pH, glucose, bilirubin, occult blood, protein, leukocytes, and urobilinogen

Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)							
Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**		**Post-Study Treatment Discontinuation**			
Evaluation	**CO-Screening**	**CO-Cycle 1**	**CO-Cycle 4 and higher**	**CO-EOT**	**CO-SFU**	**CO-LTFU**	
Visit Window	**Up to 42 days**	**Day 1**	**± 14 Days**	**+14 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q24W (± 4 weeks)**	**Instructions**
Documentation or sampling of the following are required during Screening, but results <u>not required prior to initiation of Pirtobrutinib</u>							
CT or MRI	X		CO-C7D1 and Q24W thereafter	X		X	• Refer to Section 8.1 for details. • If baseline CT or MRI assessment documenting PD by IRC was performed within 42 days of planned C1D1, a new scan does not need to be obtained • All response assessments should occur at Q24W intervals relative to CO-C1D1, regardless of any treatment delays or interruptions • At the EOT visit, a repeat CT/MRI does not need to be performed if done within the proceeding 2 weeks or if PD was previously determined • Investigator assessment of CT or MRI will be done locally at frequency of at least Q24W frequency or based on standard of care
Pirtobrutinib administration		X	X	X			• 200 mg PO administered QD (continuous) • Crossover treatment should be initiated within a window of 42 days after the IRC-confirmed PD • Patient to visit study site Q12W from CO-C4D1 for dispensation of pirtobrutinib • Date of last dose and date of decision to end treatment must be recorded in EDC prior to patient receiving first dose of treatment in crossover
Patient dosing diary		X	X				
Concomitant medication	X	X	X	X	X		

Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)

Study Period	Baseline	Study Treatment (Cycle = 28 days)		Post-Study Treatment Discontinuation			
Evaluation	CO-Screening	CO-Cycle 1	CO-Cycle 4 and higher	CO-EOT	CO-SFU	CO-LTFU	
Visit Window	Up to 42 days	Day 1	± 14 Days	**+14 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q24W (± 4 weeks)**	**Instructions**
Adverse events	X	X	X	X	X		• Collect SAEs from the time of ICF signing through 28 days after the last dose (NCI CTCAE v5.0) • Collect AEs from the time of dosing through SFU; AEs that occur prior to the first dose are considered medical history unless the AE develops or worsens due to study-related procedures • All SAEs occurring from the time ICF is signed through 28 days after the last dose must be reported to Clinical Safety within 24 hours of knowledge of the event. All SAEs that the Investigator considers related to study drug occurring after the 28-day follow-up period must be reported to the Sponsor • Second primary malignancy (SPM) events are to be reported and should continue to be reported for up to 5 years from the start of pirtobrutinib treatment, regardless of seriousness or causal attribution to pirtobrutinib treatment
Survival status		X	X	X	X	X	• Survival information may be collected via telephone if no procedures are required; survival information should be collected approximately Q24W after the SFU visit; refer to Section 6.7.5 • Subsequent anticancer therapy information should be collected Q24W after the SFU visit until death or study completion

1.3.5. Schedule of Assessments for Response Assessments, Arms A and B (Does not Apply for Crossover)

NOTE: This section is a guide to specify elements required for response assessment without duplicating activities in the SoAs above. Assessments should include disease and symptom-focused physical examination, imaging, and hematology results and bone marrow examinations as described in iwCLL 2018.

Response Assessments, Arms A and B (does not apply for crossover)						
Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**	**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1 +**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1 (± 7 Days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	Q12W (**± 4 weeks**) for up to 2 years after last dose, Q24W (**± 4 weeks**) beyond 2 years for patients who discontinue prior to PD	**Instructions**
Bone marrow [redacted] biopsy	X	Within 4-8 weeks of confirmed CR by scan and peripheral blood assessment. Optional to confirm PD				• [redacted] biopsy [redacted] required at Screening and for confirmation of CR [redacted]
CT or MRI	X	C4D1 and Q12W thereafter	X		X	• Refer to Section 8.3.1 for details • CT scan with IV contrast agent is the preferred method of assessment with scans of neck, chest, abdomen, and pelvis. However, MRI is acceptable if CT scan with contrast agent is contraindicated • All response assessments should occur at Q12W intervals relative to C1D1 regardless of any treatment delays or interruptions • At the EOT visit, a repeat CT/MRI does not need to be performed if done within the proceeding 2 weeks or if PD was previously determined • A central radiology vendor will be used to collect and store images for IRC review

Response Assessments, Arms A and B (does not apply for crossover)						
Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**	**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1 +**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1 (± 7 Days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	Q12W (**± 4 weeks**) for up to 2 years after last dose, Q24W (**± 4 weeks**) beyond 2 years for patients who discontinue prior to PD	**Instructions**
Physical Examination	X	C4D1 and Q12W thereafter	X		X	• Complete PE includes height (only at Screening), weight, basic neurological examination, and review of relevant symptoms at Screening; refer to Section 8.4.2 • Symptom-directed PE should be limited to systems of primary relevance such as cardiovascular, respiratory, those associated with symptoms, and those associated with tumor assessment (lymph nodes, liver, and spleen) and may be performed at other timepoints; include weight as clinically indicated throughout the trial
Hematology	X	C4D1 and Q12W thereafter	X		X	• Includes hemoglobin, hematocrit, RBC count, WBC count, platelet count, percent or absolute differential (neutrophils, lymphocytes, eosinophils, basophils, and monocytes) • Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results • Repeat testing during Screening is permitted; refer to Section 5.5 • On days when hematology is required for both safety and response assessments, samples should also be submitted to the central laboratory

1.3.6. Schedule of Assessments for Patient-Reported Outcomes, Arms A and B

Instrument	Cycle 1	Complete until EOT		EOT	SFU	
Visit Window	Day 1 (Completed in clinic prior to first dose of study drug)	Every 4 Weeks ± 7 days	Every 12 Weeks ± 7 days	+ 7 days of last dose or decision to terminate treatment	28 days (+7 days) after last dose or decision to terminate treatment	Instructions
EORTC QLQ-C30	X		X	X	X	• All PRO assessments must be completed electronically. • Refer to Section 8.12.1 for more details.
CCI						
EORTC IL19 (Physical Function)		X[a]				
CCI						
EQ-5D-5L	X		X	X	X	

[a] This instrument will not be administered on weeks where the EORTC QLQ-C30 and EORTC CCI are administered due to overlapping items.

2. INTRODUCTION

2.1. Study Rationale

Pirtobrutinib is an orally available, highly selective, ATP-competitive inhibitor of BTK distinct from the approved BTK inhibitors (ibrutinib approved globally for CLL/SLL and MCL; acalabrutinib approved in select countries for CLL/SLL and MCL; zanubrutinib approved in the US for CLL and MCL) on the basis of its selectivity, favorable pharmacologic and PK properties, and non-covalent binding mode (Brandhuber et al. 2018). In a Phase 1/2 study (LOXO-BTK-18001, NCT03740529), pirtobrutinib has demonstrated robust and durable antitumor activity against a variety of B-cell malignancies including CLL/SLL, regardless of prior treatment and including in patients previously treated with covalent BTK inhibitors.

The proposed Phase 3 study is a global, randomized, open-label study in patients with previously treated CLL/SLL who have received a prior covalent BTK inhibitor to assess the superiority of pirtobrutinib to Investigator's choice of either idelalisib with rituximab (IdelaR) or bendamustine with rituximab (BR). The proposed study will uniquely evaluate the role of non-covalent BTK inhibitor therapy in a prospectively identified CLL/SLL patient population pretreated with prior covalent BTK inhibitors.

2.2. Background

BTK is a member of the TEC family of non-receptor tyrosine kinases (which includes BTK, ITK, TEC, TXK, and BMX) and a key component of the B-cell receptor (BCR) signaling complex. BTK also plays a critical role in the proliferation and survival of diverse B-cell malignancies.

BTK inactivating mutations were originally identified as the cause of X-linked immunodeficiency (Xid) in mice (Rawlings et al. 1993; Thomas et al. 1993) and X-linked agammaglobulinemia (XLA) in humans (Vetrie et al. 1993). XLA is a rare, X-linked recessive disorder that causes severe bacterial infections in affected boys due to a complete absence of functional B lymphocytes and antibodies (Hendriks et al. 2011). Lifelong treatment with antibiotic prophylaxis and IV and/or subcutaneous (SC) immunoglobulins can prevent infection and lead to normal life expectancy.

In normal B-cells, antigen binding to the BCR leads to activation of the upstream kinases LYN and SYK, recruitment of phosphoinositide 3-kinase (PI3K), generation of the second messenger phosphatidylinositol 3-phosphate (PIP3) and PIP3-dependent recruitment of BTK to the plasma membrane. LYN and SYK-mediated phosphorylation of BTK on tyrosine residue 551 (Y551) stimulates the kinase activity of BTK, leading to autophosphorylation on Y223 and phosphorylation-dependent activation of the critical downstream signaling effector phospholipase C gamma 2 (PLCg2). PLCg2-mediated generation of second messengers inositol 3-phosphate (IP3) and diacyl glycerol (DAG) induces the activation of several critical signaling effectors (nuclear factor of activated T-cells [NFAT], mitogen-activated protein kinase [MAPK]/extracellular signal-regulated kinase [ERK], protein kinase C [PKC], nuclear factor kappa-light-chain-enhancer of activated B-cells [NF-kB]) which results in increased proliferation and survival.

BTK expression is restricted to a subset of B-cells and myeloid cells, and in malignancies thought to derive from them, including CLL, related to naïve B-cells, MCL, marginal zone lymphoma (MZL, each related to germinal center B-cells), and Waldenström's macroglobulinemia (WM, plasma cells). Consistent with a critical survival role for BTK in these malignancies, BTK deficiency abrogates tumor formation in CLL mouse models (Kil et al. 2013), and treatment of primary, patient-derived CLL, MCL and WM cells with the irreversible BTK inhibitor ibrutinib reduces their viability, adhesion and migration (Herman et al. 2011; Chang et al. 2013; Yang et al. 2013).

Three BTK inhibitors are now approved for the treatment of patients with B-cell malignancies. These agents have altered the treatment paradigms for many B-cell malignancies, including CLL/SLL (ibrutinib, acalabrutinib, and zanubrutinib), relapsed/refractory (r/r) MCL (ibrutinib, acalabrutinib, and zanubrutinib), WM (ibrutinib, zanubrutinib), and MZL (ibrutinib, zanubrutinib). These agents potently inhibit BTK by binding to the ATP pocket of the enzyme and forming an irreversible, covalent bond with the C481 in the BTK enzyme. Covalent ligation of BTK inhibits its kinase activity, induces BTK degradation and causes potent and prolonged BTK target engagement and inhibition in patients (Byrd et al. 2013; Byrd et al. 2016). Treatment with other, investigational irreversible BTK inhibitors has produced near total BTK suppression in circulating leukemia cells and lymphoma/leukemia lymph node reservoirs and has induced significant tumor responses (Tam et al. 2015). However, ibrutinib, acalabrutinib, and zanubrutinib are covalent inhibitors with limited oral bioavailability, high protein binding, and half-lives that are significantly shorter than their dosing intervals. The clinical efficacy of these agents is therefore attributed to their irreversible binding mode at the C481. Once bound to BTK, these agents require protein turnover to "undo" their pharmacodynamic effects of inhibition. Reliance on covalent binding may lead to diminished target coverage towards the end of the dosing interval (i.e., low trough coverage) and in rapidly proliferating tumors with higher BTK protein turnover with subsequent loss of clinical activity.

Although irreversible BTK inhibitors have transformed the treatment of several B-cell malignancies, their long-term efficacy is ultimately limited by toxicity and acquired resistance. In r/r CLL, although initial response rates to ibrutinib are high, rates of treatment discontinuation are also high (approximately 40%) with extended follow-up (Woyach et al. 2017; Mato et al. 2018). The most common reasons for treatment discontinuation are AEs in approximately 50 to 60%, CLL progression in approximately 20 to 30%, and Richter's Transformation in approximately 5 to 15% of patients. Toxicities of ibrutinib that lead to dose interruptions and treatment discontinuation include arthralgia, atrial fibrillation, rash, cytopenias, infection, pneumonitis, bleeding and diarrhea (Mato et al. 2018). These toxicities have been attributed to both on-target BTK inhibition and off-target inhibition of other kinases such as TEC (McMullen et al. 2014; Kamel et al. 2015). Acalabrutinib, which is more selective than ibrutinib against non-BTK kinase off-targets in preclinical studies, has been associated with a lower overall frequency of some (e.g., atrial fibrillation, major bleeding), but not other (e.g., cytopenias, upper respiratory infection, diarrhea) toxicities in clinical trials (Byrd et al. 2013; Byrd et al. 2016). A retrospective analysis of the RESONATE study indicated worse PFS in patients with r/r CLL with lower ibrutinib dose intensity and dose interruptions lasting for longer than 7 days, suggesting that treatment interruptions for toxicity can adversely impact long-term outcomes (Barr et al. 2017).

Recent analysis of primary CLL samples from patients with relapsed CLL who responded to, but then ultimately progressed on ibrutinib, has uncovered 2 primary mechanisms of acquired resistance, and one less common: substitution at C481, primarily with a serine residue (i.e., C481S) in the majority (67%) of patients, which prevent irreversible binding of ibrutinib (and acalabrutinib) to BTK; activating mutations in PLCg2, a critical signaling effector downstream of BTK in 13%; and less commonly, both mutations occurring in the same patient (7%) (Woyach et al. 2017). These frequencies have been validated in more recent studies (Bonfiglio et al. 2018). Other studies have uncovered C481 substitution mutations in WM and MCL, indicating that C481 substitutions represent a common mechanism of "on target" resistance to irreversible BTK inhibitors in patients (Chiron et al. 2014; Xu et al. 2017). C481 substitutions prevent irreversible ligation of ibrutinib (and other irreversible BTK inhibitors) to BTK. These mutations lead to insufficient BTK target coverage in patients and treatment failure as a result (Byrd et al. 2013; Woyach et al. 2017).

2.2.1. Current Approaches to Treatment of CLL/SLL

CLL/SLL is the most common form of adult leukemias in the Western world and accounts for approximately 30-40% of all leukemias (Wierda et al. 2020; Eichhorst et al. 2015). SLL defines the same disease manifesting predominantly in lymph nodes instead of as leukemia. The median age at diagnosis has variously been reported as between 67 and 72 years of age with male predominance (Watson et al. 2008; 2014 Review of Cancer Medicines [WHO]). CLL/SLL occurs in approximately 3.8-4.2 in 100,000 people in Europe (Sant et al. 2010; Eichhorst et al. 2015) and 4.5 in 100,000 people per year in the United States (US) (Howlader et al. 2020). Allogeneic stem cell transplantation (SCT) is the only known curative therapy, but with limited applicability to the typical patient diagnosed with CLL/SLL who generally is older with co-morbidities. Thus, treatment is not given with intent to cure and while many patients do not need treatment at diagnosis, once initiated, sequential treatments are the standard to extend survival. Ongoing efforts to identify therapies which can contribute to the meaningful improvement of patient outcomes are needed.

For newly diagnosed CLL/SLL, BTK inhibition (with zanubrutinib, ibrutinib, or acalabrutinib), chemo-immunotherapy, or BCL2 inhibition (with venetoclax) are approved standard treatments in select countries. The selection of one strategy over another is highly influenced by patient age, comorbid illness, prognostic markers, patient preference, and treatment setting. BTK inhibitors are becoming the preferred first-line therapy and have meaningfully impacted PFS and OS compared to chemoimmunotherapy (Shanafelt et al. 2019). Importantly, however, frontline BTK inhibitor-based therapies are not curative, and patients eventually relapse. Following progression on BTK inhibitors, median OS in one recent study was only 22.7 months, demonstrating an ongoing unmet need for this population (Woyach et al. 2017).

Prospective data evaluating treatment for relapsed CLL after BTK inhibitor is scarce and the data used to support the global marketing authorisations for treatments in the relapsed CLL setting were conducted in patients who were almost exclusively BTK inhibitor naïve. In a recent interim analysis of an ongoing Phase 1 study, treatment of CLL patients who had failed prior ibrutinib treatment with the targeted BCL2 inhibitor venetoclax achieved an ORR of 65% (9% CR) (Mato et al. 2018). Recent data of venetoclax with rituximab therapy in the relapsed setting has introduced the concept of treatment given for a defined fixed-duration, in contrast to the

continuous daily administration required for BTK inhibitor monotherapy given for the same indication. These data show the promise of this approach by inducing deep responses as evidenced by the high percentage of patients with high clearance rate of minimal residual disease which correlates with improved PFS (Seymour et al. 2018; Kater et al. 2018). However, despite this encouraging activity, venetoclax with rituximab does not yet define a cure with extended follow-up. Of importance, only 8 of 389 total enrolled patients had received a prior BCR inhibitor with even fewer receiving prior BTK inhibitors.

Thus, few effective salvage therapy options currently available have been evaluated specifically for patients who have progressed on irreversible BTK inhibitors. The ORR of treatments for this population are garnered from varied retrospective reports ranges from 28% to 70% and identify an ongoing need for new therapies (Mato et al. 2017; Mato et al. 2016; Jain et al. 2015). Therefore, while some post-marketing data in BTK inhibitor-treated patients have been collected, the data from such analyses are not incorporated into existing prescribing information and for this reason, the true efficacy of options for pretreated CLL after a BTK inhibitor remains investigational. Although durable remissions with CD19-specific chimeric antigen receptor-modified T-cells (CAR-T) after ibrutinib failure have been observed, CAR-T therapy as a whole appears less efficacious in CLL than in aggressive B-cell malignancies (e.g., acute leukemias and aggressive non-Hodgkin lymphomas [NHL]) and is associated with significant toxicities (Turtle et al. 2017).

Chemotherapy has been a mainstay of treatment for CLL therapy prior to the introduction of inhibitors of the B-cell receptor and remains a treatment option. Chlorambucil was the primary chemotherapy for treatment of CLL until the superiority of bendamustine monotherapy was demonstrated in the relapsed settings on the basis of multicenter, international study (Bergmann et al. 2005). The combination of bendamustine with rituximab (BR) for a treatment duration of only 6 cycles was established as a treatment option for relapsed CLL in 2011 (Fischer et al. 2011). Data from an observational study on the efficacy of BR as first salvage therapy in CLL identified a median PFS of 25 months, but the presence of del 17p, unmutated immunoglobulin heavy chain variable region gene (IGHV), and advanced disease stage were associated with shorter PFS (Cuneo et al, 2018). The same analysis evaluated outcomes in a matched indirect comparison of second line BR against ibrutinib in patients treated with frontline chemoimmunotherapy and restricted to those with intact 17p, and no OS difference was identified. When given in later lines of treatment, response to BR declines, but complete remissions can still be attained (Pound et al. 2011) Thus, BR is an effective time-limited salvage therapy for relapsed CLL, particularly for patients without del 17p.

Idelalisib is a selective inhibitor of PI3K-δ approved in the US and Europe in 2014 in combination with rituximab for relapsed CLL and in 1L for the high risk del 17p/TP53 mutated group, but only if patients are not eligible for other frontline therapies as the toxicity profile of idelalisib can be restrictive and include pneumonitis, colitis, Grade 3 or higher rash, and elevated transaminases. These toxicities appear to be immune-mediated and reflect suppression of T-cell mediated self-tolerance by inhibition of PI3K-δ (Patton et al. 2006). These toxicities are heightened with idelalisib given in the frontline setting while idelalisib with rituximab appears to harbor a more acceptable safety profile in the relapsed treatment setting for CLL due to lower T-cell counts. Although data leading to the approval of idelalisib with rituximab in relapsed CLL did not include patients previously treated with BTK inhibitors, the common usage of IdelaR has

been limited by the toxicity profile and typically follows ibrutinib and venetoclax, particularly for patients harboring del 17p (Schenkel et al. 2017; Mato et al. 2019).

For the proposed Phase 3 study the comparator arm will be Investigator's choice of either idelalisib in combination with rituximab or bendamustine in combination with rituximab. Both comparators are recognized by European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) as treatment options for patients with relapsed or refractory CLL, and both regimens are globally acceptable standard therapies with wide availability. Data on the selected comparators of idelalisib plus rituximab and bendamustine plus rituximab treatments suggest similar efficacy data to allow either option to be offered as a control arm for this Phase 3 study. For bendamustine plus rituximab, ORR is reported as 66 to 68% with median PFS 14 to 17 months (Seymour et al. 2018; Fraser et al. 2019) and for idelalisib with rituximab, ORR is 84% with median PFS of 19 months (Sharman et al. 2019). As the comparator arm does not include BCL2 inhibitor-based therapy as an option, the Sponsor anticipates that a substantial number of patients will have already received prior venetoclax prior to enrolling to this clinical trial. Thus, the expectation is that this study will enroll not only patients who have received a prior covalent BTK inhibitor, but also a substantial number of patients who have also received a BCL2 inhibitor. This study will therefore help establish the risk/benefit profile of pirtobrutinib, as well as the control arm, in this patient population where, to the Sponsor's knowledge, no prospective efficacy data currently exist. Based on current available therapies, current practice, and regulatory approvals, both chemoimmunotherapy (with BR) or PI3K-based therapy (with IdelaR) are therefore deemed appropriate treatment regimen in this population, and hence are included in the control arm providing the patients and treating physician optionality to choose the most appropriate agent class for each patient based individualized risk/benefit assessment (Fischer et al. 2019; Hillmen et al. 2019; Seymour et al. 2018).

2.3. Benefit/Risk Assessment

Pirtobrutinib has demonstrated clinical activity in the patient population specified for this study. The LOXO-BTK-18001 (NCT03740529) is a first-in-human global Phase 1/2 study evaluating the safety and efficacy of pirtobrutinib in patients with CLL/SLL and B-cell NHL who have failed or are intolerant to standard-of-care therapy. The study commenced enrollment in March 2019 to establish the safety of pirtobrutinib, assess PK, and identify a recommended Phase 2 dose (RP2D) and a maximal tolerated dose (MTD). During Phase 1 dose escalation, pirtobrutinib was well tolerated at dose levels of CCI to 300 mg QD with no dose-limiting toxicities (DLTs). Given the totality of efficacy, clinical PK, and safety data, the Sponsor and Safety Review Committee decided that ongoing dose escalation was not medically justified and therefore, no MTD was established. An RP2D was identified as 200 mg QD.

PK data show that pirtobrutinib is absorbed after oral administration with a median time to maximum plasma concentration (T_{max}) of approximately 2 hours and low clearance. Plasma halflife appears to be approximately 20 hours. Steady-state AUC_{0-24} increase in approximate proportion with daily dose. CCI

Study results from a CCI study CCI evaluating the CCI of pirtobrutinib showed that CCI

Efficacy data from the LOXO-BTK-18001 study show robust and durable antitumor activity against a variety of B-cell malignancies, including pretreated CLL/SLL. Enrolled patients have varied prior therapies, including diverse combinations of chemotherapy, anti-CD20 antibodies, BCL2 inhibitors, PI3K inhibitors, and BTK inhibitors. The vast majority of CLL/SLL patients treated on the LOXO-BTK-18001 study received a prior BTK inhibitor. Antitumor activity has been seen in the majority of patients, regardless of prior treatment, including in patients treated with covalent BTK inhibitors. Of note, durable objective responses have been seen in patients with acquired resistance to prior BTK therapy, regardless of BTK C481 mutational status.

As of 27 September 2021, clinical safety data are available from a total of 679 patients treated with pirtobrutinib in Phase 1/2 Study LOXO-BTK-18001. This includes 654 patients treated at doses ranging from CCI QD to 300 mg QD in Phase 1/2 Monotherapy cohorts and 25 patients in the Phase 1b Combination Therapy arms (including 15 patients in Arm A [pirtobrutinib plus venetoclax] and 10 patients in Arm B [pirtobrutinib plus rituximab and venetoclax]). Nearly half of treated patients were patients with CLL/SLL (326 patients, 48.0%). Treatment-emergent adverse events (TEAEs) were reported in 617 of the 679 treated patients (90.9%) in the study.

In the 654 patients in the Phase 1/2 Monotherapy cohorts in Study LOXO-BTK-18001, the most frequently reported TEAEs were fatigue (24.2% total, 9.6% related), diarrhea (19.1% total, 8.3% related), and contusion (17.1% total, 12.1% related). Drug-related TEAEs were reported in 361 of 654 patients (55.2%) in the Phase 1/2 Monotherapy cohorts; the most frequently reported drug-related TEAEs for pirtobrutinib were contusion (12.1%), fatigue (9.6%), and diarrhea (8.3%). All other drug-related TEAEs were reported in < 5% of patients (i.e., < 33 patients each). TEAEs of severity Grades 3 or 4 were reported in 271 of 654 of patients (41.4%) in the Phase 1/2 Monotherapy cohorts, with 118 (18.0%) of these Grade 3 or 4 AEs reported as related to study drug. On study death (death within 28 days of the last dose of study) due to a Grade 5 (fatal) TEAE was reported in 25 of 654 patients (3.8%) in the Phase 1/2 Monotherapy cohorts. One of the Grade 5 AEs, *Enterococcus faecium*-related septic shock, was considered to be related to study drug; this patient had multiple underlying concomitant risk factors, including underlying disease, recent splenectomy prior to enrollment and 11 prior lines of therapy; while the Investigator did not deem pirtobrutinib directly causative, study drug was believed to be contributory to the event severity.

In Phase 1b Combination Arms of Study LOXO-BTK-18001, TEAEs were reported in 15 of the 15 patients (100%) treated in Combination Arm A and in 9 of the 10 patients (90.0%) treated in Combination Arm B. The 3 most frequently reported TEAEs in Combination Arm A were neutrophil count decreased, nausea, and fatigue (6 patients each [40.0%]). The most frequently reported TEAEs in Combination Arm B were constipation, diarrhea, infusion-related reaction, and neutrophil count decreased (3 patients each [30.0%]).

For the most updated information from Study LOXO-BTK-18001, refer to the Investigator's Brochure (Pirtobrutinib IB). Additional updated information about the known and expected risks, SAEs, and reasonably anticipated AEs of pirtobrutinib, is also provided in the Pirtobrutinib IB.

Despite available therapies, pretreated CLL/SLL remains an incurable disease and patients, particularly those progressing on targeted therapies, continue to require additional treatment especially with novel agents. Thus, there continues to be an unmet need to evaluate new therapies in these patients, which the Sponsor will address for this patient population in this global Phase 3 study.

Overall Benefit/Risk Conclusion

During Phase 1 and 2 studies, pirtobrutinib has demonstrated a tolerable safety profile and a durable antitumor activity against a variety of B-cell malignancies, including pretreated CLL/SLL. Additionally, considering the measures taken to ensure patient safety in this study, the potential risks from taking the study interventions are outweighed by the potential benefits for individuals with CLL/SLL.

3. OBJECTIVES AND ENDPOINTS

Table 3.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate progression-free survival (PFS) of pirtobrutinib as monotherapy (Arm A) compared to Investigator's choice of idelalisib plus rituximab (IdelaR) or bendamustine plus rituximab (BR) (Arm B).	Assessed by Independent Review Committee (IRC): PFS per iwCLL 2018
Secondary	
To evaluate the effectiveness of Arm A compared to Arm B based on overall response rate (ORR) and time to event(s) outcomes	Assessed by Investigator: PFS per iwCLL 2018 criteria Overall survival (OS) Time to next treatment (TTNT), defined as time from the date of randomization to the date of the next systemic anticancer therapy for CLL/SLL (Section 9 for full definition). Event free survival (EFS) defined as the time from date of randomization to the date of PD or start of new treatment for CLL/SLL or discontinuation from treatment due to toxicity or death, whichever occurs first. Assessed by Investigator and IRC: ORR Duration of response (DOR)
To evaluate the safety and tolerability of each treatment arm	Including, but not limited to, serious adverse events (SAEs), adverse events (AEs), deaths and clinical laboratory abnormalities per National Cancer Institute Common Terminology Criteria in Adverse Events v5.0 (NCI CTCAE v5.0)
To evaluate the effectiveness of Arm A compared to Arm B based on patient-reported outcomes	Patient-reported outcomes of: Time to worsening (TTW) of CLL/SLL-related symptoms TTW of physical functioning
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

LOXO-BTK-20020 (BRUIN-CLL-321) is a Phase 3 global, randomized, open-label study comparing pirtobrutinib as continuous monotherapy (Arm A) to Investigator's choice of either IdelaR or BR (Arm B) in CLL/SLL patients who have been treated with a covalent BTK inhibitor, approved (ibrutinib or acalabrutinib) or investigational. The Study Schematic is provided in Section 1.2.1. Eligible patients will be randomized in 1:1, Arm A:Arm B, based on stratification factors of del 17p presence (yes/no) and receipt of prior venetoclax treatment (yes/no).

BRUIN-CLL-321 will enroll adult CLL/SLL patients with an indication for treatment as defined by iwCLL 2018 criteria (Section 10.6, Appendix 6). During Screening, Investigator's choice therapy (IdelaR or BR) must be selected by the Investigator prior to randomization for each patient. Patients who have been previously treated with IdelaR or BR and had either documented PD as determined by the Investigator, or could not tolerate the regimen, should not be retreated with same regimen. Patients assigned to oral pirtobrutinib will receive this continuously until discontinuation criteria are met (Section 7). Patients assigned to IdelaR will receive rituximab IV for a total of 8 infusion and continuous oral idelalisib until discontinuation criteria met (Section 7). Patients assigned to BR will receive up to 6 cycles of both agents intravenously and then be followed until progression, death, lost to follow-up or withdrawal of consent. Patients randomly assigned to Arm B will be allowed to cross over to Arm A upon confirmation of PD by IRC and if they meet the eligibility criteria for crossover (Section 5.3). Patients who discontinue treatment for toxicity may still be evaluated for crossover at the time of IRC-confirmed PD. Patients who discontinue treatment for any reason other than PD, death, lost to follow-up, or withdrawal of consent will be followed for tumor assessment until PD, regardless of whether the patient receives a new anticancer therapy.

4.2. Scientific Rationale for Study Design

This study will compare the efficacy and safety of pirtobrutinib administered as a continuous monotherapy with Investigator's choice of standard-of-care IdelaR or BR. The patient population will have received prior BTK inhibitor therapy as part of any number of prior therapies. Therefore, the patient population is heterogeneous with regard to treatment exposure and future prognosis. The comparator arms for this study are considered to reflect global standard-of-care for this patient population. Prior BCL2 inhibitor-based therapy is permitted which will also uniquely allow the evaluation of patients who have failed both BTK and BCL2 inhibitor therapy. This global study will generate important data characterizing the differences in safety, tolerability, and efficacy in this patient population between pirtobrutinib and IdelaR or BR.

4.3. Justification for Dose

4.3.1. Pirtobrutinib

Preclinical data supporting the selection of the starting dose of pirtobrutinib for the first-in-human Phase 1/2 study of pirtobrutinib (LOXO-BTK-18001) is provided in the Pirtobrutinib IB. During Phase 1 dose escalation, pirtobrutinib has been administered at doses ranging from CCI

QD to 300 mg QD. Response was seen at all dose levels including CCI QD and across tumor types. PK data obtained during dose escalation demonstrated that at doses of 100 mg QD or higher, CCI [redacted] During Phase 1, additional patients were enrolled to dose levels cleared for safety to confirm safety and evaluate additional preliminary efficacy. In May 2020, based on the totality of PK, safety, and clinical data in Study LOXO-BTK-18001, the Sponsor and Safety Review Committee (SRC) identified the RP2D of pirtobrutinib as 200 mg QD. As of 27 September 2021, 679 patients had been dosed with pirtobrutinib in Study LOXO-BTK-18001, and a starting dose of 200 mg QD was administered to 569 of the 679 (87.0%) treated patients in the Phase 1/2 monotherapy cohorts, and to all of the 25 patients treated in Phase 1b combination arms (including 15 patients in Arm A [pirtobrutinib plus venetoclax] and 10 patients in Arm B [pirtobrutinib plus rituximab plus venetoclax]). For the most updated information from Study LOXO-BTK-18001, refer to the Pirtobrutinib IB.

4.3.2. Idelalisib plus Rituximab

Idelalisib with rituximab was approved on the basis of a Phase 3 study conducted in previously treated CLL patients who were unable to tolerate standard chemoimmunotherapy due to co-morbidities, reduced renal function, or persistent myelotoxic effects of prior cytotoxic therapy (Furman et al. 2014). In this study, idelalisib was administered orally at 150 mg twice daily (BID) dosed continuously and combined with rituximab administered at 375 mg/m^2 for the first cycle and then 500 mg/m^2 on weeks 2, 4, 6, 12, 16, and 20 for a total of 8 doses. As this schedule resulted in meaningful clinical activity, idelalisib with rituximab has been approved for use as a combination for treatment of patients with relapsed CLL for whom rituximab alone would be considered appropriate therapy due to other co-morbidities. The dose and schedule used for marketing approval will be used in the IdelaR arm for this study. Dose modification for toxicities are detailed in Section 6.6. Premedication may be required for rituximab and should be administered per local institutional standard.

Biosimilar anti-CD20 is permitted in accordance with local prescribing practice.

Subcutaneous formulation or administration of rituximab is not allowed. Rituximab as IV push or bolus administration will not be allowed. Patients should receive the same formulation throughout the duration of the trial (either branded or biosimilar).

4.3.3. Bendamustine plus Rituximab

Bendamustine with rituximab has been administered to patients with r/r CLL with bendamustine dosed for 6 cycles at 70 mg/m^2 IV on Days 1 and 2 of each cycle and combined with rituximab administered at 375 mg/m^2 Day 1 of the first cycle and 500 mg/m^2 Day 1 of Cycles 2 to 6 (Fischer et al. 2011). At this dose and schedule, BR results in meaningful clinical activity with an ORR rate of 59% and PFS of 15 months in 78 patients evaluated. In this study, Grade 3 infections occurred in 13% of patients; dose reductions were required in 37% of patients, and 44% of patients did not receive all 6 cycles of treatment, often due to toxicity. While the bendamustine label indicates a monotherapy dose of 100 mg/m^2, the bendamustine dose of 70 mg/m^2 has been recommended for use in r/r CLL by the International Consensus Panel (Cheson et al. 2016). Thus, the same doses and schedule will be used in the BR comparator option for this study. Dose modifications for toxicities are detailed in Section 6.6.

Premedication may be required for rituximab and should be administered per local institutional standard.

Biosimilar anti-CD20 is permitted in accordance with local prescribing practice.

Subcutaneous formulation or administration of rituximab is not allowed. Rituximab as IV push or bolus administration will not be allowed. Patients should receive the same formulation throughout the duration of the trial (either branded or biosimilar).

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial globally, which is estimated at approximately CCI from the first patient randomized to allow for recruitment and follow-up.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

Age

1. Age 18 or older per local regulations at time of enrollment.

Type of Patient and Disease Characteristics

2. Confirmed diagnosis by redacted local laboratory report of CLL/SLL as defined by iwCLL 2018 criteria, including the following:
   a) B-cells coexpressing the surface antigen CD5 together with at least one B-cell antigen (CD19, CD20, CD23) and either κ or λ light-chain restricted.
   b) $\geq 5 \times 10^9$ B lymphocytes/L (5000/μL) in the peripheral blood. For SLL patients, history of $\geq 5 \times 10^9$ B lymphocytes/L (5000/μL) in the peripheral blood is allowed.
   c) Prolymphocytes may comprise ≤ 55% of blood lymphocytes.
3. A requirement for therapy consistent with iwCLL 2018 criteria for initiation of therapy such that at least 1 of the following should be met:
   a) Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (such as hemoglobin < 10 g/dL) and/or thrombocytopenia (such as platelets $\leq 100 \times 10^9$/L).
   b) Massive (i.e., spleen edge ≥ 6 cm below the left costal margin) or progressive or symptomatic splenomegaly (≥ 13 cm).
   c) Massive nodes (i.e., ≥ 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
   d) Progressive lymphocytosis with an increase of > 50% over a 2-month period or lymphocyte doubling time < 6 months. Factors contributing to lymphocytosis other than CLL/SLL (e.g., infections, steroid administration) should be excluded.
   e) Autoimmune complications including anemia or thrombocytopenia poorly responsive to corticosteroids.
   f) Symptomatic or functional extranodal involvement (e.g., skin, kidney, lung, spine).
   g) Disease-related symptoms (also known as B-symptoms) as defined by any of the following:
      i) Unintentional weight loss ≥ 10% within the previous 6 months.
      ii) Significant fatigue (i.e., Eastern Cooperative Oncology Group [ECOG] performance scale 2 or worse; cannot work or unable to perform usual activities).
      iii) Fevers ≥ 100.5°F or 38.0°C for 2 or more weeks without evidence of infection.

iv) Night sweats for ≥ 1 month without evidence of infection.

4. Known 17p deletion status (wildtype for 17p locus or positive for 17p deletion) by FISH as indicated in Section 1.2.2.
5. Previously treated with a covalent BTK inhibitor, investigational or approved, and either alone or in combination with other agents. Patients may have received an unlimited number of lines of prior therapy.
6. Eastern Cooperative Oncology Group (ECOG) 0 to 2.
7. Must have adequate organ function, as defined below. These values must be met during the Screening Period. Results from the most recent assessment during the Screening Period will be used for eligibility.

System	Laboratory Value
Adequate Bone Marrow Function (if bone marrow involvement by disease is not present)	
Absolute neutrophil count (ANC)	≥ 0.75 × 10^9/L without granulocyte-colony-stimulating factor (GCSF) support, or ≥ 0.50 × 10^9/L in patients with documented bone marrow involvement considered to impair hematopoiesis. GCSF support is permitted in patients with documented bone marrow involvement.
Platelets	≥ 50 × 10^9/L. If an Investigator has chosen bendamustine/rituximab as the Arm B treatment, platelets must be ≥ 75 × 10^9/L. Patients may enroll below these thresholds if the Investigator determines the cytopenia is related to bone marrow involvement considered to impair hematopoiesis. Patients with a platelet count < 30 x 10^9/L are excluded.
Hemoglobin	≥ 8 g/dL, or ≥ 6 g/dL in patients with documented bone marrow involvement considered to impair hematopoiesis. Transfusion support is permitted in patients with bone marrow involvement.
Note: Patients who are receiving transfusions of blood or platelets for bone marrow involvement induced cytopenias, must be responsive to transfusion support. Patients who are refractory to transfusion support are not eligible. If the patient is cytopenic, there should be no evidence of myelodysplastic syndrome or hypoplastic bone marrow.	
Hepatic	
Total bilirubin	≤ 1.5× upper limit of normal (ULN) or if with documented liver involvement ≤ 3× ULN. If total bilirubin is > 1.5× ULN the direct and/or indirect (or conjugated/unconjugated and/or unconjugated) bilirubin tests should be performed.
	Patients with Gilbert's Syndrome or hemolysis may be enrolled if indirect (unconjugated) bilirubin is < 3× ULN (indirect bilirubin = total bilirubin - direct bilirubin)
Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST)	≤ 3.0 × the ULN or with documented liver involvement ≤ 5× ULN

System	Laboratory Value
Renal	
Creatinine clearance	≥ 30 mL/minute. If an Investigator has chosen bendamustine/rituximab as the Arm B treatment, creatinine clearance must be ≥ (40 mL/minute). Using Cockcroft/Gault Formula: (140 – age) × body weight (kg) × 0.85 (if female) serum creatinine (mg/dL) × 72

8. Patients are required to have had the following washout periods prior to planned C1D1:
   a) Targeted agents or cytotoxic chemotherapy: 5 half-lives or 2 weeks, whichever is shorter
   b) Anticancer therapeutic monoclonal antibodies: 4 weeks; patients who cross over are not required to observe this washout period prior to starting crossover treatment.
   c) Palliative limited field radiation: 7 days
   d) Broad field radiation (≥ 30% of bone marrow or whole brain radiotherapy): 28 days
9. Prior treatment-related AEs must have recovered to Grade ≤ 1, pretreatment baseline, or are controlled with medications without meeting other exclusion criteria (with the exception of alopecia).

Contraception

10. Willingness of men and women of childbearing potential (WOCBP), and their partners, to observe barrier and highly effective birth control methods as outlined in Section 10.2 (Appendix 2 and below) for the duration of treatment and for 6 months following the last dose of study treatment or 12 months after the last dose of rituximab, whichever is later.

    WOCBP are defined as those following menarche and who are not postmenopausal (or 2 years of non-therapy-induced amenorrhea, or surgically sterile). WOCBP must utilize highly effective contraception methods as outlined below. In addition, male partners must use a barrier method (condoms) for the duration of treatment and for 6 months following the last dose of study treatment or 12 months after the last dose of rituximab, whichever is later. Male patients with partners who are WOCBP must use a barrier method (condoms) and their partner must also use a highly effective form of contraception as listed below for the duration of treatment and for 6 months following the last dose of study treatment or 12 months after the last dose of rituximab, whichever is later.

    Highly effective birth control methods with a failure rate of less than 1% per year when used consistently and correctly are recommended (Clinical Trial Facilitation Group [CTFG 2020]):

    a. Combined estrogen and progestin containing hormonal contraception associated with inhibition of ovulation given orally, intravaginally, or transdermally
    b. Progestin-only hormonal contraception associated with inhibition of ovulation given orally, by injection, or by implant
    c. Intrauterine device (IUD)

d. Intrauterine hormone-releasing system (IUS)

e. Bilateral tubal occlusion

f. Vasectomized partner

g. Sexual abstinence: Considered a highly effective method only if defined as refraining from heterosexual intercourse during an entire period of risk associated with the study treatment. The reliability of sexual abstinence will be evaluated in relation to the duration of the study and to the usual lifestyle of the patient.

Notes:

- Women with a history of breast cancer may not use hormone-containing contraception (a, b, or d above). One of the other listed methods above should be selected.
- Women of childbearing potential using hormonal contraception methods should also use a barrier method as a second form of contraception.
- Sperm donation and oocyte donation are prohibited during the duration of participation on this protocol and for 6 months after the last dose of study drug, or at least 12 months following last dose of rituximab, whichever is later.

Informed Consent

11. Willing and capable of giving signed informed consent as described in Section 10.1.2 Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Other Inclusions

12. Able to swallow oral study medication.
13. Able to comply with outpatient treatment, laboratory monitoring, and required clinic visits for the duration of study participation.

5.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Known or suspected Richter's transformation to diffuse large B-cell lymphoma (DLBCL), prolymphocytic leukemia, or Hodgkin's lymphoma at any time preceding enrollment.
2. Known or suspected history of central nervous system (CNS) involvement by CLL/SLL.
3. Patients who experienced a major bleeding event on a prior BTK inhibitor.

   NOTE: Major bleeding is defined as bleeding having one or more of the following features: life-threatening bleeding with signs or symptoms of hemodynamic compromise; bleeding associated with a decrease in the hemoglobin level of at least 2 g/dL; or bleeding in a critical area or organ (e.g., retroperitoneal, intraarticular, pericardial, epidural, or intracranial bleeding or intramuscular bleeding with compartment syndrome)

4. Active second malignancy; patients with treated second malignancy who are in remission with life expectancy > 2 years and with documented Sponsor approval are eligible. Examples include:
    a) Adequately treated non-melanomatous skin cancer or lentigo maligna melanoma without current evidence of disease.
    b) Adequately treated cervical carcinoma in situ without current evidence of disease.
    c) Localized (e.g., lymph node negative) breast cancer treated with curative intent with no evidence of active disease present for more than 3 years and receiving adjuvant hormonal therapy.
    d) Localized prostate cancer undergoing active surveillance.
    e) History of treated and cured Hodgkin's lymphoma or NHL within 5 years from diagnosis.
5. Major surgery, within 4 weeks of planned start of study treatment.
6. History of ongoing drug-induced pneumonitis.
7. Ongoing drug-induced liver injury, primary biliary cirrhosis and/or extrahepatic obstruction caused by cholelithiasis, and cirrhosis of the liver.
8. History of allogeneic or autologous SCT or CAR-T therapy within the past 60 days.
9. Active uncontrolled autoimmune cytopenia (e.g., autoimmune hemolytic anemia [AIHA], idiopathic thrombocytopenic purpura [ITP]) not on a stable regimen and dose for at least 4 weeks prior to study enrollment.
10. Significant cardiovascular disease defined as any of the following:
    a) Unstable angina or acute coronary syndrome within the past 2 months prior to randomization,
    b) History of myocardial infarction within 3 months prior to randomization,
    c) Documented left ventricular ejection fraction (LVEF) by any method of ≤ 40% within the 12 months prior to randomization, unless subsequent measurements (≥ 2 of any kind, separated by a minimum of 3 weeks) documents LVEF recovery > 40%,
    d) ≥ Grade 3 NYHA functional classification system of heart failure, uncontrolled or symptomatic arrhythmias
11. Prolongation of the QT interval corrected (QTc) for heart rate using Fridericia's Formula (QTcF) > 470 msec on 1 Screening ECG.
    a) QTcF is calculated using Fridericia's Formula (QTcF = QT/(RR^0.33)
    b) Correction of suspected drug-induced QTcF prolongation or prolongation due to electrolyte abnormalities can be attempted at the Investigator's discretion, and only if clinically safe to do so with either discontinuation of the offending drug or switch to another drug not known to be associated with QTcF prolongation or electrolyte supplementation.
    c) Correction of QTc for underlying bundle branch block (BBB) permissible.

12. Hepatitis B or hepatitis C testing indicating active/ongoing infection based on Screening laboratory tests, defined as:
    a) Hepatitis B virus (HBV): Patients with positive hepatitis B surface antigen (HBsAg) are excluded. Patients with positive hepatitis B core antibody (anti-HBc) and negative HBsAg require hepatitis B polymerase chain reaction (PCR) evaluation before randomization. Patients who are hepatitis B PCR-positive will be excluded.
    b) Hepatitis C virus (HCV): positive hepatitis C antibody. If positive hepatitis C antibody result, patient will need to have a negative result for hepatitis C ribonucleic acid (RNA) before randomization. Patients who are hepatitis C RNA-positive will be excluded.
    c) For optional crossover, repeat testing is not required.
13. Known active cytomegalovirus (CMV) infection. Patients with negative status are eligible.
14. Evidence of other clinically significant uncontrolled condition(s) including, but not limited to, uncontrolled systemic infection (viral, bacterial, or fungal) or other clinically significant active disease process which in the opinion of the Investigator and Medical Monitor, may pose a risk for patient participation. Screening for chronic conditions is not required.
15. Known Human Immunodeficiency Virus (HIV) infection, regardless of CD4 count. Patients with unknown or negative status are eligible.
16. Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal (GI) absorption of the oral-administered study treatments.
17. Ongoing inflammatory bowel disease.

Prior/Concomitant Therapy

18. Prior exposure to non-covalent (reversible) BTK inhibitor.
19. Concurrent use of investigational agent or anticancer therapy except hormonal therapy.
20. Patients requiring therapeutic anticoagulation with warfarin or another Vitamin K antagonist.
21. Use of > 20 mg prednisone QD or equivalent dose of steroid per day at the time of C1D1. Patients may not be on prednisone of any dose intended for antineoplastic use.
22. For patients planned to receive idelalisib: Current treatment with strong cytochrome P450 (CYP) 3A4 (CYP3A4) inhibitors or inducers (refer to Section 10.4). Because of their effect on CYP3A4, use of any of the following within 3 days of use of idelalisib and during study treatment is prohibited:
    a) Grapefruit or products from grapefruit
    b) Seville oranges or products from Seville oranges
    c) Star fruit or products from star fruit
    d) Preparations containing St. John's Wort
23. Vaccination with a live vaccine within 28 days prior to randomization.

Other Exclusions

24. Pregnancy, lactation, or plan to breastfeed during the study or within 30 days of the last dose of study treatment.

25. Patients with the following hypersensitivity:

    a) Known hypersensitivity, including anaphylaxis, to any component or excipient of pirtobrutinib. For patients planned to receive idelalisib, known hypersensitivity, including anaphylaxis, to any component or excipient of idelalisib. For patients planned to receive bendamustine, known hypersensitivity, including anaphylaxis, to any component or excipient of bendamustine.

    b) Prior toxic epidermal necrolysis with any drug, for patients who are planned to receive idelalisib

    c) Prior significant hypersensitivity to rituximab requiring discontinuation, prior allergic or anaphylactic reaction to rituximab (does not include manageable infusion-related reaction)

    d) Known allergy to allopurinol and inability to take uric acid lower agents (i.e., rasburicase or febuxostat)

    e) For optional crossover, patients with hypersensitivity to idelalisib, bendamustine, or rituximab would not be excluded.

5.3. Eligibility Criteria for Crossover Treatment

Patients who are randomly assigned to Arm B, may be eligible to cross over to Arm A treatment if they meet the following criteria:

a) IRC-confirmed PD according to iwCLL 2018 (Section 10.6, Appendix 6)

b) Have not received any other anticancer systemic therapy from the time discontinued the control treatment

c) Patients are required to meet inclusion and exclusion criteria detailed in Sections 5.1 and 5.2, respectively, to be eligible for crossover to pirtobrutinib, with the exception of Inclusion Criterion 8b (i.e., the washout period described in Inclusion Criterion 8b is not applicable to patients entering crossover treatment). Given the potential for additive risk of serious infection with rituximab and pirtobrutinib, patients should be monitored closely for signs and symptoms of infection.

Once crossover eligibility is confirmed, the Schedule of Assessments for Optional Crossover Treatment (for patients crossing over from Arm B to Arm A) (Section 1.3.4) will be followed.

Patients who are eligible for crossover treatment will retain their assigned study number during crossover; i.e., patients will NOT be assigned a new study number.

5.4. Lifestyle Considerations

5.4.1. Meals and Dietary Restrictions

Patients should refrain from consumption of grapefruit or grapefruit products, Seville oranges or Seville orange products, or star fruit or star fruit products from 3 days before the start of treatment with idelalisib until after the final dose.

Other than the previously mentioned fruit and fruit products above, there are no food or drink restrictions required for administration of pirtobrutinib or idelalisib.

Pirtobrutinib or idelalisib tablets should be swallowed whole.

5.5. Screen Failures

Repeat testing of hematology and/or chemistry tests during the protocol-designated 28-day Screening Period is permitted and does not constitute rescreening. Results from the most recently repeated hematology and/or chemistry tests during the Screening Period will be used for eligibility.

Screen failures are defined as patients who consent to participate in the clinical study, but are not subsequently randomized to a study treatment due to inability to complete or meet the criteria for participation (Sections 5.1 and 5.2) during the 28-day Screening Period. Rescreened patients must sign a new ICF and will be provided a new patient number with each rescreening. Rescreened patients will be required to repeat Screening procedures and tests, with the exception of the bone marrow biopsy CCI [redacted] (if within 90 days of planned randomization) and computed tomography (CT)/magnetic resonance imaging (MRI) scan (if within 42 days of planned randomization).

6. STUDY INTERVENTION

6.1. Study Interventions Administered

C1D1 (beginning of treatment administration) should occur within 3 business days after randomization, with randomization day being Day 0.

Table 6.1 Intervention Groups and Duration

	Arm A pirtobrutinib	**Arm B** Investigator's choice of idelalisib plus rituximab (IdelaR) or bendamustine plus rituximab (BR)			
		idelalisib plus rituximab (IdelaR)		bendamustine plus rituximab (BR)	
Treatment	pirtobrutinib	idelalisib	rituximab	bendamustine	rituximab
Dose	200 mg	150 mg	375 mg/m^2 on C1D1 and then 500 mg/m^2	70 mg/m^2	375 mg/m^2 on C1D1 and then 500 mg/m^2
Schedule	QD in 28-day continuous cycles	BID in 28-day continuous cycles	375 mg/m^2 on C1D1 and then 500 mg/m^2 Q2W for 4 infusions and Q4W for 3 infusions	70 mg/m^2 on Day 1 and Day 2 of each 28-day cycle, Cycles 1 to 6	375 mg/m^2 on C1D1 and then 500 mg/m^2 given on Day 1 of each 28-day cycle, Cycles 2 to 6
Route	Oral	Oral	IV	IV	IV
Authorized as defined by EU Clinical Trial Regulation	Not authorized in EU	Authorized and used according to EU authorization	Authorized and used according to EU authorization	Approved in the EU and used at the dose recommended by the International Consensus Panel (see Section 4.3.3)	Authorized and used according to EU authorization

Packaging and Labeling

Study interventions will be supplied by the Sponsor, or its designee, or by the site, in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

6.1.1. Selection and Timing of Doses

A cycle is defined as an interval of 28 days during treatment period. The 28-day cycle length should be maintained throughout the treatment phase regardless of dose interruptions.

Patients will begin dosing assigned treatment on C1D1 or if crossover, on CO-C1D1. Treatment will continue until progression, unacceptable toxicity, or other reason for treatment discontinuation. Patients with documented PD as determined by the Investigator may be allowed to continue study treatment if the patient is tolerating study drug and, in the opinion of the

Investigator, the patient is deriving clinical benefit from continuing study treatment and continuation of treatment is approved by the Sponsor.

A delay for a maximum of 7 days of a cycle start not due to adverse event, but due to holiday, weekend, bad weather, or other unforeseen circumstances, will be permitted and not counted as a protocol deviation. Response assessments should remain on the original schedule.

6.1.2. Arm A Pirtobrutinib: General Dosing Instructions

Each cycle will consist of 28 days. Pirtobrutinib will be given as 200 mg QD administered at approximately the same time on each day (refer to Section 6.1). Dosing is intended to be fixed (i.e., not weight-based- or body surface area [BSA]-based).

Study results from a CCI study CCI evaluating the CCI of pirtobrutinib showed that CCI Pirtobrutinib may be taken with food or drink. No fasting is required for pirtobrutinib. Refer to Section 6.5 and Section 10.4 (Appendix 4) for concomitant medication considerations.

Patients randomized to pirtobrutinib treatment must keep a daily diary to record dosing compliance of oral study treatment, which will also be assessed at each clinic visit by means of a tablet count in the returned bottle(s). Late doses (i.e., 4 or more hours after scheduled time) should be noted in the diary. Doses that are late by more than 6 hours should not be made up and recorded in the dosing diary as missed. Reasons should be recorded for any missed dose. Vomiting after dosing should be noted in the diary and a vomited dose should not be re-dosed or replaced. Assessment of treatment compliance is described in Section 6.4.

Patients will continue pirtobrutinib dosing until PD, unacceptable toxicity, or other reason for treatment discontinuation. Patients with documented PD as determined by the Investigator may be allowed to continue study treatment if the patient is tolerating study drug and, in the opinion of the Investigator, the patient is deriving clinical benefit from continuing study treatment and continuation of treatment is approved by the Sponsor.

Effects of pirtobrutinib on coagulation are unknown. Thus, patients undergoing major surgical procedures should have pirtobrutinib held at least 3 days prior and 3 days post procedure; the Sponsor should be notified of the planned procedure and planned dose hold.

6.1.3. Arm B Investigator's Choice of IdelaR or BR: General Dosing Instructions

Patients randomized to Arm B will begin dosing with Investigator's choice of either IdelaR or BR on C1D1, as outlined above in Section 6.1. Refer to local prescribing information for dosing and administration details for idelalisib, bendamustine, and rituximab or rituximab's approved biosimilar (US prescribing information is provided for reference: Idelalisib USPI; Bendamustine USPI; Rituximab USPI; Rituximab biosimilar Truxima® USPI; Rituximab biosimilar Ruxience™ USPI; Rituximab biosimilar Riabni™ USPI). Handling and administration of idelalisib, bendamustine and rituximab should be in accordance to instructions per locally approved labeling or institutional standards.

Rituximab should only be administered by a healthcare professional with appropriate medical support to manage severe infusion reactions that can be fatal if they occur.

Table 6.2 Specific Instructions for Idelalisib plus Rituximab or Bendamustine plus Rituximab

Investigator's Choice	Drug	Administration
IdelaR	**idelalisib**	• 150 mg dose idelalisib will be administered BID orally until PD or unacceptable toxicity • Idelalisib may be taken with or without food • Tablets should be swallowed whole • On days when idelalisib and rituximab are to be administered together, idelalisib can be taken any time irrespective of the rituximab infusion. • Avoid administration of strong CYP3A inducer or substrates with idelalisib, and use caution and monitor closely for toxicity with CYP3A inhibitors • Idelalisib should be prescribed and monitored according to local label; this includes monitoring of AST and ALT as summarized in Section 8.4.4.10.1, and monitoring of blood counts at least Q2W for the first 6 months of idelalisib therapy, and at least weekly in patients while neutrophil counts are less than 1.0 Gi/L. Refer to the prescribing information of idelalisib for detailed administration and safety instructions (Idelalisib USPI).
	rituximab[a]	• Rituximab will be infused IV at a dose of 375 mg/m^2 on Day 1 of the first cycle, followed by 500 mg/m^2 Q2W for 4 doses (C1D15, C2D1, C2D15, C3D1) and then Q4W for 3 doses (C4D1, C5D1, C6D1) for a total of 8 infusions. • Rituximab administration by IV push or bolus or subcutaneous administration is prohibited. • Rituximab should be administered according to local institutional standards with appropriate premedications. Refer to the prescribing information for rituximab (or for the approved biosimilar that is being used) for detailed administration and safety instructions (US prescribing information is provided for reference: Rituximab USPI; Rituximab biosimilar Truxima® USPI; Rituximab biosimilar Ruxience™ USPI; Rituximab biosimilar Riabni™ USPI).

Investigator's Choice	Drug	Administration
BR	**bendamustine**	• Bendamustine will be infused IV at a dose of 70 mg/m^2 on Day 1, Day 2 of Cycles 1 to 6. • On days when rituximab and bendamustine are to be administered, rituximab will be administered prior to bendamustine • The patient's BSA calculated at Screening should be used to calculate the dose of bendamustine throughout the study unless the patient's weight increases or decreases by > 10% from Screening. In obese patients, there is no cap on BSA and actual body weight, not adjusted weight, is recommended. Nonetheless, empiric dose adjustment is permitted in obese patients (obesity defined as body mass index ≥ 30 kg/m^2). • Refer to the local prescribing information of bendamustine for detailed administration and safety instructions (Bendamustine USPI). Note that the dose used for this study is 70 mg/m^2 (Section 4.3.3). • Avoid inducers or inhibitors of CYP1A2.
	rituximab[a]	• Rituximab will be infused IV at a dose of 375 mg/m^2 on Day 1 of the first cycle and 500 mg/m^2 on Day 1 of Cycles 2 to 6. • On days when rituximab and bendamustine are to be administered, rituximab will be administered prior to bendamustine. • Rituximab administration by IV push or bolus or subcutaneous administration is prohibited. • Rituximab should be administered according to local institutional standards with appropriate premedications. Refer to the local prescribing information for rituximab (or for the approved biosimilar that is being used) for detailed administration and safety instructions (US prescribing information is provided for reference: Rituximab USPI; Rituximab biosimilar Truxima® USPI; Rituximab biosimilar Ruxience™ USPI; Rituximab biosimilar Riabni™ USPI).

[a] Investigator's choice of therapy is limited by local approval.

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Arm A Preparation/Handling/Storage: Pirtobrutinib

Pirtobrutinib tablets are available at strengths of CCI [redacted], and 100 mg and will be provided to the sites in bottles. The site pharmacist will dispense bottles to the patient in an amount necessary to allow for outpatient administration. Tablets are to be stored at room temperature.

6.2.2. Arm B Preparation/Handling/Storage: Investigator's Choice of IdelaR or BR

Preparation, storage and handling for idelalisib, rituximab, and bendamustine, will be according to instructions provided in the local label for the individual product.

6.3. Measures to Minimize Bias: Randomization

This is an open-label study. Randomization will be used to minimize bias in the assignment of patients to treatment groups, to increase the likelihood that known and unknown patient attributes (e.g., demographic and baseline characteristics) are evenly balanced, and to enhance the validity of statistical comparisons across treatment groups.

This study will use an interactive voice/web response system (IXRS) for randomization. All patients will be centrally assigned to randomized study treatment using IXRS. Patients will be randomized 1:1 between Arm A:Arm B, and will be stratified by the status of deletion 17p (yes/no) and receipt of prior venetoclax treatment (yes/no).

If a patient withdraws from the study, then his/her enrollment/randomization code cannot be reused. Withdrawn patients will not be replaced.

6.4. Study Intervention Compliance

For patients randomly assigned to pirtobrutinib or idelalisib treatment, compliance with study treatment will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets, and reviewing patient diaries. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

A patient will be considered noncompliant if he or she takes < 75% of the planned doses of oral study drug in a cycle. A patient will also be considered noncompliant if he or she is judged by the Investigator to have intentionally or repeatedly taken ≥ 125% of the planned doses of study drug over the course of the patient's treatment.

Study treatment that is administered by IV will be administered only at the investigational sites by the authorized study site personnel. As a result, treatment compliance is ensured.

6.5. Concomitant Therapy

Concomitant medications will include ongoing medications and all medications that were administered within 14 days prior to the planned start of study drug (i.e., from Screening) through the Safety Follow-up (SFU) visit (at least 28 days [+7 days] after the last dose of study treatment) and are to be recorded in the eCRF. Information regarding reason for use and dates of administration including start and end dates should be recorded in eCRF. These concomitant medications are to include prescription and nonprescription medications, transfusions, growth factor support, vitamins, nutritional supplements, herbal supplements and other remedies. Excluded medications for eligibility are indicated in the Exclusion Criteria (Section 5.2).

6.5.1. Allowed Concomitant Medication and Supportive Care

- Oral contraceptives, hormone-replacement therapy, or other maintenance therapy (denosumab, bisphosphonates, and other medications for the treatment of osteoporosis) should be continued for the duration of the study.
- Standard supportive medications must be used in accordance with institutional guidelines and Investigator discretion. These may include:
    - Hematopoietic growth factors to treat neutropenia, anemia, or thrombocytopenia in accordance with American Society for Clinical Oncology guidelines;
    - Red blood cells (RBCs) and platelet transfusions;
    - Anti-emetic,
    - Analgesic,
    - Antidiarrheal medications; and

  - Electrolyte repletion (e.g., calcium and magnesium) to correct low electrolyte levels;

- Glucocorticoids (≤ 20 mg per day prednisone or equivalent) are allowed preferably for a duration of approximately 14 days or less, unless there is a compelling clinical rationale for a higher dose or longer duration articulated by the Investigator and approved by the Sponsor. Anticipated uses may be short courses to treat asthma or chronic obstructive pulmonary disease (COPD).
- Standard-of-care medications, including hormonal therapy for patients with prostate cancer (e.g., gonadotropin-releasing hormone [GnRH] or luteinizing hormone-releasing hormone [LHRH] agonists) and breast cancer (e.g., GnRH/LHRH agonists, aromatase inhibitors, selective estrogen receptor modulators [SERMs] or degraders [SERDs]), that the patient has been receiving for at least 28 days prior to enrollment, are allowed if the disease for which the therapy is provided is not a study exclusion or provided they are not on the list of prohibited concomitant medications (refer to Section 6.5.2).
- Local treatment while receiving study treatment (e.g., palliative radiation therapy for symptomatic nodal disease) is permitted if the patient is not considered to be clinically or radiographically progressing. If the lesion that is to be treated is a target lesion, the lesion will be censored at the time of treatment. However, the patient may remain on study provided there is other evidence of disease that can be followed for determination of progression. If the patient will receive local treatment for symptomatic progression, continuation of therapy post progression is allowed as outlined in Section 6.7.
- Prophylactic antibiotic or IV immunoglobulin (IVIG) therapy for management of patients at risk of infections is recommended. Initiation of antibiotic prophylaxis against pneumocystis infection (e.g., with trimethoprim-sulfamethoxazole, dapsone, aerosolized pentamidine, or atovaquone) before study drug administration may be warranted, and should be provided for patients receiving idelalisib, consistent with the idelalisib USPI. Local practices or guidelines regarding infection prophylaxis must be followed.
- The Sponsor recommends holding pirtobrutinib and bendamustine for at least 3 days before and after surgery where bleeding risk cannot be excluded. Any concern for disease flare due to a prolonged pirtobrutinib dose interruption should be discussed with the Sponsor, who may permit holding pirtobrutinib for a shorter period of time.
- Premedications before rituximab infusion are anticipated to include acetaminophen/paracetamol, antihistamine and /or steroids as per institutional practice. For patients on study, steroids used as premedication or as a treatment of an infusion reaction may exceed 20 mg of prednisone or equivalent if deemed clinically appropriate by the Investigator or if in accordance with institutional practice.
- The Sponsor recommends that, when medically appropriate and feasible, patients receive primary and/or applicable booster SARS-CoV-2 vaccine doses prior to initiating treatment. However, clinical judgement and patient autonomy may also guide such decisions. Should a patient develop COVID-19 while participating on this clinical trial, the use of potentially lifesaving therapy is permitted. This guidance applies to all available oral and IV antiviral therapies, as well as to antibody and immunosuppressive treatments that are part of the management of patients diagnosed with COVID-19. Ideally, these interventions should not be received via enrollment to an additional clinical trial, unless access is otherwise

unavailable. Should a patient receive COVID-19 vaccination or therapy during the study period, please follow eCRF instructions for concomitant medication recording for such administration.

6.5.2. Prohibited Concomitant Medication

- Patients receiving idelalisib should not take strong inhibitors or inducers of CYP3A4 (refer to Section 10.4) as this could alter the drug's PK.
  - This restriction includes herbal products, such as St John's wort, which may decrease the drug levels of idelalisib.
  - Patients receiving idelalisib should avoid grapefruit, grapefruit products, Seville oranges, Seville orange products, star fruit, and star fruit products, as these contain moderate inhibitors of CYP3A.
  - Moderate inhibitors or inducers of CYP3A4 should be taken with caution.
- Pirtobrutinib inhibits P-gp and is a moderate inhibitor of CYP2C8 and BCRP in the clinic. Concomitant use of pirtobrutinib with sensitive P-gp, CYP2C8, or BCRP substrates increases their plasma concentrations, which may increase the risk of adverse reactions related to these substrates. Recommendations for sensitive P-gp, CYP2C8, or BCRP substrates provided in their approved product labeling should be followed (refer to Section 10.4).
- The coadministration of bendamustine with CYP1A2 inhibitors may increase bendamustine plasma concentrations and may result in increased incidence of adverse reactions. Consider alternative therapies that are not CYP1A2 inhibitors during treatment with bendamustine.
- The coadministration of bendamustine with CYP1A2 inducers may decrease bendamustine plasma concentrations and may result in decreased efficacy. Consider alternative therapies that are not CYP1A2 inducers during treatment with bendamustine. Please refer to local labels for bendamustine (US prescribing information provided for reference: Bendamustine USPI). Except as indicated in Sections 5.1 and 6.5.1, patients are not allowed to receive concomitant systemic anticancer agents, hematopoietic growth factors for prophylaxis in Cycle 1, anticancer therapeutic monoclonal antibodies, drugs with immunosuppressant properties, or any other investigational agents. No new or alternative systemic anticancer therapy is allowed prior to documentation of PD in accordance with protocol-specified disease response criteria.
- Live-virus vaccines should not be given at any time during study treatment, including prior to and while receiving rituximab treatment, or during trial participation unless B-cell levels have returned to normal.
- Concurrent administration of idelalisib with other hepatotoxic drugs should be avoided.

6.5.3. Subsequent Anticancer Therapy

Administration of subsequent anticancer therapy for CLL/SLL is not allowed until:

- PD any time during treatment as established according to the iwCLL 2018 criteria
- Withdrawal from study treatment as described in Section 7

After study drug treatment is complete, the following information on subsequent anticancer therapies will be collected approximately Q12W after the SFU visit for the first 2 years, and approximately Q24W thereafter until death, withdrawal by patient, lost to follow-up, or study terminated by Sponsor, whichever comes first:

- Receipt of all subsequent anticancer therapies
- iwCLL indication for initiation of subsequent anticancer therapy
- Response to all subsequent anticancer therapies

6.6. Dose Modification Guidelines

Dose modifications are allowed for management of study treatment-related toxicities. If dose modification of study treatment is required for any AE not related to study treatment, the planned dose modification should be reviewed with the Sponsor. Toxicity must resolve to Grade ≤ 1 or baseline prior to resuming the next cycle except AEs with no immediate medical consequence that can be controlled with adequate treatment (e.g., pain, alopecia, neuropathy, fatigue, nausea, vomiting, diarrhea, Grade 2 hypothyroidism, or Grade 2 hypertension).

Any overdose or incorrect administration of pirtobrutinib, bendamustine, idelalisib or rituximab should be noted on the Study Drug Administration eCRF. AEs associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Regardless of treatment arms, for dose delays, the cycle schedule will be shifted accordingly (refer to instructions for data entry in the eCRF guidelines). The protocol schedule of radiographic imaging CT/ MRI scans will remain fixed, however.

For patients in Arm A: Pirtobrutinib may be held for CCI from the last dose to allow time to recover from toxicity.

For patients in Arm B: Initiation of a dose of idelalisib, bendamustine, or rituximab may be delayed for a maximum of 28 days to allow a patient sufficient time for recovery from study treatment-related toxicity. In exceptional circumstances, a longer delay is permitted upon agreement between the Investigator and the Sponsor.

All dose interruptions and dose modifications and the reasons for those changes will be recorded in the eCRF.

Dose reductions should be made according to the instructions outlined in Sections 6.6.1 and 6.6.2.

6.6.1. Dose Modifications and Toxicity Management Guidelines for Arm A: Pirtobrutinib

Dose hold and/or reduction will be implemented for any patient who experiences a Grade 3 or greater non-hematologic toxicity or any patient who experiences any of the clinically significant hematologic AEs defined in Table 6.3 (i.e., ≥ Grade 3, or > 1 grade change from baseline if baseline is Grade 2 or above) as assessed NCI CTCAE v5.0.

For each patient, a maximum of 2 dose reductions will be allowed, unless there is a compelling clinical rationale for additional dose reduction(s) articulated by the Investigator and approved by the Sponsor.

Table 6.3 Adverse Events Requiring Dose Modification for Pirtobrutinib

Adverse Events	Occurrences Requiring Dose Modification	ARM A (Pirtobrutinib) Dose Modification	Instructions
• Grade 3 or greater non-hematologic toxicity[a], • Grade 3 neutropenia with fever and/or infection, • Grade 4 neutropenia lasting ≥ 7 days, • Grade 3 thrombocytopenia with bleeding, or • Grade 4 thrombocytopenia	**First occurrence**	No change	Hold pirtobrutinib until recovery to Grade 1 or baseline; may restart at original dose level (200 mg QD)
	Second occurrence	100 mg QD	Hold pirtobrutinib until recovery to Grade 1 or baseline; may restart at one dose level lower (100 mg QD)[b]
	Third occurrence	50 mg QD	Hold pirtobrutinib until recovery to Grade 1 or baseline; may restart at one dose level lower (50 mg QD)
	Fourth occurrence	Discontinue	Discontinue

[a] For patients with abnormal baseline liver function, pirtobrutinib dose interruption and modification recommendations should be implemented if patients experience an increase of ≥ 3× baseline AST or ALT, or an AST or ALT increase of ≥ 2× baseline with concurrent total bilirubin ≥ 2× ULN.

[b] If dose was reduced at first occurrence, reduce by an additional dose level if subsequent events occur.

If the pirtobrutinib dose is reduced for apparent treatment-related toxicity, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the patient tolerates a reduced dose of pirtobrutinib for ≥ 2 weeks then the dose may be re-escalated to the next higher dose level, at the discretion of the Investigator and with written approval of the Sponsor. Repeat re-escalation, not to exceed the starting dose, may be considered if tolerated as outlined. Such re-escalation may be warranted if AE that led to the dose reduction was not treatment-related.

In the event of dosing delays or holds due to toxicity, and subsequent restarting of study drugs, the cycle schedule will be shifted accordingly (refer to instructions for data entry in the eCRF guidelines). The protocol schedule of radiographic imaging CT/MRI scans will remain fixed, however.

6.6.2. Dose Modification and Toxicity Management Guidelines for Arm B: Idelalisib, Rituximab, Bendamustine

6.6.2.1. Dose Modification for Idelalisib

Refer to the idelalisib local label for dose modification details, and for toxicity management guidelines (US prescribing information is provided for reference: Idelalisib USPI). A summary of dose modification guidelines from the USPI for idelalisib is provided below and in Table 6.4. These serve as a guide and do not replace Investigator judgement and applicable local label recommendations if more stringent.

For other severe or life-threatening toxicities related to idelalisib, withhold drug until toxicity is resolved. If resuming idelalisib after interruption for other severe or life-threatening toxicities, reduce the dose to 100 mg BID. Recurrence of other severe or life-threatening idelalisib-related toxicity upon rechallenge should result in permanent discontinuation of idelalisib.

In the event of dosing delays or holds due to toxicity, and subsequent restarting of study drugs, the cycle schedule will be shifted accordingly (refer to instructions for data entry in the eCRF guidelines). The protocol schedule of radiographic imaging CT/MRI scans will remain fixed, however.

If idelalisib is discontinued, patients can continue to receive rituximab up to the maximum number of infusions allowed on this protocol.

Table 6.4 Recommended Dose Modifications for Idelalisib

Toxicity	**Dose Modification for Specific Toxicity**		
ALT/AST	**> 3-5 × ULN**	**> 5-20 × ULN**	**> 20 × ULN**
	Maintain idelalisib dose. Monitor at least weekly until ≤ 1 × ULN	Withhold idelalisib. Monitor at least weekly until ALT/AST are ≤ 1 × ULN, then may resume idelalisib at 100 mg BID	Discontinue idelalisib permanently
Bilirubin	**> 1.5-3 × ULN**	**> 3-10 × ULN**	**> 10 × ULN**
	Maintain idelalisib dose. Monitor at least weekly until ≤ 1 × ULN	Withhold idelalisib. Monitor at least weekly until bilirubin is ≤ 1 × ULN, then may resume idelalisib at 100 mg BID	Discontinue idelalisib permanently
Diarrhea*	**Moderate diarrhea**	**Severe diarrhea or hospitalization**	**Life-threatening diarrhea**
	Maintain idelalisib dose. Monitor at least weekly until resolved	Withhold idelalisib. Monitor at least weekly until resolved, then may resume idelalisib at 100 mg BID	Discontinue idelalisib permanently
Pneumonitis	**Any symptomatic pneumonitis**		
	Discontinue idelalisib in patients with any severity of symptomatic pneumonitis		

Toxicity	Dose Modification for Specific Toxicity		
Infections	**Grade 3 or higher sepsis or pneumonia**		
	Interrupt idelalisib until infection has resolved.		
	Evidence of CMV infection or viremia		
	Interrupt idelalisib in patients with evidence of active CMV infection of any grade or viremia (positive PCR or antigen test) until the viremia has resolved. If idelalisib is resumed, monitor patients by PCR or antigen test for CMV reactivation at least monthly.		
	Evidence of pneumocystis jiroveci pneumonia (PJP)		
	Interrupt idelalisib in patients with suspected PJP infection of any grade. Permanently discontinue idelalisib if PJP infection is confirmed.		
Intestinal Perforation	**Evidence of intestinal perforation**		
	Permanently discontinue idelalisib in patients who experience intestinal perforation.		
Severe Cutaneous Reactions	**Suspected/confirmed SJS, TEN, or DRESS,** or other severe or life-threatening (Grade ≥ 3) cutaneous reactions		
	Interrupt idelalisib in patients with suspected SJS, TEN, or DRESS until the etiology of the reaction has been determined. Permanently discontinue idelalisib in patients with confirmed SJS, TEN, or DRESS, or other severe or life-threatening (Grade ≥ 3) cutaneous reactions.		
Hypersensitivity Reactions	**Evidence of hypersensitivity reactions**		
	Permanently discontinue idelalisib in patients who develop serious hypersensitivity reactions.		
Neutropenia	**ANC 1.0 to < 1.5 Gi/L**	**ANC 0.5 to < 1.0 Gi/L**	**ANC < 0.5 Gi/L**
	Maintain idelalisib dose	Maintain idelalisib dose. Monitor ANC at least weekly	Interrupt idelalisib until resolution. Monitor ANC at least weekly until ANC ≥ 0.5 Gi/L, then may resume idelalisib at 100 mg BID
Thrombocytopenia	**Platelets 50 to < 75 Gi/L**	**Platelets 25 to < 50 Gi/L**	**Platelets < 25 Gi/L**
	Maintain idelalisib dose	Maintain idelalisib dose. Monitor platelet counts at least weekly	Interrupt idelalisib. Monitor platelet count at least weekly. May resume idelalisib at 100 mg BID when platelets ≥ 25 Gi/L

Note: No dosage modification is recommended for lymphocytosis, which has been observed in some patients taking idelalisib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings.

Source: Zydelig® (idelalisib), United States Prescribing Information (USPI)

*Moderate diarrhea: increase of 4–6 stools per day over baseline; severe diarrhea: increase of ≥ 7 stools per day over baseline.

6.6.2.2. Dose Modification for Bendamustine

Please refer to the bendamustine local label for the current dose modification and toxicity management guidelines for bendamustine (US prescribing information provided for reference: Bendamustine USPI). The following information provides summary of dose modification from the USPI for bendamustine. The conventional criteria for toxicity may be difficult to evaluate and require careful consideration of the underlying disease. Dose modifications for hematologic toxicity in patients with CLL/SLL should be made with the consideration of an increased frequency of abnormal hematologic parameters at baseline.

If the patient has disease-related splenomegaly or significant bone marrow involvement resulting in cytopenia determined to be non-clinically significant, treatment may continue at the Investigator's discretion without dose modification.

Additional guidance for dose modification of bendamustine is available in the package insert (refer to the local label). Bendamustine administration should be delayed in the event of Grade 4 hematologic toxicity or clinically significant Grade ≥ 2 nonhematologic toxicity. Once nonhematologic toxicity has recovered to Grade ≤ 1 and/or the blood counts have improved (ANC ≥ 1×10^9/L, platelets ≥ 75×10^9/L), bendamustine can be reinitiated at the discretion of the treating physician. In addition, dose reduction may be warranted (refer to Warnings and Precautions for Myelosuppression in the local label for bendamustine).

Bendamustine should be used with caution in patients with mild hepatic impairment. Bendamustine should not be used in patients with moderate (AST or ALT 2.5-10× ULN and total bilirubin 1.5-3× ULN) or severe (total bilirubin > 3× ULN) hepatic impairment.

Bendamustine should be used with caution in patients with mild or moderate renal impairment and should not be used in patients with creatinine clearance (CrCl) < 40 mL/min. If bendamustine is discontinued, patients can continue to receive rituximab up to the maximum number of infusions allowed on this protocol.

Table 6.5 Dose Modifications for Bendamustine

Clinically Significant Hematologic Toxicity	
First Reduction	Reduce the dose to 50 mg/m^2 IV on Days 1 and 2 of each cycle
Second Reduction	Reduce the dose to 25 mg/m^2 IV on Days 1 and 2 of each cycle
Clinically Significant Non-hematologic Toxicity	
First Reduction	Reduce the dose to 50 mg/m^2 IV on Days 1 and 2 of each cycle

In the event of dosing delays due to toxicity, study treatment dosing of both bendamustine and rituximab should be held, and re-administered together once toxicity has resolved to Grade 1 or better (or to study baseline).

In the event of dosing delays or holds due to toxicity, and subsequent restarting of study drugs, the cycle schedule will be shifted accordingly (refer to instructions for data entry in the eCRF guidelines). The protocol schedule of radiographic imaging CT/MRI scans will remain fixed, however. In the event that Day 1 of bendamustine/rituximab of a given cycle is given, and Day 2 bendamustine is held, the Day 2 bendamustine dose will not be made up.

Patients should be asked about symptoms suggestive of infusion-related reactions after their first cycle of therapy. Monitor clinically and discontinue drug for severe reactions. Patients should be asked about symptoms suggestive of infusion reactions after their first cycle of therapy.

Patients who experienced Grade 3 or worse allergic-type reactions were not typically rechallenged. Measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids should be considered in subsequent cycles in patients who have previously experienced Grade 1 or 2 infusion reactions. Discontinuation should be considered in patients with Grade 3 or 4 infusion reactions.

Study drug treatment (both bendamustine and rituximab) may be held a maximum of 28 consecutive days for a clinically significant toxicity. Study treatment should be discontinued in the event of a toxicity lasting > 28 days, unless reviewed and approved by the Sponsor.

If bendamustine is discontinued, patients can continue to receive rituximab up to the maximum number of infusions allowed on this protocol.

6.6.2.3. Dose Modification for Rituximab

No dose modification is allowed for rituximab, unless it is required to manage infusion-related reactions or adverse events. Patients at high risk for infusion-related reactions with rituximab may, at the Investigator's discretion, receive the initial dose of rituximab split over 2 consecutive days (C1D1 and Cycle 1 Day 2 [C1D2]). Refer to the rituximab local label (or label for the approved biosimilar that is being used) for administration of rituximab (US prescribing information is provided as a reference: Rituximab USPI; Rituximab biosimilar Truxima® USPI). Rituximab should be administered according to local institutional standards with appropriate premedications.

If rituximab is discontinued, patients can continue to receive idelalisib or bendamustine as outlined in this protocol.

If bendamustine or idelalisib are discontinued, patients can continue to receive rituximab up to the maximum number of infusions allowed on this protocol.

6.7. Intervention after the End of the Study

The end of the study is defined in Section 4.4. Investigators will continue to follow the SoAs provided in Section 1.3 until notified by the Sponsor that the end of the study has occurred.

6.7.1. Treatment after Study Completion

For patients randomized to Arm A: It is anticipated that a patient on this study will receive study treatment with pirtobrutinib until the patient is able to obtain commercially available pirtobrutinib in their respective country, if the patient does not meet criteria requiring discontinuation of treatment, and the patient's participation in the study has not ended. Upon commercial availability in each patient's respective country, there may be additional options for the patient to continue to receive pirtobrutinib once the regulatory requirements are satisfied. These may include, but are not limited to CCI [redacted], patient assistance (should the patient qualify), or commercial pirtobrutinib. The study may be terminated if pirtobrutinib does not obtain marketing approval or the development of pirtobrutinib is no longer being pursued by the Sponsor.

For patients receiving Arm B: As study drugs used in Arm B are all locally approved and marketed, the patients on this study treatment may continue treatment as commercially available therapy via physician prescription.

The Sponsor reserves the right to discontinue the study for clinical or administrative reasons at any time.

6.7.2. Crossover to Pirtobrutinib

The SoA for optional crossover treatment (for patients crossing over from Arm B to Arm A) is provided in Section 1.3.4.

6.7.2.1. Rationale for Crossover

Due to the promising benefit/risk profile of pirtobrutinib in Arm A, and the safety profile observed to date, patients who are randomized to Arm B may be eligible for crossover to provide access to pirtobrutinib while on study, and will continue to be monitored for safety and efficacy. Additionally, allowing crossover will provide the opportunity for patients who either completed the assigned treatment or discontinued treatment due to toxicity to continue to be followed per protocol.

6.7.2.2. Patients who Cross Over upon IRC-Confirmed PD

The EOT assessment should be completed within 7 days of last dose (date of last dose must be recorded in electronic data capture [EDC]) or decision to terminate initial treatment (when patient is assigned to treatment and decision to end treatment is made before first dose is taken, record the date of end of treatment decision in EDC) as indicated in SoA (Section 1.3.4).
The SFU assessment is required after the EOT assessment unless crossover C1D1 has occurred prior to 28 days after the final dose of Arm B treatment. If crossover C1D1 has occurred prior to 28 days after the final dose of Arm B treatment, the SFU assessment is not required (i.e., the EOT assessment or the CO-C1D1 predose assessment will take the place of the SFU assessment).

6.7.2.3. Patients who Complete Bendamustine plus Rituximab Treatment in Arm B or Discontinue Treatment in Arm B for Reasons other than PD

Patients who complete treatment with bendamustine plus rituximab treatment in Arm B or discontinue treatment in Arm B for reasons other than PD, but may potentially crossover upon IRC-confirmed PD at a later time point, should have the following:

- The EOT assessment should be completed within 7 days of last dose (date of last dose must be recorded) or decision to terminate initial treatment (when patient is assigned to treatment and decision to end treatment is made before first dose is taken, record the date of end of treatment decision) as indicated in SoA (Section 1.3.4).
- The SFU assessment should follow the EOT assessment, unless crossover C1D1 has occurred prior to 28 days after the final dose of Arm B treatment, in which case the EOT assessment or CO-C1D1 predose assessment will take the place of the SFU assessment.

- LTFU assessment and procedures will be conducted in accordance with SoAs in Section 1.3.2 or Section 1.3.3.
- Crossover Screening assessments should be conducted within 42 days of IRC-confirmed PD, as indicated in SoA (Section 1.3.4).

6.7.3. End of Treatment

Patients who discontinue treatment for reasons other than PD should remain on study and continue to have disease assessments performed per protocol as part of LTFU (refer to Section 6.7.5; patients who cross over are discussed in Section 6.7.2). For all study treatments, the EOT assessments and procedures will be conducted in accordance with the SoAs (Section 1.3).

Patients receiving BR who discontinue from the study treatment for reasons other than PD and before completion of the planned 6 cycles of therapy should remain on study and continue to have disease assessments performed per protocol as follow-up for progression and survival. For all patients treated with BR, whether discontinuing prematurely or at the completion of 6 cycles of therapy, an EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment. Patients will have a separate SFU visit to determine the status of any unresolved AEs (Section 6.7.4).

6.7.4. Safety Follow-up

The SFU assessments will be conducted in accordance with the SoAs (Section 1.3). Safety follow-up procedures may be performed as part of the EOT visit if the latter was performed 28 days (+ 7 days) after final dose of the last cycle.

For patients on continuous pirtobrutinib or idelalisib (for IdelaR), at the decision to discontinue study treatment, the EOT visit is required within 7 days of stopping treatment. A SFU visit 28 days (+ 7 days) after the EOT visit should be performed if EOT occurred for AEs to determine the status of any unresolved AEs.

For patients who cross over to Arm A from Arm B, the SFU visit is not required if Arm A treatment is initiated less than 28 days after the final dose of Arm B treatment (i.e., the EOT assessment or the CO-C1D1 predose assessment will take the place of the SFU assessment).

6.7.5. Long-Term Follow-up

The LTFU assessments and procedures will be conducted in accordance with the SoAs (Section 1.3). After treatment discontinuation, LTFU will occur approximately Q12W (± 4 weeks) for up to 2 years and Q24W (± 4 weeks) thereafter, until the patient withdraws consent for further participation, is lost to follow-up, has died, or close of the study. If a patient discontinues study treatment for reasons other than PD, death, lost to follow-up, or withdrawal of consent, the patient will be followed for disease assessment at regular intervals until PD by imaging as specified in Section 10.6 (Appendix 6) utilizing the same modality(ies) used for the baseline imaging assessment. In addition to monitoring for progression, assessments may include subsequent anticancer therapy(ies) and survival status. Investigators should follow up and report occurrence of a second primary malignancy (SPM) for up to 5 years from the start of study treatment (refer to Section 8.5.8).

LTFU may be conducted by telephone when response assessment is not scheduled. Unscheduled interactions which may also constitute a long-term follow-up assessment can be reported in the appropriate eCRF.

For any patient who is lost to follow-up, the study site will attempt to ascertain survival information via public database search. If survival status still cannot be ascertained, patients will be considered lost to follow-up and will be censored appropriately.

7. DISCONTINUATION OF STUDY INTERVENTION AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Patients will be advised that they are free to discontinue study treatment at any time and that they will be followed for survival after discontinuing treatment (refer to SoAs in Section 1.3, and to Section 6.7.5). Over the course of the study, the Investigator and/or the Sponsor should discontinue a patient from treatment for any of the reasons listed below:

- PD per iwCLL 2018 criteria

  Exception: Patients with documented PD who are tolerating treatment, are deriving clinical benefit from continuing study treatment in the opinion of the Investigator, and who are likely to experience a worse outcome with discontinuing rather than continuing therapy at the time of progression (e.g., no remaining treatment options with known benefit), may continue treatment with prior Sponsor approval. Arm B patients who continue study treatment beyond IRC-confirmed progression are not eligible for crossover.
- Unacceptable toxicity
- Intercurrent illness compromising ability to fulfill protocol requirements
- The patient becomes pregnant during the study
- Requirement for alternative treatment in the opinion of the Investigator, unless such treatment is temporary (e.g., local radiation or surgery needed to palliate symptoms of the disease that does not otherwise meet the definition of PD)
- If receiving pirtobrutinib, dose delay CCI for hematologic toxicity, unless a clinical need for prolonged delay has been determined by the Investigator with documented Sponsor approval. For Arm B patients with dose delay > 28 days for unacceptable toxicity, consult product package insert.
- Patient is noncompliant, with study procedures and/or treatment upon review with the Sponsor
- Any medical condition that the Investigator determines to be a clinically significant finding which is identified after enrollment and which may jeopardize the patient's safety if study treatment is continued.
- Withdrawal of consent
- Investigator decides that the patient should be discontinued from study treatment.
- Lost to follow-up
- Death
- Study terminated by Sponsor

At the time a patient discontinues treatment, all safety data normally required at the EOT visit will be obtained if possible, as outlined in Section 6.7.3. Patients will enter LTFU where they may be required to undergo disease assessments (refer to Section 6.7.4). Patients who discontinue on Arm B may be considered for crossover to Arm A as determined by eligibility (refer to Section 5.3).

7.2. Patient Discontinuation/Withdrawal from the Study

Patients will be discontinued under the following circumstances

- Participation in the study needs to be stopped for medical, safety, regulatory, compliance or other reasons consistent with applicable laws, regulations, and GCP
- Death
- Patient is lost to follow-up
- Patient or patient's designee withdraws consent
- Study terminated by the Sponsor

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.2.1. Discontinuation of Inadvertently Enrolled Patients

If the Sponsor or Investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, the Sponsor and Investigator will determine if it is medically appropriate to continue. The Investigator must obtain documented approval from the Sponsor to allow the inadvertently enrolled patient to continue in the study.

Patients will adhere to the protocol-specified assessments including SFU which is as outlined in the SoAs (Section 1.3), Section 8.5 (Adverse Events and Serious Adverse Events), and Section 8.4 (Safety Assessments).

7.3. Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Discontinuation of specific sites or of the study as a whole is described in Section 10.1.11.2.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoAs. Protocol waivers or exemptions are not allowed. Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment. Adherence to the study design requirements, including those specified in the SoAs, is essential and required for study conduct.

8.1. Screening

All Screening evaluations must be completed and reviewed by the appropriate site personnel to confirm that potential patients meet all eligibility criteria.

The Investigator will maintain a Screening log to record details of all patients screened and to confirm eligibility or record reasons for Screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (e.g., blood counts, scans) and obtained before signing of the ICF may be utilized for Screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoAs (Section 1.3).

Screening results within 3 days of C1D1 are acceptable as C1D1 results.

8.2. Medical History

Patient complete medical history should include disease-related signs and symptoms, initial date of CLL/SLL diagnosis, Rai stage, and prior CLL/SLL-related therapies should be documented including regimen, duration and response to prior therapies when available.

Any disease-related complications including immune-mediated complications (immune-mediated thrombocytopenia or hemolysis) should be recorded if data is available.

8.3. Efficacy Assessments

8.3.1. Response Assessment

Response will be assessed by the Investigator and the IRC based on physical examination, imaging, hematology results and bone marrow examinations as described using the iwCLL 2018 response criteria which will include partial remission with lymphocytosis (PR-L), complete remission with an incomplete marrow recovery (CRi) and nodular partial remission (nPR) (Hallek et al. 2018, Cheson et al. 2012; Section 10.6, Appendix 6). A central radiology vendor will be used to collect images for IRC review. All patients must have clinical examinations and response assessments during the course of treatment, while on study, and during follow-up as indicated in the SoAs (Section 1.3).

With approved BTK inhibitors, lymphocytosis and leukocytosis are well-documented on-target effects that occur early during administration of study treatment. These reactions are not reflective of PD in the absence of other signs of PD (e.g., splenomegaly, enlarging lymph nodes, disease-related constitutional symptoms) and will not be considered PD. Guidance for recording of disease-related symptoms is provided in Section 8.4.2.1.

All measurable disease must be documented at Screening and reassessed at scheduled timepoints indicated in the SoAs (Section 1.3).

Radiologic disease assessment will be conducted by the Investigator in accordance with the SoAs (Section 1.3) and the Imaging Manual. Investigators should use the same method consistently for an individual patient throughout the study. Both CLL and SLL responses will be assessed per iwCLL 2018 criteria (Section 10.6, Appendix 6). Target lesions must be nodal lesions (lymph nodes) ≥ 1.5 cm. CT scan with IV contrast agent is the preferred method of assessment with scans of neck, chest, abdomen, and pelvis. However, MRI is acceptable if CT scan with contrast agent is contraindicated (refer to Imaging Manual for detailed instructions).

For patients with documented disease involving blood/bone marrow, but with no documented baseline radiographic findings and thus where radiology is not required for routine response assessment, imaging is to be performed Q24W according to the SoAs (Section 1.3).

If patient terminates treatment prior to a scheduled response assessment, the patient should have that response assessment done at the EOT visit. This assessment does not need to be repeated if performed within 2 weeks prior to the EOT visit, or if tumor progression was previously determined.

A bone marrow CCI biopsy should be collected during Screening and for confirmation of CR per the SoAs (Section 1.3), and submitted for central assessment. Refer to Section 8.9.1. Guidance on sample collection and timing is provided in the Laboratory Manual.

According to iwCLL 2018, diagnosis of Richter's transformation is established by biopsy of the affected site (not required for this study). However, if per local standard-of-care or at Investigator discretion, an ancillary whole PET-CT scan (not required for study) is performed, the results of this scan should be captured in the EDC as directed in the CRF Completion Guidelines.

8.3.1.1. COVID-19 Vaccination and Response Assessment

COVID-19 vaccination has been shown to cause transient, reactive adenopathy in approximately 10% of patients. Typically enlarged axillary, cervical, and supraclavicular lymph nodes in the vicinity of the drainage area of the injection site have been observed transiently (Herishanu et al. 2021; Lehman et al. 2021; Tu et al. 2021). Such transient enlargement of lymph nodes may resemble PD, and therefore, may confound interpretation of response assessment. Although response assessment should be performed according to the SoAs (Section 1.3), the following recommendations should be considered for potential COVID-19 vaccination patients:

- If a COVID-19 vaccine is scheduled around the same time as an imaging visit for this study, it is preferable that if scheduling permits, the scans should be done before the COVID-19 vaccination.
- If a vaccination has already occurred near the imaging visit, the imaging schedule should continue to be followed, without delaying patient care.
- If adenopathy is observed in the vicinity of the drainage area of the COVID-19 vaccination injection site, a follow-up scan after 6 to 8 weeks should be considered as this adenopathy should be transient and should resolve in this time period.

8.3.2. IRC Assessment

Response assessments will be assessed by the IRC. Disease assessment (including scans and other disease assessments) will continue until IRC-confirmed PD. These data will constitute the primary assessment for PFS analysis, following IRC review. All scans, regardless of patient treatment status should be sent for IRC review, except for scans from patients in crossover arm. Prior to crossover from Arm B to Arm A (Section 6.7.2), a patient may continue treatment and remain under close observation until progression is confirmed by the IRC.

8.4. Safety Assessments

8.4.1. Vital Signs

Vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) will be assessed after the patient has rested in the sitting position.

8.4.2. Physical Examination

The Screening physical examination will include, at a minimum, the general appearance of the patient, height (Screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

Symptom-directed physical exams will be done during the treatment period, at the EOT and SFU visits, and during the post-treatment disease follow-up.

8.4.2.1. Disease-Related Symptoms

Disease-related symptoms will be assessed and recorded in the patient records and are defined per Hallek 2018 as:

a) Unintentional weight loss of 10% of more within the previous 6 months;
b) Significant fatigue (i.e., ECOG PS 2 or worse; inability to work or perform usual activities);
c) Fevers higher than 100.5°F or 38°C for 2 or more weeks without other evidence of infection; or
d) Night sweats for more than 1 month without evidence of infection

8.4.3. Electrocardiograms

ECG monitoring should be performed in accordance with the SoA for the treatment arm (Arm A SoA in Section 1.3.1; Arm B SoAs in Sections 1.3.2 and 1.3.3; Crossover SoA in Section 1.3.4). To minimize variability, it is important that patients are in a resting position for at least 5 minutes prior to ECG evaluation. Body position should be consistently maintained for each ECG to prevent changes in heart rate. ECGs for each patient should be obtained from the same machine whenever possible. Any clinically significant changes in ECGs that occur during the study should be reported as an AE in the eCRF which will also collect pertinent clinical information.

Loxo may request de-identified copies of the ECGs for adjudication. Sites are required to submit ECG tracings for Sponsor review in these circumstances.

- Manually review ECGs to confirm accuracy. ECGs must be interpreted by a qualified physician (the Investigator or qualified designee) at the site for immediate patient management.
- If the ECG is abnormal,
  - Assess for all possible causes (concomitant medications, electrolyte abnormalities, underlying cardiac conditions, etc.).
  - Clinical chemistry should be assessed and if electrolytes are abnormal, they should be repeated as indicated. Potassium should be ≥ 4 meq/L and less than ULN and magnesium and calcium should be within normal limits.
  - Serial repeat ECG collection to ensure resolution should be conducted as clinically appropriate.
- If patients have an underlying BBB, ECGs must be manually reviewed by a qualified physician and the QTc value must be corrected (utilizing locally approved correction factors or based upon guidance provided in Section 10.7, Appendix 7) and this value should be entered into the eCRF.
- If an unscheduled ECG is done at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG testing.
- If triplicate ECGs are obtained to confirm a Grade 3 AE (QTcF ≥ 501 msec) as outlined in the NCI CTCAE v5.0 criteria, ECGs should be collected preferably 1-minute apart, and the cumulative collection time for all 3 ECGs should not exceed 5 minutes.
- Patients should be clinically monitored for symptoms of cardiac arrhythmias (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. ECG should be done as clinically indicated for assessment with electrolyte panel. If a clinically significant arrhythmia is discovered (e.g., atrial fibrillation/atrial flutter), the clinical circumstances surrounding the time of onset (if known; e.g., time/date of onset, activity and/or lifestyle changes/factors at the time of onset, associated symptoms, laboratory values) must be documented in the eCRF and study required documents and provided as requested by the Sponsor.

8.4.4. Clinical Safety Laboratory Assessments

All protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and the SoAs (Section 1.3). Sites with documentation specifying certain analytes or procedures are not collected per site policy or local regulation will not be considered protocol deviations if Sponsor approval is granted.

Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition. Clinically significant laboratory results should be reported as AEs (AE section of the eCRF) if the results require a change of study treatment or require medical intervention.

- The Investigator must review the laboratory report, document this review, and record any clinically significant abnormalities occurring during the study.
- The laboratory reports must be filed with the source documents.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, additional etiologies should be identified and reported as an AE as appropriate.
    - If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the Investigator especially if resulting in study treatment management (e.g., dose modification), reporting of the abnormality (e.g., AE or SAE) should be performed and recorded in the eCRF.

Local laboratories will be utilized for routine laboratory tests and SFU (e.g., blood chemistries from serum or plasma, hematology, and urinalysis). Special assessments will be performed centrally, including hematology tests associated with IRC assessment of response and CCI [redacted]. Additional guidance regarding testing and handling and processing of samples for central assessment is provided in the Laboratory Manual.

8.4.4.1. Hematology

Hematology should be assessed locally in accordance with the SoAs (Section 1.3). In addition, at each response assessment, a sample is required to be submitted centrally, as a component of the IRC assessment of disease response. Patients on crossover will be assessed locally by the Investigator. Hematology assessments will include: hemoglobin, hematocrit, RBC count, white blood cell (WBC) count, platelet count, percent or absolute differential (neutrophils, lymphocytes, eosinophils, basophils, and monocytes).

8.4.4.2. Blood Chemistry

Blood chemistry from serum or plasma should be assessed locally in accordance with the SoAs (Section 1.3) and should include assessment of the following: sodium, potassium, chloride, glucose, creatinine, total protein, albumin, total bilirubin, ALT, AST. Alkaline phosphatase can be performed as needed. Direct (or indirect) bilirubin should be performed at any time total bilirubin is abnormal. As indicated in the SoA, lactate dehydrogenase (LDH), calcium, magnesium, phosphorus and uric acid are required at Screening and D1 of each Cycle 1 to 6.

If an unscheduled ECG is done at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) should be done to coincide with the ECG testing if clinically feasible (this is also noted in ECG instructions on each SoA in Section 1.3).

8.4.4.3. Beta-2 Microglobulin

Beta-2 microglobulin test should be assessed locally in accordance with the SoAs (Section 1.3).

8.4.4.4. Serum Immunoglobulins

Local assessment of serum immunoglobulins includes IgG, IgM and IgA levels.

8.4.4.5. CMV Testing

Local CMV testing at Screening must include serologic testing for CMV IgG, IgM and deoxyribonucleic acid (DNA) PCR testing. Patients receiving idelalisib should be monitored every 3 months in accordance with the SoA (Section 1.3.2) with local CMV DNA PCR testing.

8.4.4.6. Coagulation

The coagulation panel should include activated partial thromboplastin time (aPTT) and prothrombin time (PT) or international normalized ratio (INR) and should be assessed locally.

8.4.4.7. Urinalysis

Urinalysis that includes color, specific gravity, pH, glucose, bilirubin, occult blood, protein, leukocytes, and urobilinogen should be assessed locally in accordance with the SoAs (Section 1.3).

8.4.4.8. Pregnancy Testing

For women of childbearing potential (WOCBP): Pregnancy testing (serum or urine) must be conducted at Screening and as outlined in the SoAs (Section 1.3) or as required per local regulations and/or institutional guidelines and may be performed locally. Pregnancy reporting guidance is provided in Section 8.5.7. All WOCBP, defined as women who are following menarche and who are not postmenopausal (or 2 years of non-therapy-induced amenorrhea) or surgically sterile will have a serum or urine pregnancy test at Screening. If any urine pregnancy test is positive, study treatment will be delayed until the patient pregnancy status is confirmed by a serum pregnancy test. If serum pregnancy test is positive, the patient will be permanently discontinued from study treatment.

8.4.4.9. Viral Testing

Hepatitis testing should be assessed at Screening in accordance with the SoA (Section 1.3) and should include testing for hepatitis B (hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [HBsAb], and total hepatitis B core antibody [HBcAb]) and hepatitis C virus (HCV) antibody serology. Screening for CMV includes IgM, IgG and CMV DNA by PCR. Follow-up testing will be performed as indicated clinically, or Q12W in patients receiving IdelaR. If other testing indicates acute or chronic infection or reactivation of infection, obtain viral load (e.g., quantitative hepatitis B virus [HBV]-DNA, HCV-RNA). Patients with evidence of active hepatitis B and/or hepatitis C infection (as defined in the exclusion criteria) are excluded from participation in the trial.

Patients with known active CMV infection and/or a history of positive HIV test (regardless of CD4 count) are excluded from participation in the trial due to potential drug-drug interactions between antiretroviral medications and pirtobrutinib and risk of opportunistic infections with both HIV and approved BTK inhibitors.

8.4.4.10. Hepatic Safety Monitoring

Hepatic laboratory work-up outlined in Section 10.3 (Appendix 3) should be collected in the event that a patient experiences elevated AST/ALT and bilirubin meeting the following criteria, at any time from Screening through EOT:

- AST or ALT > 3× ULN with total bilirubin 2× ULN

Hepatic safety monitoring should be performed in accordance with local label for the individual product.

For patients enrolled with abnormal liver function at baseline (AST and/or ALT ≥ 1.5× ULN at baseline), a dose interruption should be implemented (as indicated in Table 6.3) if the AST or ALT ≥ 3× baseline or AST or ALT ≥ 2× baseline with concurrent total bilirubin ≥ 2× ULN, until liver function returns to baseline. If the abnormality persists or worsens, further clinical and laboratory monitoring and evaluation, for possible causes of abnormal liver tests, should be initiated by the Investigator and possibly in collaboration with a hepatobiliary consultation as clinically appropriate. At a minimum, this evaluation should include a physical exam, a thorough medical history (including symptoms and recent illness), history of concomitant medications (including over the counter and herbal preparations and dietary supplements), and history of drug and alcohol use. In addition, a blood test for PT-INR and abdominal imaging studies (e.g., ultrasound) should be obtained. Additional laboratory examinations (including, for example, serological tests for viral hepatitis A, B, C, E) should also be considered.

For patients who are anti-HBc positive at Screening, it is advised to monitor HBV DNA levels closely during treatment (every 1-3 months) through 6 months after discontinuation. If HBV DNA becomes detectable, it is advised to consider discontinuation of study drug and to consult a hepatologist (for further assessment and treatment), and to communicate with the Sponsor.

8.4.4.10.1. Hepatic Safety Monitoring: Idelalisib

For patients receiving idelalisib, monitor hepatic function according to the local label:

- Monitor ALT and AST in all patients Q2W for the first 3 months of treatment
- Monitor ALT and AST Q4W for the next 3 months
- Monitor ALT and AST every 1 to 3 months thereafter
- If the ALT or AST rises above 3× the ULN: Monitor AST and ALT weekly for liver toxicity until resolved
- If the ALT or AST is greater than 5× the ULN: Withhold idelalisib and continue to monitor AST, ALT and total bilirubin weekly until the abnormality is resolved

In the event of transaminase elevation, refer to Section 6.6.2.1 for the summary table of recommended dose modifications for idelalisib, or refer to idelalisib local label for dose modification details. The concurrent administration of idelalisib with other hepatotoxic drugs should be avoided.

8.4.4.10.2. Hepatic Safety Monitoring: Rituximab

For patients who are anti-HBc-positive at Screening, it is advised to monitor HBV DNA levels closely during treatment (every 1-3 months) through 6 months after discontinuation. If HBV

DNA becomes detectable, it is advised to consider discontinuation of study drug and to consult a hepatologist (for further assessment and treatment), and to communicate with the Sponsor.

8.5. Adverse Events and Serious Adverse Events and Other Safety Reporting

Investigators are responsible for monitoring the safety of participants who have entered this study and for alerting the Sponsor or its designee of any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant. The Investigator is responsible for the appropriate medical care of participants during the study and must document their review of each safety report.

8.5.1. Definitions

8.5.1.1. Adverse Events

An AE is any unfavorable medical occurrence in a patient administered an investigational product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the investigational product, whether or not considered related to the investigational product.

All AEs that occur prior to the first dose are considered medical history and will be recorded as such in the eCRF unless the AE develops or worsens due to study-related procedures.

Documentation must be supported by an entry in the patient's source medical records. Laboratory test abnormalities considered by the Investigator to be clinically relevant should be reported in the eCRF as an AE. Each AE is to be evaluated for duration, severity, and causal relationship with the investigational product or other factors.

Disease progression of the primary tumor in and of itself is captured as an efficacy assessment and should not be captured as an AE (including fatal AEs). If toxicities due to PD exist, and are new or worsened from baseline, these should be reported as AEs. If a new primary malignancy appears, it will also be considered an AE.

Lymphocytosis associated with BTK inhibitor treatment is a well-documented on-target effect and should only be considered an AE if clinically significant.

An overdose in and of itself is not considered an adverse event. However, if a patient who experiences an overdose has signs and symptoms that meet any AE or SAE criterion, this must be reported in the appropriate manner and timeframe and must be documented as clinical sequelae of an overdose. The Sponsor should be notified of any overdose, accidental or otherwise, and should be provided confirmation that no adverse event was experienced as a result. Refer to Section 8.6.

A DMC will be established to oversee the safety aspects of the study. Refer to Section 9.6.

The event term of 'death' itself should not be reported as an AE; rather, any AEs associated with the occurrence of death or AEs considered to be Grade 5 in severity (fatal) should be reported.

8.5.1.2. Serious Adverse Events

An SAE is any untoward medical occurrence that, at any dose:

- results in death
- is life-threatening
- requires hospitalization or prolongation of existing hospitalization
- results in disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should also be considered serious.

Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. However, if institutional guidelines mandate hospitalization for a planned procedure (e.g., transfusion of blood products, such as packed red blood cells (PRBCs), platelets or plasma), the underlying AE requiring intervention should not be reported as an SAE unless it meets other serious criteria. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned.

Unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.

8.5.2. Grading and Intensity of Adverse Events

The Investigator will grade the severity of each AE using, when applicable, the NCI CTCAE, v5.0. In the event of an AE for which no grading scale exists, the Investigator will classify the AE as mild, moderate, severe, life-threatening/debilitating, or fatal, as defined below.

- Grade 1 mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL).
- Grade 3 severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 life-threatening* consequences; urgent intervention indicated.
- Grade 5 death related to AE.

**Life-threatening:* an AE that places the patient at immediate risk of death. It does not include an adverse reaction that, had it occurred in a more severe form, might have caused death. Laboratory values which meet Grade 4 NCI CTCAE v5.0 severity based on numeric value may not necessarily meet life-threatening criteria.

8.5.3. Relationship to Underlying Disease, Other Medical Condition or Concomitant Medications

The Investigator will categorize each AE as to its potential relationship to underlying disease, other medical conditions or concomitant medications using the categories of Yes (causally related) and No (not related) as described in Section 8.5.2 and defined below. The assessment of the relationship of an AE to the underlying disease, other medical conditions, or concomitant medications is a clinical decision based on all available information at the time.

No:
The time course between the occurrence or worsening of the AE and underlying disease, other medical conditions, or concomitant medications indicates an alternative causal relationship (other than study drug) and another cause is considered more likely.

Yes:
The time course between the occurrence or worsening of the AE and the underlying disease, other medical conditions, or concomitant medications is consistent with a causal relationship to study drug and another cause is considered unlikely.

The following factors should also be considered:

- Temporal sequence from treatment with the study drug.
- Preclinical and prior clinical data regarding whether a particular AE could be an effect of the study drug (or class of drug).
- Pharmacology and PK of the investigational product.

An unexpected AE is an experience not previously reported or an AE that occurs with specificity, severity, or frequency that is not consistent with the current Pirtobrutinib IB or local labels for idelalisib, rituximab or bendamustine. For contraindications for idelalisib, bendamustine, and rituximab or rituximab's approved biosimilar, refer to local prescribing information.

8.5.4. Adverse Event Reporting

The Sponsor or its representative is required to report certain study events in an expedited manner to the FDA, the European Medicines Agency's EudraVigilance electronic system according to EU Regulation 536/2014, and to all country regulatory authorities where the study is being conducted, according to local applicable regulations.

8.5.5. Serious Adverse Event Reporting

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The Sponsor has processes for safety reports for identification, recording, and

expedited reporting of suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators (see Section 10.1.3).

In the event of an accidental or intentional overdose by a patient, the site staff must immediately inform Clinical Safety. The eCRF must be updated to reflect this information. In the event that the overdose is associated with an AE and/or SAE, the 2 events should be linked. In the event an AE and or SAE is associated with an overdose, the appropriate report form must be completed detailing the AE and the overdose details.

All SAEs, regardless of causality, that occur from time of informed consent to SFU (28 days [+ 7 days] after the last dose), are to be recorded on the appropriate eCRF and must be reported to Clinical Safety within 24 hours of the knowledge of the occurrence (this refers to any AE that meets any of the aforementioned serious criteria). All SAEs that the Investigator considers related to study drug occurring after the 28-day follow-up period must be reported to the Sponsor.

SAE Reporting via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the SAE coordinator.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contact information for SAE reporting can be found in the SAE form.

The Investigator will be requested to supply detailed information regarding the event. SAEs must also be reported to the IRB/ IEC and a copy of that report must be retained at the investigative site and filed in the Investigator Site File in accordance with the requirements of that institution.

Although not considered an AE per se, the Sponsor must be notified of any patient or patient's partner who becomes pregnant during a clinical study (refer to Section 8.5.7).

8.5.6. Serious Adverse Event Follow-up

For all SAEs occurring during the study, the Investigator must submit follow-up reports to the Sponsor regarding the status of the SAE and the patient's subsequent course until the SAE has resolved, or until the condition stabilizes or is deemed chronic (in the case of persistent impairment), or the patient dies.

8.5.7. Pregnancy Reporting

If the patient or partner of a patient participating in the study becomes pregnant during the study or within 6 months of discontinuing study drug or 12 months after discontinuing rituximab, whichever is later, the Investigator should report the pregnancy to Clinical Safety within 24 hours of being notified. Clinical Safety will then forward the Pregnancy form to the Investigator for completion.

A patient becoming pregnant while on study drug will immediately be withdrawn from the study and early termination study procedures will be performed.

The patient or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Clinical Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5.8. Second Primary Malignancy Reporting

The Investigator must follow up with all patients for up to 5 years from the start of study treatment to monitor for the occurrence of any SPM events. SPM events should be reported to the Sponsor, regardless of seriousness or causal attribution to study medication. For patients who cross over to pirtobrutinib, patients are to be followed for 5 years starting from when they started taking pirtobrutinib.

8.6. Treatment of Overdose

For Arm A, refer to the Pirtobrutinib IB for further information, recommendations and guidance.

For Arm B, refer to the local product label for idelalisib, rituximab, or bendamustine for available information on the signs, symptoms, and treatment of overdose.

8.7. Pharmacokinetics

At the visits and times specified in the SoA (Section 1.3), blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of pirtobrutinib in Arm A only.

A maximum of 6 samples may be collected at additional time points during the study if warranted and agreed upon between both the Investigator and the Sponsor. Instructions for the collection and handling of blood samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sampling and prior dose will be recorded.

CCI be collected CCI and CCI Samples are to be drawn CCI and exact time of sample collection should be recorded. In addition, time of previous dose should be recorded. CCI may also be assessed in patients when considered necessary by the Investigator to understand exposure in relationship to possible safety.

CCI will be retained for CCI following last patient visit for the study. During this time, CCI

CCI

8.9. Genetics

8.9.1. Bone Marrow [redacted] Biopsy

[redacted], in accordance with the SoAs (Section 1.3). Biopsy is required at Screening [redacted]. For central assessment of CR, bone marrow biopsy [redacted] samples should also be collected in accordance with the SoAs (Section 1.3) [redacted]. Optional bone marrow biopsy [redacted] sample for confirmation of PD may be collected to establish the criteria of PD per iwCLL 2018 if indicated. Guidance on sample collection and timing is provided in the SoAs (Section 1.3) and the Laboratory Manual.

8.9.2. Pathology and Molecular Reports

Anonymized/redacted pathology report(s) confirming histologic diagnosis and relevant prognostic biomarkers (e.g., IGHV, TP53 mutations, karyotype status, fluorescence in-situ hybridization [FISH] for del 17p, del 11q), should be submitted. [redacted]

CCI

CCI

8.11. Immunogenicity Assessments

Not applicable for this Phase 3 protocol.

8.12. Medical Resource Utilization and Health Economics

8.12.1. Patient-Reported Outcomes

Patient-reported outcome questionnaires will be administered electronically according to the SoA for patient-reported outcomes (PRO; Section 1.3) in countries where the questionnaires have been translated into the native language of the region and linguistically validated. Only patients who are literate in an available translation will complete the questionnaires. The PROs will be used to evaluate changes in CLL/SLL symptoms, physical function, and other health-related quality of life (HRQoL) outcomes of Arm A compared to Arm B, and generate health utility data. Questionnaires will be administered electronically using a provisioned ePRO device or through web-based method. Patients will complete the specified baseline assessments electronically at clinic at C1D1 prior to their first dose of study drug. Subsequent ePRO assessments will be self-completed electronically according to the SoA for PROs (Section 1.3). At EOT and SFU, the site will trigger the specified EOT and SFU assessments on the patient's ePRO device; therefore patients will be asked to bring their device with them for all clinic visits. If possible, baseline (C1D1), EOT, and SFU questionnaire completion should occur prior to extensive interaction with site health practitioners regarding the patient's status, or receipt of laboratory results and/or additional treatments.

While individual patients may vary in their response time, data from prior research among patients with advanced cancers suggest that 20 items can be completed in an average of less than 4 minutes using an electronic device.

8.12.1.1. EORTC QLQ-C30

Health-related quality of life will be assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0 (EORTC QLQ-C30; Aaronson et al. 1993). At some patient visits the full scale will be administered and at other times, only selected items.

The full EORTC QLQ-C30 self-reported general cancer instrument consists of 30 items covering 3 dimensions regarding the patient's experience in the past 7 days:

- Global health status/quality of life (2 items)
- Functional scales (15 total items addressing either physical, role, emotional, cognitive, or

social functioning)

- Symptom scales (13 total items addressing either fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, or financial impact)

8.12.1.3. EORTC IL19: Physical Function

The EORTC IL19 consists of 5 items that are identical to the physical functioning score (items 1-5) of the EORTC QLQ-C30. This assessment will be completed by patients at time-points in between administration of the full EORTC QLQ-C30 in order to minimize patient burden.

8.12.1.5. EQ-5D-5L

Health status will be assessed using the 5-level-EuroQol (EQ-5D-5L; Janssen et al. 2013). These utility measures are an important input for economic evaluations by global health technology assessment organizations that examine the value of treatment interventions. Patients will complete the 5-dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), 5-level (no problem, slight, moderate, severe, or extreme problem) assessment according to the SoA. Additionally, patients will indicate their current health status by marking on a visual analog scale ranging from 100 (best imaginable health state) to 0 (worst imaginable health state) as of "today." The EQ-5D-5L is designed for self-completion by respondents, is cognitively simple, takes only a few minutes to complete, and will be administered electronically at the study site according to the SoA prior to receiving study treatment.

CCI [redacted]

8.12.2. Medical Resource Utilization

Medical resource utilization will be collected in the eCRF by the Investigator and study site personnel for all patients throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected will include:

- Hospitalization (yes or no) and duration of hospitalization (admission and discharge dates)
- Emergency room visits (yes and number of events, or no)
- Supportive care medications (GCSF use, analgesics, transfusions)

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

Treatment with pirtobrutinib will provide a clinically meaningful increase in PFS over treatment with Investigator's choice of either idelalisib plus rituximab (IdelaR) or bendamustine plus rituximab (BR) (Arm B) in BTK inhibitor pretreated CLL/SLL patients.

9.2. Sample Size Determination

The study is expected to enroll approximately 250 patients. Patients will be randomized in a 1:1 ratio between pirtobrutinib (Arm A) and comparator (Arm B). The study is sized to achieve approximately CCI power to detect a targeted hazard ratio (HR) of CCI in PFS which, under the model assumptions, translates into a CCI relative improvement in median PFS comparing pirtobrutinib arm to the comparator arm, at the CCI .

This sample size calculation was based on a median PFS time of CCI in the comparator arm versus a median PFS time of CCI in pirtobrutinib arm. The accrual period is assumed to be approximately CCI , and CCI by the time of the final PFS analysis.

9.3. Populations for Analyses

For purposes of analysis, the populations are defined as follows:

Table 9.1 Analysis Populations

Population	Description
Intention to treat (ITT)	All randomized patients, even if a patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Patients will be analyzed according to the treatment group they were assigned to regardless of what actual treatment they receive.
Safety	All randomized patients who take at least 1 dose (including a partial dose) of study treatment. Analysis of safety data will be based on the actual treatment a patient received on the first study treatment administration regardless of which treatment they were randomized to receive ("as treated").

Data collected for Arm B patients who cross over to pirtobrutinib monotherapy may be analyzed and reported as a stand-alone group, independent of Arm A or Arm B.

9.4. Statistical Analyses

One final analysis is planned. The analysis is planned when approximately CCI have been observed, which is expected to occur approximately CCI -after the first patient has been randomized, under the assumption of treatment effect and enrollment projection (Section 9.2).

9.4.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of the Sponsor or its designee.

All tests of treatment effects will be conducted at a [redacted], unless otherwise stated.

Continuous variables will be summarized using descriptive statistics (i.e., number of patients, mean, median, standard deviation, minimum, and maximum). Categorical variables will be summarized by frequency and its corresponding percentage.

Handling of missing, unused, and spurious data is addressed prospectively in the overall statistical methods described in the Statistical Analysis Plan (SAP), where appropriate. Adjustments to the planned analyses are described in the CSR.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. More details for the analyses will be provided in the SAP. The SAP will be finalized before database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

9.4.2. Study Endpoints

The primary, secondary, [redacted] endpoints are displayed with the objectives for the study in Section 3.

9.4.3. Treatment Group Comparability

9.4.3.1. Patient Disposition

A detailed description of patient disposition will be provided.

9.4.3.2. Patient Characteristics

Patient demographic and baseline characteristics will be summarized using the ITT population. Baseline disease characteristics, prior anticancer therapies, historical illness, and pre-existing conditions will also be summarized.

9.4.3.3. Concomitant Medication

A summary of preferred names of concomitant medication by treatment arm by decreasing frequency will be generated.

9.4.3.4. Prior and Subsequent Anticancer Therapy

Prior and subsequent anticancer therapy used to treat CLL will be summarized based on line of therapy and type of therapy.

9.4.3.5. Extent of Exposure

The duration on therapy, dose omissions, dose reductions, dose delays, and dose intensity for each drug will be summarized for all treated patients by arms as appropriate.

9.4.4. Efficacy Analyses

All efficacy analyses will be performed using the ITT population, unless otherwise specified.

9.4.4.1. Analysis of Primary Endpoint

The primary efficacy endpoint of PFS is defined as the time from the date of randomization until PD (assessed by the IRC per iwCLL 2018 criteria, Section 10.6, Appendix 6) or death from any cause, whichever occurs first. Patients not meeting these criteria and alive by the analysis data cutoff date will be censored and the detailed censoring rules will be specified in the SAP.

CCI , will be used for the primary comparison of PFS. The HR and its 95% confidence interval (CI) will be computed from CCI . In addition, median PFS and its 95% CI, as well as PFS rates and associated 95% CI at selected timepoints, will be provided using the CCI . Sensitivity analyses for PFS will be described in the SAP.

The final analysis is planned when approximately CCI have been observed, which are expected to occur approximately CCI after the first patient has been randomized under the assumption of treatment effect and enrollment projection (Section 9.2). Superiority for final analyses are anticipated to be assessed CCI

9.4.4.2. Analyses of Secondary Endpoints

The SAP will describe the key secondary endpoints to be tested and the statistical methods to be used to ensure CCI

PFS per Investigator assessment is defined as the time from the date of randomization until PD (per iwCLL 2018 criteria, Section 10.6, Appendix 6) or death from any cause, whichever occurs first. Similar censoring rules and analysis methods will be applied as described for PFS per IRC.

ORR is defined as the proportion of patients who achieve a best overall response (BOR) of CR, CRi, nPR, or partial remission (PR) at or before the initiation of subsequent anticancer therapy. The ORR, with CCI , will be summarized for each treatment arm. ORR will be compared between Arm A and Arm B using CCI . The ORR will be evaluated according to both IRC and Investigator assessment per iwCLL 2018 criteria. ORR including PR with lymphocytosis (PRL) will be assessed by the Investigator and IRC will also be analyzed with the same analysis method used for ORR.

DOR is defined as the time from the date of the first documented response of CR, CRi, nPR, or PR to the earlier of the documentation of definitive PD (per iwCLL 2018 criteria, Section 10.6) or death from any cause. Following first documentation of CR, CRi, nPR, or PR patients who are alive and without documented PD as of a data analysis cutoff date will be censored. Similar censoring rules will be applied as described for PFS. DOR according to both IRC and Investigator assessment will be evaluated. Median DOR CCI , as well as DOR rates and associated CCI

OS is defined as the time from randomization until death from any cause. If the patient is alive or lost to follow-up at the time of data analysis, OS data will be censored on the last date the patient is known to be alive.

TTNT is defined as time from the date of randomization to the date of the initiation of the next systemic anticancer therapy for CLL/SLL or the first dose date of pirtobrutinib for Arm B

patients who crossed over to receive pirtobrutinib or death due to any cause, whichever occurred first.

EFS is defined as the time from date of randomization to the date of PD or start of new treatment for CLL/SLL or discontinuation from treatment due to toxicity or death, whichever occurs first.

The analysis methods for OS, TTNT, and EFS will be similar to those described for PFS. Details of the censoring rules for these endpoints will be provided in SAP.

9.4.5. Safety Analyses

Safety data will be summarized for the safety population. The baseline value for the safety analysis is defined as the value collected at the time closest to and before the start of study drug administration.

9.4.5.1. Adverse Events

AEs will be graded by the Investigator according to the NCI CTCAE v5.0 or higher for nonhematologic and hematologic AEs. Each AE verbatim term will be coded to a system organ class and a preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

All TEAEs will be summarized by treatment arm. AE incidence rates will also be summarized by severity and relationship to study drug.

Grade 3 or Grade 4 TEAEs; TEAEs leading to permanent study drug treatment discontinuation; TEAEs leading to dose modification; serious TEAEs; and TEAEs resulting in death will be summarized by treatment arm.

9.4.5.2. Clinical Laboratory Tests

For gradable clinical laboratory parameters, a summary of worst postbaseline toxicity grade will be provided in the treatment-emergent period by treatment arm and worst toxicity grade. The difference in percentages will be displayed.

Additional safety endpoints including ECOG, vital signs, and weight will be summarized descriptively with further details provided in the SAP.

9.4.6. Pharmacokinetic/Pharmacodynamic Analyses

Pirtobrutinib plasma concentrations will be summarized by descriptive statistics. CCI [redacted]

9.4.7. Other Analyses

9.4.7.1. Patient-Reported Outcomes and Medical Resource Utilization

For each PRO instrument, percentage compliance will be calculated as the number of completed assessments divided by the number of expected assessments at each time point. Data will be separately summarized using descriptive statistics.

Time to worsening in CLL/SLL-related symptoms and physical functioning will be described [redacted]. A comparative analysis between the 2 arms will be conducted using [redacted]. Further details of the PRO secondary endpoints will be provided in the PRO SAP.

Details for the analyses [redacted] will also be provided in the PRO SAP.

Frequency counts of hospitalizations, emergency room visits, GCSF use, and transfusions will be reported descriptively for each treatment arm.

9.4.7.2. Subgroup Analyses

Details of subgroup analysis will be provided in SAP.

[redacted]

9.5. Interim Analyses

No interim analysis is planned.

9.6. Data Monitoring Committee

The DMC will review the safety data periodically and provide recommendations according to the DMC charter.

The first safety data review will be performed by the DMC after approximately [redacted]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable International Council for Harmonisation (ICH) GCP Guidelines.
- Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any substantial amendments or addenda and amended ICFs to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- The Investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
    - Reporting to the Sponsor or designee significant issues related to patient safety, patient rights, or data integrity.

10.1.2. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the patient or his/her legally authorized representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance

Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study, before initiation of any study-related Screening procedure and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.
- Patients must be consented for crossover treatment.
- A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative and is kept on file.
- Patients who are rescreened are required to sign a new ICF.

10.1.3. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions (SUSARs) will be reported to the IRB/IEC according to their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

10.1.4. Sponsor Safety Reporting to Regulatory Authorities

SAE Regulatory Reporting

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Pirtobrutinib IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.1.5. Data Protection

- Patients will be assigned a unique identifier by the Sponsor to protect the patient's personal data. Any patient information, such as records, datasets, or tissue samples that are transferred to the Sponsor will contain the identifier only. Patient names or any information which would make the patient identifiable will not be transferred.

- The patient must be informed that the patient's personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent. This is done by the site personnel through the informed consent process.
- The patient must be informed through the informed consent by the site personnel that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The Sponsor has processes in place to ensure data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.6. Independent Review Committee Structure

The primary endpoint, PFS, will be assessed by IRC. A blinded independent review committee will consist of independent radiologists to perform response assessments and determination of PD per iwCLL 2018 criteria (Section 10.6, Appendix 6).

10.1.7. Dissemination of Clinical Study Data

Dissemination of study data will be performed according to all applicable Sponsor and international policies. The Sponsor will disclose a summary of study information, including tabular study results on publicly available websites, where required by local law or regulations within the specified timeframes.

10.1.8. Data Quality Assurance

- All patient data relating to the study will be recorded in the eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for the time period outlined in the Clinical Trial Agreement (CTA) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the

Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

To ensure accurate, complete, and reliable data, the Sponsor or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate
- Provide Sponsor start-up training to instruct the Investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- Make periodic visits to the study site
- Be available for consultation and stay in contact with the study site personnel by e-mail, telephone, and/or fax
- Review and verify data reported to detect potential errors

In addition, the Sponsor or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by the Sponsor or its representatives and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The Investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the Investigator will provide the Sponsor, applicable regulatory agencies, and applicable IRBs/IECs with direct access to original source documents.

10.1.9. Data Capture System

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor.

An EDC system will be used in this study for the collection of eCRF data. The Investigator maintains a separate source for the data entered by the Investigator or designee into the Sponsor-provided EDC system. The Investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the eCRF.

Additionally, ePRO data questionnaires and scales will be directly recorded by the patient, into an instrument (e.g., an electronic device). The ePRO data will serve as the source documentation and the Investigator does not maintain a separate, written or electronic record of these data.

Data collected via the Sponsor-provided data capture system will be stored at a third party. The Investigator will have continuous access to the data during the study and until decommissioning of the data capture system.

10.1.10. Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.11. Study and Site Closure

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include, but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and assures appropriate patient therapy and/or follow-up.

10.1.11.1. Discontinuation of the Study

The study will be discontinued if the Sponsor judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

10.1.11.2. Discontinuation of Study Sites

Study site participation may be discontinued if the Sponsor, the Investigator, or the IRB/IEC of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

10.2. Appendix 2: Contraceptive Guidance and Pregnancy Information

Willingness of men and WOCBP, and their partners, to observe barrier and highly effective birth control methods as outlined below for the duration of treatment and for 6 months following the last dose of study treatment or 12 months after the last dose of rituximab, whichever is later.

WOCBP are defined as those following menarche, and who are not postmenopausal (or 2 years of non-therapy-induced amenorrhea, or surgically sterile). WOCBP must utilize highly effective contraception methods as outlined below. In addition, male partners must use a barrier method (condoms) for the duration of treatment and for 6 months following the last dose of study treatment or 12 months after the last dose of rituximab, whichever is later. Male patients with partners who are WOCBP must use a barrier method (condoms) and their partner must also use a highly effective form of contraception as listed below for the duration of treatment and for 6 months following the last dose of study treatment or 12 months after the last dose of rituximab, whichever is later.

Highly effective birth control methods with a failure rate of less than 1% per year when used consistently and correctly are recommended (CTFG 2020):

a. Combined estrogen and progestin containing hormonal contraception associated with inhibition of ovulation given orally, intravaginally, or transdermally

b. Progestin-only hormonal contraception associated with inhibition of ovulation given orally, by injection, or by implant

c. Intrauterine device (IUD)

d. Intrauterine hormone-releasing system (IUS)

e. Bilateral tubal occlusion

f. Vasectomized partner

g. Sexual abstinence: Considered a highly effective method only if defined as refraining from heterosexual intercourse during an entire period of risk associated with the study treatment. The reliability of sexual abstinence will be evaluated in relation to the duration of the study and to the usual lifestyle of the patient.

   Notes:

   - Women with a history of breast cancer may not use hormone-containing contraception (a, b, or d). One of the other listed methods above should be selected.
   - Women of childbearing potential using hormonal contraception methods should also use a barrier method as a second form of contraception.

Birth control methods that are considered unacceptable or insufficient alone for this clinical trial include (CTFG 2020):

a. progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
b. male or female condom with or without spermicide
c. cap, diaphragm or sponge with spermicide
d. combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods)
e. periodic abstinence (calendar, symptothermal, or post-ovulation methods)
f. withdrawal (coitus interruptus)
g. spermicide only
h. lactational amenorrhea method

Notes:

- Condom/diaphragm with spermicide is not adequate alone.
- Women with a history of breast cancer may not use hormone-containing contraception (a). One of the other listed methods above should be selected.
- Sperm donation and oocyte donation are prohibited during the duration of participation on this protocol and for 6 months after the last dose of study drug, or at least 12 months following last dose of rituximab, whichever is later.

10.3. Appendix 3: Liver Safety

The hepatic monitoring tests will be conducted in accordance with the SoAs (Section 1.3). Selected tests may be obtained in the event of a clinically significant treatment-emergent hepatic abnormality while on study and should be obtained in accordance with local guidelines and/or as directed by a local hepatologist when appropriate. Studies may be required in follow-up and will be decided upon between the Investigator and the Sponsor when appropriate.

Hepatic Monitoring Tests	
Hepatic Hematology	**Haptoglobin**
HGB	
HCT	**Hepatic Coagulation**
Erythrocytes (RBC)	Prothrombin time
Leukocytes (WBC)	INR
Neutrophils	
Lymphocytes	**Hepatic Serologies**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
ALP	
ALT	**Other Serology Testing**
AST	CMV/EBV testing (antibody and/or DNA)
GGT	HBV DNA testing
CPK	
	Recommended Autoimmune Serology
	Antinuclear antibody [a]
	Antismooth muscle antibody [b]

[a] Assayed by local laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

10.4. Appendix 4: Restricted and Prohibited Concomitant Medication

The following tables describe the drug class and associated medications that will be restricted or be used with caution during the study treatment period. Patients who, in the assessment by the Investigator, require the use of any of the prohibited treatments for clinical management should be removed from the study. Refer to Section 6.5 for additional information.

Note: The lists below are not exhaustive. Also refer to: http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm.

Note: Non-systemic (e.g., topical creams, eye drops, mouthwashes, etc.) applications are permissible.

Table 10.1 Inhibitors of CYP3A4

Inhibitors of CYP3A4	
Strong inhibitors [a]	**Moderate inhibitors** [b]
boceprevir	amprenavir
clarithromycin	aprepitant
conivaptan	atazanavir
grapefruit juice /products	ciprofloxacin
indinavir	darunavir
itraconazole	diltiazem
ketoconazole	erythromycin
lopinavir	fluconazole
mibefradil	fosamprenavir
nefazodone	imatinib
nelfinavir	verapamil
posaconazole	
ritonavir	
saquinavir	
telaprevir	
telithromycin	
voriconazole	
Star fruit /products	
Seville oranges /products	

a Increases the AUC of sensitive index substrates of a given metabolic pathway by ≥ 5-fold.

b Increases the AUC of sensitive index substrates of a given metabolic pathway by 2- to 5-fold.

Note: The list above is not exhaustive. Also refer to: http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

Table 10.2 Inducers of CYP3A4

Inducers of CYP3A4	
Strong Inducers	**Moderate Inducers**
apalutamide	bosentan
carbamazepine	efavirenz
enzalutamide	etravirine
mitotane	phenobarbital
phenytoin	primidone
rifampin	
St. John's wort	

Note: Strong and moderate inducers decrease the AUC of sensitive index substrates of a given metabolic pathway by ≥ 80%, and ≥ 50% to < 80% respectively.

Note: The list above is not exhaustive. Also refer to: http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

Table 10.3 CYP3A Sensitive Substrates

CYP3A Sensitive Substrates			
abemaciclib	darunavir	lopinavir	simvastatin
acalabrutinib	dasatinib	lovastatin	sirolimus
alectinib	dronedarone	lumefantrine	tacrolimus
alfentanil	ebastine	lurasidone	ticagrelor
aprepitant (also fosaprepitant)	eliglustat	maraviroc	tipranavir
atazanavir	elvitegravir	midazolam	tolvaptan
atorvastatin	entrectinib	midostaurin	triazolam
avanafil	eplerenone	naloxegol	ulipristal
avapritinib	everolimus	neratinib	uprogepant
bosutinib	felodipine	nisoldipine	vardenafil
brotizolam	ibrutinib	paritaprevir	venetoclax
budesonide	indinavir	quetiapine	vinblastine
buspirone	isavuconazole (prodrug is isavuconazonium sulfate)	quinidine	zanubrutinib
cobimetinib	ivabradine	saquinavir	
conivaptan	ivacaftor (also ivacaftor with lumacaftor, ivacaftor with tezacaftor)	sildenafil	
darifenacin	lomitapide	simeprevir	

Note: Drugs not marketed in the US or Europe have been omitted.
Source: University of Washington Drug Interaction Solutions List of CYP3A Sensitive Substrates accessed 14 May 2020.

Table 10.4 P-gp Substrates

Examples of P-gp Substrates	
dabigatran	loperamide
digoxin	verapamil
fexofenadine	

Note: The above list is not exhaustive. Also refer to: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

Table 10.5 CYP2C8 Substrates

Examples of CYP Substrates	
montelukast	rosiglitazone
pioglitazone	repaglinide

Note: the above list is not exhaustive. Also refer to: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

Table 10.6 BCRP Substrates

Examples of BCRP Substrates
rosuvastatin
sulfasalazine

Note: the above list is not exhaustive. Also refer to: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

10.5. Appendix 5: Creatinine Clearance Formula

Creatinine clearance (CrCl) will be assessed using the following formula:

Note: This formula has to be used for calculating CrCl from local laboratory results only.

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{body weight}^{a}) \times 0.85 \text{ (if female)}}{\text{serum creatinine (mg/dL)} \times 72}$$

[a] Age in years, weight in kilograms.

Source: Cockcroft and Gault 1976.

10.6. Appendix 6: iwCLL 2018 Response Criteria

Group	Parameter	CR	PR	PD	SD
A	Lymph nodes[a]	None ≥ 1.5 cm	Decrease ≥ 50% (from baseline)[a]	Increase ≥ 50% from nadir	Change of -49% to +49%
	Liver and/or spleen size[b]	Spleen size < 13 cm; liver size normal	Decrease ≥ 50% (from baseline)	Increase ≥ 50% from nadir	Change of -49% to +49%
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥ 50% from baseline	Increase ≥ 50% over nadir	Change of -49% to +49%
B	Platelet count	≥ 100 × 10^9/L	≥ 100 × 10^9/L or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL	Change of -49% to +49%
	Hemoglobin	≥ 11.0 g/dL (un-transfused and without erythropoietin)	≥ 11.0 g/dL or increase ≥ 50% over baseline	Decrease of ≥ 2 g/dL from baseline secondary to CLL	Increase < 11.0 g/dL or < 50% over baseline, or decrease < 2 g/dL
	Marrow	Normo-cellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥ 50% on successive biopsies	No change in marrow infiltrate

Source: (Hallek et al. 2018).

Abbreviations: CLL = chronic lymphocytic leukemia; CR = complete remission (all of the criteria have to be met); PD = progressive disease (at least 1 of the criteria of group A or group B has to be met); PR = partial remission (for a PR, at least 2 of the parameters of group A and 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve); SD = stable disease (all of the criteria have to be met; constitutional symptoms alone do not define PD).

a Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination in clinical studies or by physical examination in general practice).

b Spleen size is considered normal if < 13 cm. There is not firmly established international consensus of the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in clinical studies and be recorded according to the definition used in a study protocol.

In addition to the CR, PR, PD and SD response definition as listed in the table above, the protocol requires response assessments of CRi, nPR, and PR-L, as explained below:

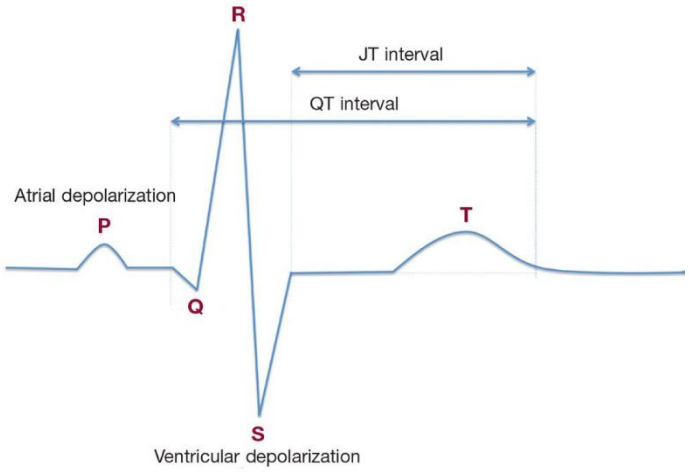
- BTK inhibitors are known to cause lymphocytosis due to redistribution of lymphocytes. In BTK inhibitors or compounds with similar mechanism of action, initial absolute lymphocyte count (ALC) progression with associated PR in other categories during therapy is usually indicative of PR-L (Cheson and Byrd et al. 2012).
- For CRi response, patients must fulfill all criteria for a CR with persistent anemia, neutropenia or thrombocytopenia and the Investigator must attribute these cytopenias as related to investigational drug and not due to the underlying disease.
- For nPR, patients must fulfill all criteria for a CR, but the bone marrow biopsy/CCI shows B-lymphoid nodules which are evidence for residual disease.

Isolated new lymphocytosis initially occurring during Cycle 1 will not be used as criteria for determining PD.

10.7. Appendix 7: QTcF Measurement Adjustment in Patients with a Widened QRS Complex > 110 ms

Fridericia's formula: QTcF (s) = QT (s)/(RR (s) $^{0.33}$)

The duration of the ECG QT interval reflects the combination of cardiac depolarization which is reflected by the QRS interval and cardiac repolarization, which is defined by the JT interval.



Normal values for the rate-corrected QTc interval are defined largely from populations of patients with normal QRS durations, without bundle branch blocks or intraventricular conduction delays. The Fridericia heart rate-corrected QTc interval is the most commonly used methodology in drug development, since it usually is the most accurate. In the setting of a widened QRS complex (> 110 ms), however, using the QTcF interval measurement may lead to overestimating cardiac repolarization, since the QTcF would be prolonged due to the contribution from the widened QRS complex; in other words, the QTcF interval could be prolonged despite cardiac repolarization being normal (i.e., a normal JTc interval). For example, if the QRS duration was 150 ms and the QTcF was 500 ms, cardiac repolarization is not meaningfully prolonged when it is considered that a normal QRS duration is conservatively 90 ms. So, in this case, 60 ms (150 ms–90 ms) of the QTcF of 500 ms is due to excessive QRS prolongation and thus the QTcF "adjusted" for the QRS widening is 440 ms (500 ms– [150 ms– 90 ms]).

Thus, for this protocol, in patients with a QRS duration > 110 ms, a QTcF adjusted for the widened QRS duration will be used to assess if a patient meets criteria for protocol exclusion, drug hold, or discontinuation using the below formula:

"Adjusted QTcF" = measured QTcF - [measured QRS- 90 ms].

10.8. Appendix 8: Abbreviations and Definitions

Term	Definition
ADL	activities of daily living
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AIHA	autoimmune hemolytic anemia
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration versus time curve
BBB	bundle branch block
BCL2	B-cell lymphoma 2
BCR	B-cell receptor
BCRP	breast cancer resistance protein
BID	twice a day
BMX	bone marrow tyrosine kinase gene on chromosome X
BOR	best overall response
BR	bendamustine with rituximab
BSA	body surface area
BTK	Bruton's tyrosine kinase
C1D1	Cycle 1 Day 1
C1D2	Cycle 1 Day 2
C1D8	Cycle 1 Day 8
C1D15	Cycle 1 Day 15
C2D1	Cycle 2 Day 1
C2D15	Cycle 2 Day 15
C3D1	Cycle 3 Day 1
C4D1	Cycle 4 Day 1
C5D1	Cycle 5 Day 1
C6D1	Cycle 6 Day 1
C7D1	Cycle 7 Day 1
C481	cysteine residue at position 481
CAP	College of American Pathologists
CAR-T	chimeric antigen receptor-modified T-cells
cfDNA	cell free DNA
CFR	Code of Federal Regulations
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CLL/SLL	chronic lymphocytic leukemia/small lymphocytic lymphoma

Term	Definition
CMV	cytomegalovirus
CNS	central nervous system
CO	crossover
COPD	chronic obstructive pulmonary disease
CPK	creatine phosphokinase
CR	complete remission
CRF	case report form
CRi	complete remission with incomplete marrow recovery
CrCl	creatinine clearance
CSR	clinical study report
CT	computed tomography
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria in Adverse Events
CTFG	Clinical Trial Facilitation Group
CYP	cytochrome P450
CYP3A4	cytochrome P450 3A4
DAG	diacyl glycerol
DCR	disease control rate
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
DRESS	drug reaction with eosinophilia and systemic symptoms
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data capture
EFS	event free survival
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
EORTC	European Organisation for Research and Treatment of Cancer Quality of Life questionnaire
EORTC IL19	European Organisation for Research and Treatment of Cancer Item Library 19
CCI	[redacted]
CCI	[redacted]
EORTC QLQ-C30 PF	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0
EOT	End of Treatment
ePRO	electronic patient-reported outcome
EQ-5D-5L	5-level-EuroQol
ERK	extracellular signal-regulated kinase

Term	Definition
ESMO	European Society for Medical Oncology
EU	European Union
FOIA	Freedom of Information Act
FDG	fluorodeoxyglucose
GCP	Good Clinical Practice
GCSF	granulocyte-colony-stimulating factor
GI	gastrointestinal
GnRH	gonadotropin-releasing hormone
GVHD	graft versus host disease
HBc	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
IB	Investigator's Brochure
IC90	90% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IdelaR	idelalisib with rituximab
IEC	International Electrotechnical Committee
IgA	immunoglobulin A
IgG	immunoglobulin G
IGHV	immunoglobulin heavy chain variable region gene
IgM	immunoglobulin M
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IP3	inositol 3-phosphate
IRB	Institutional Review Board
IRC	Independent Review Committee
ISO/IEC	International Organization for Standardization/International Electrotechnical Committee
ITK	inducible T-cell kinase
ITP	idiopathic thrombocytopenic purpura

Term	Definition
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (i.e., the planned treatment regimen) rather than the actual treatment given. It has the consequence that patient allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
IXRS	interactive voice/web response system
LDH	lactate dehydrogenase
LHRH	luteinizing hormone-releasing hormone
LTFU	Long-Term Follow-up
LVEF	left ventricular ejection fraction
LYN	a protein kinase that in humans is encoded by the LYN gene
MAPK	mitogen-activated protein kinase
MCL	mantle cell lymphoma
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximal tolerated dose
MZL	marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NFAT	nuclear factor of activated T-cells
NF-kB	nuclear factor kappa-light-chain-enhancer of activated B-cells
NHL	non-Hodgkin lymphomas
nPR	nodular partial remission
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease; disease progression
PE	physical exam
PFS	progression-free survival
CCI	[redacted]
CCI	[redacted]
P-gp	P-glycoprotein
PI3K	phosphoinositide 3-kinase
PIP3	phosphatidylinositol 3-phosphate
PJP	pneumocystis jiroveci pneumonia
PK	pharmacokinetics
PKC	protein kinase C
PLCg2	phospholipase C gamma 2

Term	Definition
PO	*per os*, oral
PR	partial remission
PRBCs	packed red blood cells
PR-L	PR with lymphocytosis
PRO	patient-reported outcomes
PT	prothrombin time
Q2W	every 2 weeks
Q4W	every 4 weeks
Q12W	every 12 weeks
Q24W	every 24 weeks
QD	once daily
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
REB	Research Ethics Board
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
r/r	relapsed/refractory
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCT	stem cell transplantation
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SERD	selective estrogen receptor degrader
SERM	selective estrogen receptor modulator
SFU	Safety Follow-up
SJS	Stevens-Johnson syndrome
SoA	Schedule of Assessments
SPM	second primary malignancy
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TEC	intracellular non-receptor tyrosine kinases
TEN	toxic epidermal necrolysis
TLS	tumor lysis syndrome
T_{max}	time to maximum plasma concentration
TTNT	time to next treatment
TTW	time to worsening
TXK	human tyrosine kinase expressed in T-cells that shares sequence identity with TEC family kinases and maps to 4p12
US	United States
ULN	upper limit of normal

Term	Definition
WBC	white blood cells
WM	Waldenström's macroglobulinemia
WOCBP	woman of childbearing potential
XLA	X-linked agammaglobulinemia
Xid	X-linked immunodeficiency
Y223	autophosphorylation site within the BTK SH3 domain (Y223 phosphorylation is decisive for kinase activity of BTK)
Y551	tyrosine residue 551

10.9. Appendix 9: Country-Specific Requirements

The country-specific addenda included in this appendix must be followed in each of the respective countries, in addition to all procedures required by the current version of Protocol LOXO-BTK-20020. The consolidation of the individual country-specific addenda into this appendix is to facilitate transition of this trial to the CTIS system under the new clinical trial regulation in the Europian Union (EU).

All additions have been identified by underline, and deletions have been identified by ~~strikethrough~~.

10.9.1. Belgium

This addendum includes all revisions to the current global protocol based on feedback from the Belgium Regulatory Authority and as outlined in the Belgium Addendum 8.1. Belgium-specific changes to the global protocol are presented below.

10.9.1.1. Protocol Section 5.1 Inclusion Criteria

[Revised Inclusion Criterion 10 as shown.]

10. Willingness of men and women of childbearing potential (WOCBP), and their partners, to observe barrier and highly effective birth control methods as outlined in Section 10.2 (Appendix 2), and below, for the duration of treatment and for 6 months following the last dose of study treatment or 12 months after the last dose of rituximab, whichever is later.

    When idelalisib is taken with hormonal contraceptives (e.g., birth control pills), supplementation with a barrier method is required.

10.9.1.2. Protocol Section 10.2 Appendix 2: Contraceptive Guidance and Pregnancy Information

[Revised paragraphs 1 and 2 as shown.]

~~Willingness of men~~ Men and WOCBP, and their partners, must be willing to observe barrier and highly effective birth control methods as outlined below for the duration of treatment and for 6 months following the last dose of study treatment or 12 months following ~~after~~ the last dose of rituximab, whichever is later.

When idelalisib is taken with hormonal contraceptives (e.g., birth control pills), supplementation with a barrier method is required.

10.9.1.3. Protocol Section 1.3.1 Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy

[Clarified text in the row for bone marrow CCI biopsy, as shown. Only the heading rows and the row containing revisions are shown below.]

Arm A: Pirtobrutinib Monotherapy

Study Period	**Baseline**	**Arm A: Pirtobrutinib Study Treatment (Cycle = 28 days)**				**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1**		**Cycles 2-6**	**Cycle 7 +**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 8 (± 3 days)**	**Day 1 (± 7 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q12W (± 4 weeks)** for up to 2 years after last dose, **Q24W (± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	**Instructions**
Bone marrow CCI biopsy	X			Within 4-8 weeks of confirmed CR by scan and peripheral blood assessment~~. Optional~~ (required) and to confirm PD (optional)					• CCI biopsy CCI required at Screening and for confirmation of CR CCI

10.9.2. Czech Republic

This addendum includes all revisions to the current global protocol based on feedback from the Czech Republic Regulatory Authority and as outlined in the Czech Republic Addendum 6.1. Czech Republic-specific changes to the global protocol are presented below.

10.9.2.1. Protocol Section 5.1 Inclusion Criteria

[Revised Inclusion Criterion 10 as shown.]

10. Willingness of men and women of childbearing potential (WOCBP), and their partners, to both observe barrier and/or highly effective birth control methods as outlined in Section 10.2 (Appendix 2), and below, for the duration of treatment and for 6 months following the last dose of study treatment or 12 months after the last dose of rituximab, whichever is later.

    WOCBP are defined as ~~those~~ women following menarche and who are not postmenopausal (or 2 years of non-therapy-induced amenorrhea, or surgically sterile). WOCBP must utilize highly effective contraception methods as outlined below. In addition, male partners must use a barrier method (condoms), observe sexual abstinence, or use sterilization methods such as vasectomy, for the duration of treatment and for 6 months following the last dose of study treatment or 12 months after the last dose of rituximab, whichever is later. Male patients with partners who are WOCBP must use a barrier method (condoms) and their partner must also use a highly effective form of contraception as listed below for the duration of treatment and for 6 months following the last dose of study treatment or 12 months after the last dose of rituximab, whichever is later.

Highly effective birth control methods with a failure rate of less than 1% per year when used consistently and correctly are recommended (Clinical Trial Facilitation Group [CTFG 2020]):

a. Combined estrogen and progestin containing hormonal contraception associated with inhibition of ovulation given orally, intravaginally, or transdermally
b. Progestin-only hormonal contraception associated with inhibition of ovulation given orally, by injection, or by implant
c. Intrauterine device (IUD)
d. Intrauterine hormone-releasing system (IUS)
e. Bilateral tubal occlusion
f. Vasectomized partner
g. Sexual abstinence: Considered a highly effective method only if defined as refraining from heterosexual intercourse during an entire period of risk associated with the study treatment. The reliability of sexual abstinence will be evaluated in relation to the duration of the study and to the usual lifestyle of the patient.

Notes:

- Women with a history of breast cancer may not use hormone-containing contraception (a, b, or d ~~above~~). One of the other listed methods above should be selected.
- ~~Women of childbearing potential~~ WOCBP using hormonal contraception methods should also use a barrier method as a second form of contraception.
- Sperm donation and oocyte donation are prohibited during the duration of participation on this protocol and for at least 6 months after the last dose of study drug, ~~or at least~~ and 12 months following last dose of rituximab, whichever is later.

10.9.2.2. Protocol Section 5.2 Exclusion Criteria

[Revised Exclusion Criterion 15 as shown.]

15. Known Human Immunodeficiency Virus (HIV) infection, regardless of CD4 count. Patients with ~~unknown or~~ negative status are eligible.

10.9.2.3. Protocol Section 6.5.1 Allowed Concomitant Medication and Supportive Care

[Revised bullet 6 as shown.]

- Prophylactic antibiotic or IV immunoglobulin (IVIG) therapy for management of patients at risk of infections is recommended. Initiation of antibiotic prophylaxis against pneumocystis infection (e.g., with trimethoprim-sulfamethoxazole, dapsone, aerosolized pentamidine, or atovaquone) before study drug administration may be warranted and should be provided for patients receiving idelalisib, consistent with the idelalisib USPI. Local practices or guidelines regarding infection prophylaxis may ~~must~~ be followed.

10.9.2.4. Protocol Section 8.4.4.8 Pregnancy Testing

[Revised section as shown.]

For women of childbearing potential (WOCBP): Pregnancy testing ~~(serum or urine)~~ must be conducted at Screening (serum) and at other visits (serum or urine) as outlined in the SoAs (Appendix Sections 10.9.2.7, 10.9.2.8, 10.9.2.9, 10.9.2.10, 10.9.2.11, and Section 1.3) or as required per local regulations and/or institutional guidelines and may be performed locally. Pregnancy reporting guidance is provided in Section 8.5.7. All WOCBP, defined as women who are following menarche and who are not postmenopausal (or 2 years of non-therapy-induced amenorrhea) or surgically sterile will have a serum ~~or urine~~ pregnancy test at Screening. ~~If any urine pregnancy test is positive, study treatment will be delayed until the patient pregnancy status is confirmed by a serum pregnancy test.~~ If serum pregnancy test is positive, the patient will be permanently discontinued from study treatment. The serum or urine pregnancy tests must be performed monthly until 6 months after the last dose in patients receiving pirtobrutinib, 1 month after the last dose in patients receiving idelalisib, and 12 months after the last dose in patients receiving rituximab, or as required per local regulations and/or institutional guidelines.

10.9.2.5. Protocol Section 8.4.4.9 Viral Testing

[Revised paragraph 2 as shown.]

Patients with known active CMV infection, a positive HIV test, ~~and/~~or a history of positive HIV test (regardless of CD4 count) are excluded from participation in the trial due to potential drug-drug interactions between antiretroviral medications and pirtobrutinib and risk of opportunistic infections with both HIV and approved BTK inhibitors.

10.9.2.6. Protocol Section 10.2 Appendix 2: Contraceptive Guidance and Pregnancy Information

[Revised paragraph 2 as shown.]

WOCBP are defined as ~~those~~women following menarche, and who are not postmenopausal (or 2 years of non-therapy-induced amenorrhea, or surgically sterile). WOCBP must utilize highly effective contraception methods as outlined below. In addition, male partners must use a barrier method (condoms) for the duration of treatment and for 6 months following the last dose of study treatment or 12 months after the last dose of rituximab, whichever is later. Male patients with partners who are WOCBP must use a barrier method (condoms), or observe sexual abstinence, or use sterilization methods such as vasectomy, and their partner must also use a highly effective form of contraception as listed below for the duration of treatment and for 6 months following the last dose of study treatment or 12 months after the last dose of rituximab, whichever is later.

[Revised bullet 2 of "Notes" under "**Highly effective birth control methods,"** as shown.]

- ~~Women of childbearing potential~~ WOCBP using hormonal contraception methods should also use a barrier method as a second form of contraception. Sperm donation and oocyte donation are prohibited during the duration of participation on this protocol and for at least 6 months after the last dose of study drug, and 12 months following last dose of rituximab, whichever is later.

10.9.2.7. Protocol Section 1.3.1 Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy

[Revised the rows for hematology, hepatitis B/C active disease status and HIV serology, serum or urine pregnancy test, and bone marrow CCI biopsy. Only the heading rows and rows containing revisions are shown below.]

Arm A: Pirtobrutinib Monotherapy

Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**				**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1**		**Cycles 2-6**	**Cycle 7 +**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 8 (± 3 days)**	**Day 1 (± 7 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	Q12W **(± 4 weeks)** for up to 2 years after last dose, Q24W **(± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	**Instructions**
Hematology	X	X	X	X	~~C7D1 and Q12W thereafter~~X	X	X	X	• Includes hemoglobin, hematocrit, RBC count, WBC count, platelet count, percent or absolute differential (neutrophils, lymphocytes, eosinophils, basophils, and monocytes) • Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results • Repeat testing during Screening is permitted; refer to Section 5.5 • On days when hematology is required for both safety and response assessments, samples should also be submitted to the central laboratory
Hepatitis B/C active disease status and HIV serology	X								• HBV and HCV testing, and HIV serology, to determine if patients have active infection • Refer to Section 5.2 for exclusions

Arm A: Pirtobrutinib Monotherapy

Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**				**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1**		**Cycles 2-6**	**Cycle 7 +**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 8 (± 3 days)**	**Day 1 (± 7 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	Q12W (**± 4 weeks**) for up to 2 years after last dose, Q24W (**± 4 weeks**) beyond 2 years for patients who discontinue prior to PD	**Instructions**
Serum or urine pregnancy test (WOCBP only)	X	X ~~C7D1 and Q12W thereafter~~							• Test at Screening should be a serum test • Perform within 24 hours of first dose of study treatment~~, and as indicated in table, or as required per local regulations and/or institutional guidelines~~ • Testing should be monthly while receiving pirtobrutinib, and testing should continue monthly for at least 6 months from the last dose of pirtobrutinib • Refer to Section 10.2 Appendix 2
Bone marrow [redacted] biopsy	X			Within 4-8 weeks of confirmed CR by scan and peripheral blood assessment~~. Optional~~ (required) and ~~Optional~~ to confirm PD (optional)					• [redacted] biopsy required at Screening and for confirmation of CR [redacted]

10.9.2.8. Protocol Section 1.3.2 Schedule of Assessments for Arm B: Idelalisib plus Rituximab

[Revised the rows for hepatitis B/C active disease status and HIV serology, serum or urine pregnancy test, and bone marrow CCI [redacted] biopsy. Only the heading rows and rows containing revisions are shown below.]

Arm B: Idelalisib plus Rituximab (IdelaR)

Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**							**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1**		**Cycle 2**		**Cycles 3-6**		**Cycle 7+**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q12W (± 4 weeks)** for up to 2 years after last dose, Q24W (**± 4 weeks**) beyond 2 years for patients who discontinue prior to PD	**Instructions**
Hepatitis B/C active disease status and HIV serology	X											• HBV and HCV testing, and HIV serology, to determine if patients have active infection • Refer to Section 5.2 for exclusions
Serum or urine pregnancy test (WOCBP only)	X	X										• Test at Screening should be a serum test • Perform within 24 hours of first dose of study treatment~~, and as indicated in table, or as required per local regulations and/or institutional guidelines~~ • Testing should be monthly while receiving idelalisib and/or rituximab, and testing should continue monthly for at least 1 month after the last dose of idelalisib and 12 months after the last dose of rituximab • Refer to Section 10.2, Appendix 2

Arm B: Idelalisib plus Rituximab (IdelaR)

Study Period	Baseline	Study Treatment (Cycle = 28 days)							Post-Study Treatment Discontinuation			
Evaluation	Screening	Cycle 1		Cycle 2		Cycles 3-6		Cycle 7+	EOT	SFU	LTFU	
Visit Window	Up to 28 days	Day 1	Day 15 (± 3 days)	Day 1 (± 3 days)	Day 15 (± 3 days)	Day 1 (± 3 days)	Day 15 (± 3 days)	Day 1 (± 7 days)	+ 7 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	Q12W (± 4 weeks) for up to 2 years after last dose, Q24W (± 4 weeks) beyond 2 years for patients who discontinue prior to PD	Instructions
Bone marrow [redacted] biopsy	X					Within 4-8 weeks of confirmed CR by scan and peripheral blood assessment~~. Optional~~ (required) and ~~Optional~~ to confirm PD (optional)						• [redacted] biopsy [redacted] required at Screening and for confirmation of CR [redacted]

10.9.2.9. Protocol Section 1.3.3 Schedule of Assessments for Arm B: Bendamustine plus Rituximab

[Revised the rows for hepatitis B/C active disease status and HIV serology, and serum or urine pregnancy test. Only the heading rows and rows containing revisions are shown below.]

Arm B: Bendamustine plus Rituximab (BR)

Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**				**Post-Study Treatment Discontinuation**			**Instructions**
Evaluation	**Screening**	**Cycle 1**		**Cycles 2-6**		**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 2**	**Day 1 (± 3 days)**	**Day 2**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	Q12W (**± 4 weeks**) for up to 2 years after last dose, Q24W (**± 4 weeks**) beyond 2 years for patients who discontinue prior to PD	
Hepatitis B/C active disease status and HIV serology	X								• HBV and HCV testing, and HIV serology, to determine if patients have active infection • Refer to Section 5.2 for exclusions
Serum or urine pregnancy test (WOCBP only)	X	X							• Test at Screening should be a serum test • Perform within 24 hours of first dose of study treatment~~, and as indicated in table, or as required per local regulations and/or institutional guidelines~~ • Testing should be monthly while receiving bendamustine and/or rituximab, and testing should continue for at least 12 months after the last dose of rituximab • Refer to Section 10.2

10.9.2.10. Protocol Section 1.3.4 Schedule of Assessments for Optional Crossover Treatment (for Patients Crossing Over from Arm B to Arm A)

[Revised the SoA shown in Section 1.3.4; visit days and procedures have been revised to align with the monotherapy SoA that is shown in Section 1.3.1 and Appendix Section 10.9.2.7. The new/revised SoA for optional crossover treatment for the Czech Republic is shown below in underscore text; this replaces the SoA shown in Section 1.3.4 in entirety.]

Optional Crossover Treatment (for Patients Crossing Over from Arm B to Arm A)

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			
Evaluation	CO-Screening	CO-Cycle 1		CO- Cycles 2-6	CO-Cycle 7+	CO-EOT	CO-SFU	CO-LTFU	
Visit Window	Up to 42 days	Day 1	Day 8 (±3 days)	Day 1 (± 7 days)	Day 1 (± 7 days)	+7 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	± 4 weeks	Instructions
Informed consent	X								• The ICF for crossover must be signed before any protocol-specified procedures are performed. Refer to Appendix Section 10.1.2 • Crossover screening procedures must be completed within 42 days of IRC-confirmed PD
Physical examination	X	X	X	X	CO-C7D1 and Q12W thereafter	X	X	Q12W for up to 2 years after last dose, Q24W beyond 2 years for patients who discontinue prior to PD	• Complete PE includes height (only at Screening), weight, basic neurological examination and review of relevant symptoms at Screening (refer to Section 8.4.2) • Symptom-directed PE should be limited to systems of primary relevance such as cardiovascular, respiratory, and those associated with tumor assessment (lymph nodes, liver, and spleen) and may be performed at other timepoints; include weight as clinically indicated throughout the trial

Optional Crossover Treatment (for Patients Crossing Over from Arm B to Arm A)

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			
Evaluation	CO-Screening	CO-Cycle 1		CO- Cycles 2-6	CO-Cycle 7+	CO-EOT	CO-SFU	CO-LTFU	
Visit Window	Up to 42 days	Day 1	Day 8 (±3 days)	Day 1 (± 7 days)	Day 1 (± 7 days)	+7 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	± 4 weeks	Instructions
									• Screening results obtained within 3 days of CO-C1D1 are acceptable as CO-C1D1 results
ECOG PS	X	X	X	X	CO-C7D1 and Q12W thereafter	X	X		
Vital signs	X	X	X	X	CO-C7D1 and Q12W thereafter	X	X		• Includes systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature
12-lead ECG	X	X	X	X	CO-C7D1 and Q12W thereafter				• Obtain ECGs at specified visits and when patients are symptomatic. Refer to Section 8.4.3 • ECGs should be collected: – At Screening, single ~~triplicate~~ ECG – If an unscheduled ECG is done at any time, an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG – If a clinically significant arrhythmia is detected, details must be in EDC

Optional Crossover Treatment (for Patients Crossing Over from Arm B to Arm A)

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			
Evaluation	CO-Screening	CO-Cycle 1		CO- Cycles 2-6	CO-Cycle 7+	CO-EOT	CO-SFU	CO-LTFU	
Visit Window	Up to 42 days	Day 1	Day 8 (±3 days)	Day 1 (± 7 days)	Day 1 (± 7 days)	+7 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	± 4 weeks	Instructions
Hematology	X	X	X	X	X	X	X	Q24W for up to 2 years after last dose Q24W beyond 2 years for patients who discontinue prior to PD	• Includes hemoglobin, hematocrit, RBC count, WBC count, platelet count, percent or absolute differential (neutrophils, lymphocytes, eosinophils, basophils, and monocytes) • Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results • Repeat testing during Screening is permitted; refer to Section 5.5
Blood chemistries	X	X	X	X	CO-C7D1 and Q12W thereafter	X	X		• Blood chemistry from serum or plasma should include assessment of: Sodium, potassium, chloride, glucose, creatinine, total protein, albumin, total bilirubin, ALT, and AST • Repeat testing during Screening is permitted; refer to Section 5.5 • Tests for LDH, calcium, magnesium, phosphorus and uric acid are only required on Day 1 of CO-C1 • Screening results within 3 days of CO-C1D1 are acceptable as CO-C1D1 results • Direct (or indirect) bilirubin should be performed any time total bilirubin is abnormal
Coagulation panel	X	As clinically indicated							aPTT and PT (or INR)

Optional Crossover Treatment (for Patients Crossing Over from Arm B to Arm A)

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			
Evaluation	CO-Screening	CO-Cycle 1		CO- Cycles 2-6	CO-Cycle 7+	CO-EOT	CO-SFU	CO-LTFU	
Visit Window	Up to 42 days	Day 1	Day 8 (±3 days)	Day 1 (± 7 days)	Day 1 (± 7 days)	+7 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	± 4 weeks	Instructions
Serum or urine pregnancy test (WOCBP only)	X	X							• Test at Screening should be a serum test • Perform within 24 hours of first dose of study treatment • Testing should be monthly, and testing should continue for at least 6 months after the last dose of pirtobrutinib, 1 month after the last dose of idelalisib, and 12 months after the last dose of rituximab • Refer to Appendix Section 10.2
Urinalysis	X	X	As clinically indicated						Dipstick analysis is acceptable and should include color, specific gravity, pH, glucose, bilirubin, occult blood, protein, leukocytes, and urobilinogen
CT or MRI	X			C4D1	CO-C7D1 and Q12W thereafter	X		Q12W for up to 2 years after last dose Q24W beyond 2 years for patients who discontinue prior to PD	• Refer to Section 8.3.1 for details. • If baseline CT or MRI assessment documenting PD by IRC was performed within 42 days of planned C1D1, a new scan does not need to be obtained • All response assessments should occur at Q24W intervals relative to CO-C1D1, regardless of any treatment delays or interruptions • At the EOT visit, a repeat CT/MRI does not need to be performed if done within the proceeding 2 weeks or if PD was previously determined • Investigator assessment of CT or MRI will be done locally at frequency of at least

Optional Crossover Treatment (for Patients Crossing Over from Arm B to Arm A)

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			
Evaluation	CO-Screening	CO-Cycle 1		CO- Cycles 2-6	CO-Cycle 7+	CO-EOT	CO-SFU	CO-LTFU	
Visit Window	Up to 42 days	Day 1	Day 8 (±3 days)	Day 1 (± 7 days)	Day 1 (± 7 days)	+7 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	± 4 weeks	Instructions
									Q24W frequency or based on standard of care
Pirtobrutinib administration		X	X	X	X	X			• 200 mg PO administered QD (continuous) • Crossover treatment should be initiated within a window of 42 days after the IRC-confirmed PD • Patient to visit study site Q12W from CO-C4D1 for dispensation of pirtobrutinib • Date of last dose and date of decision to end treatment must be recorded in EDC prior to patient receiving first dose of treatment in crossover
Patient dosing diary		X	X	X					
Concomitant medication	X	X	X	X	X	X	X		Refer to Section 6.5
Adverse events	X	X	X	X	X	X	X		• Collect SAEs from the time of ICF signing through 28 days after the last dose (NCI CTCAE v5.0) • Collect AEs from the time of dosing through SFU; AEs that occur prior to the first dose are considered medical history unless the AE develops or worsens due to study-related procedures • All SAEs occurring from the time ICF is signed through 28 days after the last dose must be reported to Clinical Safety within 24 hours of knowledge of the event. All

Optional Crossover Treatment (for Patients Crossing Over from Arm B to Arm A)

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			
Evaluation	CO-Screening	CO-Cycle 1		CO- Cycles 2-6	CO-Cycle 7+	CO-EOT	CO-SFU	CO-LTFU	
Visit Window	Up to 42 days	Day 1	Day 8 (±3 days)	Day 1 (± 7 days)	Day 1 (± 7 days)	+7 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	± 4 weeks	Instructions
									SAEs that the Investigator considers related to study drug occurring after the 28-day follow-up period must be reported to the Sponsor • Second primary malignancy (SPM) events are to be reported and should continue to be reported for up to 5 years from the start of pirtobrutinib treatment, regardless of seriousness or causal attribution to pirtobrutinib treatment
Survival status		X	X	X	X	X	X	Q12W for up to 2 years after last dose Q24W beyond 2 years	• Survival information may be collected via telephone if no procedures are required; survival information should be collected approximately Q24W after the SFU visit; refer to Section 6.7.5 • Subsequent anticancer therapy information should be collected Q24W after the SFU visit until death or study completion

10.9.2.11. Protocol Section 1.3.5 Schedule of Assessments for Response Assessments, Arms A and B (Does Not Apply for Crossover)

[Revised the SoA shown in Section 1.3.5; visit days and procedures have been revised to align with the monotherapy SoA that is shown in Section 1.3.1 and Appendix Section 10.9.2.7. The new/revised SoA for response assessments is shown below in underscore text, and the deleted SoA is shown as strikethrough text; this replaces the SoA shown in Section 1.3.5 in entirety.]

Response Assessments, Arms A and B (Does Not Apply for Crossover)

Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**				**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1**		**Cycle 2-6**	**Cycle 7 +**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 8 (± 3 Days)**	**Day 1 (± 7 Days)**	**Day 1 (± 7 Days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	Q12W **(± 4 weeks)** for up to 2 years after last dose, Q24W **(± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	**Instructions**
Bone marrow [redacted] biopsy	X			Within ~~4~~8 weeks of confirmed CR by scan and peripheral blood assessment (required) and to confirm PD (optional)					• [redacted] biopsy [redacted] required at Screening and for confirmation of CR [redacted]
CT or MRI	X			C4D1	C7D1 and Q12W thereafter	X		X	• Refer to Section 8.3.1 for details. • CT scan with IV contrast agent is the preferred method of assessment with scans of neck, chest, abdomen and pelvis. However, MRI is acceptable if CT scan with contrast agent is contraindicated • All response assessments should occur at Q12W intervals relative to C1D1 regardless of any treatment delays or interruptions • At the EOT visit, a repeat CT/MRI does

Response Assessments, Arms A and B (Does Not Apply for Crossover)

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			
Evaluation	Screening	Cycle 1		Cycle 2-6	Cycle 7 +	EOT	SFU	LTFU	
Visit Window	Up to 28 days	Day 1	Day 8 (± 3 Days)	Day 1 (± 7 Days)	Day 1 (± 7 Days)	+ 7 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	Q12W (± 4 weeks) for up to 2 years after last dose, Q24W (± 4 weeks) beyond 2 years for patients who discontinue prior to PD	Instructions
									not need to be performed if done within the proceeding 2 weeks or if PD was previously determined • A central radiology vendor will be used to collect and store images for IRC review
Physical examination	X			C4D1	C7D1 and Q12W thereafter	X		X	• Complete PE includes height (only at Screening), weight, basic neurological examination and review of relevant symptoms at Screening (refer to Section 8.4.2) • Symptom-directed PE should be limited to systems of primary relevance such as, cardiovascular, respiratory, those associated with symptoms, and those associated with tumor assessment (lymph nodes, liver, and spleen) and may be performed at other timepoints; include weight as clinically indicated throughout the trial

Response Assessments, Arms A and B (Does Not Apply for Crossover)

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			
Evaluation	Screening	Cycle 1		Cycle 2-6	Cycle 7 +	EOT	SFU	LTFU	
Visit Window	Up to 28 days	Day 1	Day 8 (± 3 Days)	Day 1 (± 7 Days)	Day 1 (± 7 Days)	+ 7 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	Q12W (± 4 weeks) for up to 2 years after last dose, Q24W (± 4 weeks) beyond 2 years for patients who discontinue prior to PD	Instructions
Hematology	X			C4D1	Day 1 every cycle for Arm A, C7D1 and Q12W thereafter for Arm B	X		X	• Includes hemoglobin, hematocrit, RBC count, WBC count, platelet count, percent or absolute differential (neutrophils, lymphocytes, eosinophils, basophils, and monocytes). • Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results • Repeat testing during Screening is permitted; refer to Section 5.5 • On days when hematology is required for both safety and response assessments, samples should also be submitted to the central laboratory

10.9.3. Germany

This addendum includes all revisions to the current global protocol based on feedback from the German Regulatory Authority and as outlined in the Germany Addendum 7.1. Germany-specific changes to the global protocol are presented below.

10.9.3.1. Protocol Section 5.2 Exclusion Criteria

[Revised Exclusion Criterion 15 as shown.]

15. Known Human Immunodeficiency Virus (HIV) infection, regardless of CD4 count. Patients with ~~unknown or~~ negative status are eligible.

[Revised Exclusion Criterion 25(c) as shown.]

25. Patients with the following hypersensitivity:

    c) Prior significant hypersensitivity to rituximab, murine proteins, hyaluronidase, or to any of the other excipients (sodium citrate, polysorbate, sodium chloride, sodium hydroxide, hydrochloric acid, water for injection) requiring discontinuation or prior allergic or anaphylactic reaction to rituximab, murine proteins, hyaluronidase, or to any of the other excipients (sodium citrate, polysorbate, sodium chloride, sodium hydroxide, hydrochloric acid, water for injection). This does not include manageable infusion-related ~~reaction)~~ reactions.

10.9.3.2. Protocol Section 8.4.4.9 Viral Testing

[Revised paragraph 2 as shown.]

Patients with known active CMV infection, a positive HIV test, ~~and/~~or a history of positive HIV test (regardless of CD4 count) are excluded from participation in the trial due to potential drug-drug interactions between antiretroviral medications and pirtobrutinib and risk of opportunistic infections with both HIV and approved BTK inhibitors.

10.9.3.3. Protocol Section 10.2 Appendix 2: Contraceptive Guidance and Pregnancy Information

[Revised paragraph 1 sentence 1 as shown.]

~~Willingness of men and~~ WOCBP, and their partners, must be willing to observe barrier and/or highly effective birth control methods as outlined below for the duration of treatment and for 6 months following the last dose of study treatment or 12 months after the last dose of rituximab, whichever is later.0

10.9.3.4. Protocol Section 1.3.1 Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy

[Revised the rows for hematology, blood chemistries, hepatitis B/C active disease status and HIV serology, serum or urine pregnancy test, and bone marrow [redacted] biopsy. Only the heading rows and rows containing revisions are shown below.]

Arm A: Pirtobrutinib Monotherapy

Study Period	**Baseline**	**Arm A: Pirtobrutinib Study Treatment (Cycle = 28 days)**				**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1**		**Cycles 2-6**	**Cycle 7 +**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 8 (± 3 days)**	**Day 1 (± 7 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q12W (± 4 weeks)** for up to 2 years after last dose, **Q24W (± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	**Instructions**
Hematology	X	X	X	X	C7D1 and ~~Q12W~~ Q4W thereafter	X	X	X	• Includes hemoglobin, hematocrit, RBC count, WBC count, platelet count, percent or absolute differential (neutrophils, lymphocytes, eosinophils, basophils, and monocytes) • Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results • Repeat testing during Screening is permitted; refer to Section 5.5 • On days when hematology is required for both safety and response assessments, samples should also be submitted to the central laboratory
Blood chemistries	X	X	X	X	C7D1 and ~~Q12W~~ Q4W thereafter	X	X		• Blood chemistry from serum or plasma should include assessment of: sodium, potassium, chloride, glucose, creatinine, total protein, albumin, total bilirubin, ALT and AST • Repeat testing during Screening is permitted; refer to Section 5.5 • LDH, calcium, magnesium, phosphorus and uric acid are required at Screening and Day 1 of C1 to C6

Arm A: Pirtobrutinib Monotherapy

Study Period	Baseline	Arm A: Pirtobrutinib Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	**Screening**	**Cycle 1**		**Cycles 2-6**	**Cycle 7 +**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 8 (± 3 days)**	**Day 1 (± 7 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q12W (± 4 weeks)** for up to 2 years after last dose, **Q24W (± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	
									• Refer to Section 8.4.4.10 for hepatic safety monitoring • Screening results within 3 days of C1D1 are acceptable as C1D1 results • Direct (or indirect) bilirubin should be performed any time total bilirubin is abnormal
Hepatitis B/C active disease status and HIV serology	X								• HBV and HCV testing, and HIV serology, to determine if patients have active infection • Refer to Section 5.2 for exclusions
Serum or urine pregnancy test (WOCBP only)	X	X							• Perform within 24 hours of first dose of study treatment • Testing should be monthly while receiving pirtobrutinib, and testing should continue monthly for at least 6 months from the last dose of pirtobrutinib • Refer to Section 10.2, Appendix 2
~~Serum or urine pregnancy test (WOCBP only)~~	~~X~~	~~X~~		~~X~~	~~C7D1 and Q12W thereafter~~				~~• Perform within 24 hours of first dose of study treatment~~, and ~~as indicated in table, or as required per local regulations and/or institutional guidelines~~ ~~• Refer to Section 10.2, Appendix 2~~
Bone marrow [redacted] biopsy	X			Within 4-8 weeks of confirmed CR by scan and peripheral blood assessment~~. Optional~~ (required) and to confirm PD (optional)					• [redacted] biopsy [redacted] required at Screening and for confirmation of CR [redacted]

10.9.3.5. Protocol Section 1.3.2 Schedule of Assessments for Arm B: Idelalisib plus Rituximab

[Revised the rows for 12-lead ECG, hematology, blood chemistries, hepatitis B/C active disease status and HIV serology, serum or urine pregnancy test, and bone marrow CCI biopsy. Only the heading rows and rows containing revisions are shown below.]

Arm B: Idelalisib plus Rituximab (IdelaR)

Study Period	**Baseline**	**Arm B: IdelaR** **Study Treatment (Cycle = 28 days)**							**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1**		**Cycle 2**		**Cycles 3-6**		**Cycle 7+**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q12W (± 4 weeks)** for up to 2 years after last dose, **Q24W (± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	**Instructions**
12-lead ECG	X	X	X	X	X	X			X			• Obtain ECGs at specified visit • Refer to Section 8.4.3 • At Screening, single ECG should be collected
Hematology	X	X	X	X	X	X	X	C7D1 and ~~Q12W~~ Q4W thereafter	X	X	X	• Includes hemoglobin, hematocrit, RBC count, WBC count, platelet count, percent or absolute differential (neutrophils, lymphocytes, eosinophils, basophils, and monocytes) • Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results • Repeat testing during Screening is permitted; refer to Section 5.5 • On days when hematology is required for both safety and response assessments, samples should also be submitted to the central laboratory

Arm B: Idelalisib plus Rituximab (IdelaR)

Study Period	Baseline	Arm B: IdelaR Study Treatment (Cycle = 28 days)							Post-Study Treatment Discontinuation			
Evaluation	**Screening**	**Cycle 1**		**Cycle 2**		**Cycles 3-6**		**Cycle 7+**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q12W (± 4 weeks)** for up to 2 years after last dose, **Q24W (± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	**Instructions**
Blood chemistries	X	X	X	X	X	X	X	C7D1 and ~~Q12W~~ Q4W thereafter	X	X		• Blood chemistry from serum or plasma should include assessment of: sodium, potassium, chloride, glucose, creatinine, total protein, albumin, total bilirubin, ALT, and AST • Repeat testing during Screening is permitted; refer to Section 5.5 • LDH, calcium, magnesium, phosphorus and uric acid are required at Screening and Day 1 of C1 to C6 • Screening results within 3 days of C1D1 are acceptable as C1D1 results
Hepatitis B/C active disease status and HIV serology	X											• HBV and HCV testing, and HIV serology, to determine if patients have active infection • Refer to Section 5.2 for exclusions
Serum or urine pregnancy test	X	X		X		X		X				• Perform within 24 hours of first dose of study treatment • Testing should be monthly while receiving idelalisib and/or rituximab, and testing

Arm B: Idelalisib plus Rituximab (IdelaR)

Study Period	Baseline	Arm B: IdelaR Study Treatment (Cycle = 28 days)							Post-Study Treatment Discontinuation			
Evaluation	**Screening**	**Cycle 1**		**Cycle 2**		**Cycles 3-6**		**Cycle 7+**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q12W (± 4 weeks)** for up to 2 years after last dose, **Q24W (± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	**Instructions**
(WOCBP only)												should continue monthly for at least 1 month after the last dose of idelalisib and 12 months after the last dose of rituximab • Refer to Section 10.2, Appendix 2
~~Serum or urine pregnancy test (WOCBP only)~~	~~X~~	~~X~~		~~X~~		~~X~~		~~C7D1 and Q12W thereafter~~				~~Perform within 24 hours of first dose of study treatment, and as indicated in table,~~ or ~~as required per local regulations~~ and~~/or institutional guidelines~~ ~~Refer to Section 10.2, Appendix 2~~
Bone marrow [redacted] biopsy	X					Within 4-8 weeks of confirmed CR by scan and peripheral blood assessment~~. Optional~~ (required) and to confirm PD (optional)						• [redacted] biopsy [redacted] required at Screening and for confirmation of CR [redacted]

10.9.3.6. Protocol Section 1.3.3 Schedule of Assessments for Arm B: Bendamustine plus Rituximab

[Revised the rows for 12-lead ECG, hepatitis B/C active disease status and HIV serology, and serum or urine pregnancy test. Only the heading rows and rows containing revisions are shown below.]

Arm B: Bendamustine plus Rituximab (BR)

Study Period	**Baseline**	**Arm B: BR Study Treatment (Cycle = 28 days)**				**Post-Study Treatment Discontinuation**			**Instructions**
Evaluation	**Screening**	**Cycle 1**		**Cycles 2-6**		**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 2**	**Day 1 (± 3 days)**	**Day 2**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	Q12W (**± 4 weeks**) for up to 2 years after last dose, Q24W (**± 4 weeks**) beyond 2 years for patients who discontinue prior to PD	
12-lead ECG	X	X		X		X			• Obtain ECGs at specified visit • Refer to Section 8.4.3 • At Screening, single ECG should be collected
Hepatitis B/C active disease status and HIV serology	X								• HBV and HCV testing, and HIV serology, to determine if patients have active infection • Refer to Section 5.2 for exclusions
Serum or urine pregnancy test (WOCBP only)	X	X		X		X			• Perform within 24 hours of first dose of study treatment • Testing should be monthly while receiving bendamustine and/or rituximab, and testing should continue for at least 12 months after the last dose of rituximab • Refer to Section 10.2, Appendix 2
~~Serum or urine pregnancy test (WOCBP only)~~	~~X~~	~~X~~		~~X~~		~~X~~			~~Perform within 24 hours of first dose of study treatment,~~ and ~~as indicated in table,~~ or ~~as required per local regulations~~ and~~/or institutional guidelines~~ ~~Refer to Section 10.2, Appendix 2~~

10.9.3.7. Protocol Section 1.3.4 Schedule of Assessments for Optional Crossover Treatment (for Patients Crossing Over from Arm B to Arm A)

[Revised the SoA shown in Section 1.3.4; visit days and procedures have been revised to align with the monotherapy SoA that is shown in Section 1.3.1 and Appendix Section 10.9.3.4. The new/revised SoA for optional crossover treatment for the Czech Republic is shown below in underscore text; this replaces the SoA shown in Section 1.3.4 in entirety.]

Optional Crossover Treatment (for Patients Crossing Over from Arm B to Arm A)

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	CO-Screening	CO-Cycle 1		CO-Cycles 2-6	CO-Cycle 7+	CO-EOT	CO-SFU	CO-LTFU	
Visit Window	Up to 42 days	Day 1	Day 8 (±3 days)	Day 1 (± 7 days)	Day 1 (± 7 days)	+14 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	Q12W for up to 2 years after last dose Q24W beyond 2 years for patients who discontinue prior to PD (± 4 weeks)	
Informed consent	X								• The ICF for crossover must be signed before any protocol-specified procedures are performed. Refer to Section 10.1.2, Appendix 1 • Crossover screening procedures must be completed within 42 days of IRC-confirmed PD
Physical examination	X	X	X	X	CO-C7D1 and Q12W thereafter	X	X	X	• Complete PE includes height (only at Screening), weight, basic neurological examination and review of relevant symptoms at Screening (refer to Section 8.4.2) • Symptom-directed PE should be limited to systems of primary relevance such as, cardiovascular, respiratory, and those associated with tumor assessment (lymph nodes, liver, and spleen) and may be performed at other timepoints; include weight as clinically indicated throughout the trial

Optional Crossover Treatment (for Patients Crossing Over from Arm B to Arm A)

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			
Evaluation	CO-Screening	CO-Cycle 1		CO-Cycles 2-6	CO-Cycle 7+	CO-EOT	CO-SFU	CO-LTFU	
Visit Window	Up to 42 days	Day 1	Day 8 (±3 days)	Day 1 (± 7 days)	Day 1 (± 7 days)	+14 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	Q12W for up to 2 years after last dose Q24W beyond 2 years for patients who discontinue prior to PD (± 4 weeks)	Instructions
									• Screening results obtained within 3 days of CO-C1D1 are acceptable as CO-C1D1 results
ECOG PS	X	X	X	X	CO-C7D1 and Q12W thereafter	X	X		
Vital signs	X	X	X	X	CO-C7D1 and Q12W thereafter	X	X		• Includes systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature
Results of tests in the section below are required for crossover eligibility determination									
12-lead ECG	X	X	X	X	CO-C7D1 and Q12W thereafter	X			• Obtain ECGs at specified visits and when patients are symptomatic. Refer to Section 8.4.3 • ECGs should be collected: – At Screening, single ECG – If an unscheduled ECG is done at any time, an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG – If a clinically significant arrhythmia is detected, details must be entered in the EDC

Optional Crossover Treatment (for Patients Crossing Over from Arm B to Arm A)

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	CO-Screening	CO-Cycle 1		CO-Cycles 2-6	CO-Cycle 7+	CO-EOT	CO-SFU	CO-LTFU	
Visit Window	Up to 42 days	Day 1	Day 8 (±3 days)	Day 1 (± 7 days)	Day 1 (± 7 days)	+14 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	Q12W for up to 2 years after last dose Q24W beyond 2 years for patients who discontinue prior to PD (± 4 weeks)	
Hematology	X	X	X	X	CO-C7D1 and Q4W thereafter	X	X	X	• Includes hemoglobin, hematocrit, RBC count, WBC count, platelet count, percent or absolute differential (neutrophils, lymphocytes, eosinophils, basophils, and monocytes) • Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results • Repeat testing during Screening is permitted; refer to Section 5.5
Blood chemistries	X	X	X	X	CO-C7D1 and Q4W thereafter	X	X		• Blood chemistry from serum or plasma should include assessment of: Sodium, potassium, chloride, glucose, creatinine, total protein, albumin, total bilirubin, ALT, and AST • Repeat testing during Screening is permitted; refer to Section 5.5 • LDH, calcium, magnesium, phosphorus and uric acid are only required on Day 1 of CO-C1 • Screening results within 3 days of CO-C1D1 are acceptable as CO-C1D1 results • Direct (or indirect) bilirubin should be performed any time total bilirubin is abnormal
Coagulation panel	X	As clinically indicated							aPTT and PT (or INR)

Optional Crossover Treatment (for Patients Crossing Over from Arm B to Arm A)

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	CO-Screening	CO-Cycle 1		CO-Cycles 2-6	CO-Cycle 7+	CO-EOT	CO-SFU	CO-LTFU	
Visit Window	Up to 42 days	Day 1	Day 8 (±3 days)	Day 1 (± 7 days)	Day 1 (± 7 days)	+14 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	Q12W for up to 2 years after last dose Q24W beyond 2 years for patients who discontinue prior to PD (± 4 weeks)	
Serum or urine pregnancy test (WOCBP only)	X	X							• Perform within 24 hours of first dose of study treatment • Testing should be monthly while receiving pirtobrutinib and continue monthly for at least 6 months after the last dose of pirtobrutinib • Refer to Appendix Section 10.2
Urinalysis	X	X	As clinically indicated						Dipstick analysis is acceptable and should include color, specific gravity, pH, glucose, bilirubin, occult blood, protein, leukocytes, and urobilinogen
Documentation or sampling of the following are required during Screening, but results not required prior to initiation of pirtobrutinib									
CT or MRI	X			C4D1	CO-C7D1 and Q12W thereafter	X		X	• Refer to Section 8.1 for details. • If baseline CT or MRI assessment documenting PD by IRC was performed within 42 days of planned C1D1, a new scan does not need to be obtained • All response assessments should occur at Q12W intervals relative to CO-C1D1, regardless of any treatment delays or interruptions • At the EOT visit, a repeat CT/MRI does not need to be performed if done within the preceding 2 weeks or if PD was previously determined • Investigator assessment of CT or MRI will be done locally at frequency of at least Q12W frequency or based on standard of care

Optional Crossover Treatment (for Patients Crossing Over from Arm B to Arm A)

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			
Evaluation	CO-Screening	CO-Cycle 1		CO-Cycles 2-6	CO-Cycle 7+	CO-EOT	CO-SFU	CO-LTFU	
Visit Window	Up to 42 days	Day 1	Day 8 (±3 days)	Day 1 (± 7 days)	Day 1 (± 7 days)	+14 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	Q12W for up to 2 years after last dose Q24W beyond 2 years for patients who discontinue prior to PD (± 4 weeks)	Instructions
Pirtobrutinib administration		X	X	X	X	X			• 200 mg PO administered QD (continuous) • Crossover treatment should be initiated within a window of 42 days after the IRC-confirmed PD • Patient to visit study site Q12W from CO-C4D1 for dispensation of pirtobrutinib • Date of last dose and date of decision to end treatment must be recorded in EDC prior to patient receiving first dose of treatment in crossover.
Patient dosing diary		X	X	X	X	X			
Concomitant medication		X	X	X	X	X	X		Refer to Section 6.5
Adverse events		X	X	X	X	X	X		• Collect SAEs from the time of ICF signing through 28 days after the last dose (NCI CTCAE v5.0) • Collect AEs from the time of dosing through SFU; AEs that occur prior to the first dose are considered medical history unless the AE develops or worsens due to study-related procedures • All SAEs occurring from the time ICF is signed through 28 days after the last dose must be reported to Clinical Safety within 24 hours of knowledge of the event. All SAEs that the Investigator considers related to study drug occurring after the 28-day

Optional Crossover Treatment (for Patients Crossing Over from Arm B to Arm A)

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			
Evaluation	CO-Screening	CO-Cycle 1		CO-Cycles 2-6	CO-Cycle 7+	CO-EOT	CO-SFU	CO-LTFU	
Visit Window	Up to 42 days	Day 1	Day 8 (±3 days)	Day 1 (± 7 days)	Day 1 (± 7 days)	+14 days of last dose or decision to terminate treatment	28 days (+ 7 days) after last dose or decision to terminate treatment	Q12W for up to 2 years after last dose Q24W beyond 2 years for patients who discontinue prior to PD (± 4 weeks)	Instructions
									follow-up period must be reported to the Sponsor • Second primary malignancy (SPM) events are to be reported and should continue to be reported for up to 5 years from the start of pirtobrutinib treatment, regardless of seriousness or causal attribution to pirtobrutinib treatment
Survival status		X	X	X	X	X	X	X	• Survival information may be collected via telephone if no procedures are required; survival information should be collected approximately Q24W after the SFU visit; refer to Section 6.7.5 • Subsequent anticancer therapy information should be collected Q24W after the SFU visit until death or study completion

10.9.3.8. Protocol Section 1.3.5 Schedule of Assessments for Response Assessments, Arms A and B (Does Not Apply for Crossover)

[Revised the "NOTE," as shown.]

NOTE: This section is a guide to specify elements required for response assessment without duplicating activities in the SoAs above. Assessments should include disease and symptom-~~focused~~ directed physical examination, imaging, and hematology results and bone marrow examinations as described in iwCLL 2018.

[Revised the SoA rows for bone marrow CCI biopsy, CT or MRI, physical examination, and hematology. Only the heading rows and rows containing revisions are shown below.]

Response Assessments, Arms A and B (Does Not Apply for Crossover)						
Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**	**Post-Study Treatment Discontinuation**			**Instructions**
Evaluation	**Screening**	**Cycle 1 +**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1 (± 7 Days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q12W (± 4 weeks)** for up to 2 years after last dose, **Q24W (± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	
Bone marrow CCI biopsy	X	Within 4-8 weeks of confirmed CR by scan and peripheral blood assessment~~. Optional~~ (optional) and to confirm PD (required)				• CCI biopsy CCI required at Screening and for confirmation of CR CCI
CT or MRI	X	C4D1, C7D1, and Q12W thereafter	X		X	• Refer to Section 8.3.1 for details • CT scan with IV contrast agent is the preferred method of assessment with scans of neck, chest, abdomen, and pelvis. However, MRI is acceptable if CT scan with contrast agent is contraindicated • All response assessments should occur at Q12W intervals relative to C1D1 regardless of any treatment delays or interruptions • At the EOT visit, a repeat CT/MRI does not need to be performed if done within the proceeding 2 weeks or if PD was previously determined

Response Assessments, Arms A and B (Does Not Apply for Crossover)						
Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**	**Post-Study Treatment Discontinuation**			**Instructions**
Evaluation	**Screening**	**Cycle 1 +**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1 (± 7 Days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q12W (± 4 weeks)** for up to 2 years after last dose, **Q24W (± 4 weeks)** beyond 2 years for patients who discontinue prior to PD	
						• A central radiology vendor will be used to collect and store images for IRC review
Physical Examination	X	C4D1, C7D1, and Q12W thereafter	X		X	• Complete PE includes height (only at Screening), weight, basic neurological examination, and review of relevant symptoms at Screening; refer to Section 8.4.2 • Symptom-directed PE should be limited to systems of primary relevance such as cardiovascular, respiratory, those associated with symptoms, and those associated with tumor assessment (lymph nodes, liver, and spleen) and may be performed at other timepoints; include weight as clinically indicated throughout the trial
Hematology	X	C4D1, C7D1, and Q12W thereafter	X		X	• Includes hemoglobin, hematocrit, RBC count, WBC count, platelet count, percent or absolute differential (neutrophils, lymphocytes, eosinophils, basophils, and monocytes) • Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results • Repeat testing during Screening is permitted; refer to Section 5.5 • On days when hematology is required for both safety and response assessments, samples should also be submitted to the central laboratory

10.9.4. France

This addendum includes all revisions to the current global protocol based on feedback from the French Regulatory Authority and as outlined in the France Addendum 5.0. France-specific changes to the global protocol are presented below.

10.9.4.1. Protocol Section 5.1 Inclusion Criteria

[Added new Inclusion Criterion 5 as shown. Revised numbering of Inclusion Criteria 5 through 10 (now numbered as 6 through 11).]

5. Patients with 17p deletion must have received prior venetoclax or be ineligible for treatment with venetoclax.

[Revised sentence 1 of Inclusion Criterion 11 as shown.]

11. Willingness of men and women of childbearing potential (WOCBP), and their partners, to both observe ~~barrier and/or~~ highly effective birth control methods as outlined in Protocol Section 10.2 (Protocol Appendix 2~~ and below~~) for the duration of treatment and for 6 months following the last dose of study treatment or 12 months after the last dose of rituximab, whichever is later.

10.9.4.2. Protocol Section 5.2 Exclusion Criteria

[Added new Exclusion Criterion 24 as shown. Revised numbering of Exclusion Criteria 24 and 25 (now numbered as 25 and 26).]

24. Patients who have been pretreated with IdelaR or BR and had either documented PD as determined by the Investigator, or could not tolerate the regimen, should not be retreated with the same regimen.

[Added new Exclusion Criteria 27 and 28 as shown.]

27. Patients with progressive multifocal leukoencephalopathy (PML) or history thereof.

28. Patients with medical conditions which, at the Investigator's discretion, would preclude the use of both comparator treatments.

10.9.4.3. Protocol Section 6.6.1 Dose Modifications and Toxicity Management Guidelines for Arm A: Pirtobrutinib

[Revised Table 6.3 heading row and "First occurrence" row as shown.]

Adverse Events	Occurrences Requiring Dose Modification	~~ARM A (Pirtobrutinib) Dose Modification~~ (Starting dose 200 mg QD)	ARM A (Pirtobrutinib) Modification / Instructions
• Grade 3 or greater non-hematologic toxicity [a], • Grade 3 neutropenia with fever and/or infection, • Grade 4 neutropenia lasting ≥ 7 days, • Grade 3 thrombocytopenia with bleeding, or • Grade 4 thrombocytopenia	**First occurrence**	No change	Hold pirtobrutinib until recovery to Grade 1 or baseline; may ~~restart at original~~ reduce by a dose level (~~200~~ to 100 mg QD)
	Second occurrence	100 mg QD	Hold pirtobrutinib until recovery to Grade 1 or baseline; may restart at one dose level lower (100 mg QD) [b]
	Third occurrence	50 mg QD	Hold pirtobrutinib until recovery to Grade 1 or baseline; may restart at one dose level lower (50 mg QD)
	Fourth occurrence	Discontinue	Discontinue

[a] For patients with abnormal baseline liver function, pirtobrutinib dose interruption and modification recommendations should be implemented if patients experience an increase of ≥ 3× baseline AST or ALT, or an AST or ALT increase of ≥ 2× baseline with concurrent total bilirubin ≥ 2× ULN.

[b] If dose was reduced at first occurrence, reduce by an additional dose level if subsequent events occur.

10.9.4.4. Protocol Section 10.2 Appendix 2: Contraceptive Guidance and Pregnancy Information

[Revised paragraph 1 sentence 1 as shown.]

Willingness of men and WOCBP, and their partners, to observe ~~barrier and/or~~ highly effective birth control methods as outlined below for the duration of treatment and for 6 months following the last dose of study treatment or 12 months after the last dose of rituximab, whichever is later.

10.9.4.5. Protocol Section 1.3.1 Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy

[Revised the row for bone marrow CCI biopsy; only the heading rows and the row containing revisions are shown below.]

Arm A: Pirtobrutinib Monotherapy									
Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**				**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1**		**Cycles 2-6**	**Cycle 7 +**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 8 (± 3 days)**	**Day 1 (± 7 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	Q12W (**± 4 weeks**) for up to 2 years after last dose, Q24W (**± 4 weeks**) beyond 2 years for patients who discontinue prior to PD	**Instructions**
Bone marrow CCI biopsy	X			Within 4-8 weeks of confirmed CR by scan and peripheral blood assessment~~.~~ ~~Optional~~ (required) and ~~Optional~~ to confirm PD (optional)					• CCI biopsy CCI required at Screening and for confirmation of CR CCI

10.9.4.6. Protocol Section 1.3.2 Schedule of Assessments for Arm B: Idelalisib plus Rituximab

[Added a row for triglycerides; revised the row for bone marrow CCI biopsy; only the heading rows and the rows containing revisions are shown below.]

Arm B: Idelalisib plus Rituximab (IdelaR)												
Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**							**Post-Study Treatment Discontinuation**			
Evaluation	**Screening**	**Cycle 1**		**Cycle 2**		**Cycles 3-6**		**Cycle 7+**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 3 days)**	**Day 15 (± 3 days)**	**Day 1 (± 7 days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q12W (± 4 weeks)** for up to 2 years after last dose, Q24W (± **4 weeks**) beyond 2 years for patients who discontinue prior to PD	**Instructions**
Triglycerides		X		X		X		X	X	X		• On C1D1, testing must occur predose since this will be used as the baseline value for monitoring
Bone marrow CCI biopsy	X					Within 4-8 weeks of confirmed CR by scan and peripheral blood assessment~~. Optional~~ (required) and ~~Optional~~ to confirm PD (optional)						• CCI biopsy CCI required at Screening and for confirmation of CR CCI

10.9.4.7. Protocol Section 1.3.4 Schedule of Assessments for Optional Crossover Treatment (for Patients Crossing Over from Arm B to Arm A)

[Revised the row for CT or MRI, and the row for survival status, as shown; only the heading rows and rows containing revisions are shown below.]

Optional Crossover Treatment (for Patients Crossing Over from Arm B to Arm A)							
Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**		**Post-Study Treatment Discontinuation**			
Evaluation	**CO-Screening**	**CO-Cycle 1**	**CO-Cycle 4 and higher**	**CO-EOT**	**CO-SFU**	**CO-LTFU**	
Visit Window	**Up to 42 days**	**Day 1**	**± 14 Days**	**+14 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	**Q24W (± 4 weeks)**	**Instructions**
CT or MRI	X		CO-C7D1 and Q24W thereafter	X		~~X~~ Q24W for up to 2 years after last dose Q24W beyond 2 years	• Refer to Section 8.1 for details. • If baseline CT or MRI assessment documenting PD by IRC was performed within 42 days of planned C1D1, a new scan does not need to be obtained • All response assessments should occur at Q24W intervals relative to CO-C1D1, regardless of any treatment delays or interruptions • At the EOT visit, a repeat CT/MRI does not need to be performed if done within the proceeding 2 weeks or if PD was previously determined • Investigator assessment of CT or MRI will be done locally at frequency of at least Q24W frequency or based on standard of care
Survival status		X	X	X	X	~~X~~ Q24W for up to 2 years after last dose Q24W beyond 2 years	• Survival information may be collected via telephone if no procedures are required; survival information should be collected approximately Q24W after the SFU visit; refer to Section 6.7.5 • Subsequent anticancer therapy information should be collected Q24W ~~after~~ from the end of SFU ~~visit~~ for the first 2 years after discontinuation from study treatment and approximately Q24W thereafter until death or study completion

10.9.4.8. Protocol Section 1.3.5 Schedule of Assessments for Response Assessments, Arms A and B (Does Not Apply for Crossover)

[Revised the row for bone marrow CCI biopsy; only the heading rows and the row containing revisions are shown below.]

Response Assessments, Arms A and B (Does Not Apply for Crossover)						
Study Period	**Baseline**	**Study Treatment (Cycle = 28 days)**	**Post-Study Treatment Discontinuation**			**Instructions**
Evaluation	**Screening**	**Cycle 1 +**	**EOT**	**SFU**	**LTFU**	
Visit Window	**Up to 28 days**	**Day 1 (± 7 Days)**	**+ 7 days** of last dose or decision to terminate treatment	**28 days (+ 7 days)** after last dose or decision to terminate treatment	Q12W (± **4 weeks)** for up to 2 years after last dose, Q24W (± **4 weeks)** beyond 2 years for patients who discontinue prior to PD	
Bone marrow CCI biopsy	X	Within 4-8 weeks of confirmed CR by scan and peripheral blood assessment~~.~~ ~~Optional~~ (required) and to confirm PD (optional)				• CCI biopsy CCI required at Screening and for confirmation of CR CCI

10.10. Appendix 10: Exceptional Circumstances: Provisions for Changes in Study Conduct During Exceptional Circumstances

10.10.1. Purpose for Appendix

This appendix includes specific changes to the global protocol that are allowed under exceptional circumstances as outlined in Protocol Addendum 3.0 and as presented below.

Implementation of this Appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the Sponsor in partnership with the Investigator.

Exceptional Circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the Investigators, patients, or both to attend onsite visits or to conduct planned study procedures.

Implementing Changes under Exceptional Circumstances

In an exceptional circumstance, after receiving the Sponsor's written approval, sites may implement changes if permitted by local regulations.

IRBs/IECs, regulatory bodies and any other relevant local authorities, as required, will be notified as early as possible to communicate implementation of changes in study conduct due to exceptional circumstances. To protect the safety of study patients, urgent changes may be implemented before such communications are made, but all changes will be reported as soon as possible following implementation. If approval by IRBs/IECs, regulatory bodies, or both is required per local regulations, confirmation of this approval will be retained in the study records.

In the event written approval is granted by the Sponsor for changes in study conduct, additional written guidance, if needed, will be provided by the Sponsor.

Considerations for Making a Change

The prevailing consideration for making a change is ensuring the safety of study patients. Additional important considerations for making a change are compliance with GCP, enabling patients to continue safely in the study and maintaining the integrity of the study. The allowances made herein have taken into consideration the risk:benefit of the patient population with regard to their study disease diagnosis and presumed impact that these changes would have on patient safety and study integrity.

Informed Consent

Additional consent from the patient will be obtained, if required, for:

- Participation in remote visits, as defined in Section "Remote Visits,"
- A change in the method, location, or both, of study intervention administration,
- Dispensation of additional study intervention during an extended treatment period,

- Alternate delivery of study intervention and ancillary supplies, and
- Provision of their personal or medical information required prior to implementation of these activities.

10.10.2. Specific Changes to this Protocol

This is the Exceptional Circumstance Addendum to Protocol LOXO-BTK-20020. The purpose of this addendum is to allow temporary flexibility in study visits, assessments, and study drug dispensation as a result of the COVID-19 pandemic or other exceptional circumstances.

Changes in Study Conduct During Exceptional Circumstances

Changes in study conduct not described in this addendum, or not consistent with applicable local regulations, are not allowed.

The changes in study conduct that are discussed within this addendum will not be considered protocol deviations.

10.10.2.1. Remote Visits

In source documents and the electronic Case Report Form (eCRF), the study site should capture the visit location and method, with a specific explanation that includes the term "COVID-19 related" (when applicable) for any data missing because of missed in-person site visits.

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to, concomitant medications, review of systems, Eastern Cooperative Oncology Group (ECOG) performance status, dosing information, patient-reported outcome measures, and information regarding local healthcare utilization/hospitalization.

Mobile healthcare: Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when patients cannot travel to the site due to an exceptional circumstance, if written approval is provided by the Sponsor. Procedures performed at such visits include, but are not limited to, review of systems, physical exams, and laboratory studies (e.g., hematology, chemistry, etc.).

Other alternative locations: Other procedures that may be done at an alternate location in exceptional circumstances include, but are not limited to, review of systems, physical exam, ECG tracings, laboratory studies (e.g., hematology, chemistry), and radiologic imaging.

- Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of adverse events (AEs), serious adverse events (SAEs), and product complaints remain unchanged. Furthermore, every effort should be made to enable patients to return to onsite visits as soon as reasonably possible, while ensuring the safety of both the patients and the site staff.

10.10.2.2. Local Laboratory Testing Option

Local laboratory testing may be conducted in lieu of central laboratory testing (refer to Appendix Section 10.10.4). The local laboratory must be qualified in accordance with applicable local regulations.

10.10.2.3. Study Intervention, Ancillary Supplies, and Patient Diaries

When a patient is unable to go to the site to receive study supplies during normal onsite visits, the site should work with the Sponsor to determine appropriate actions. These actions may include:

- Asking the patient to go to the site and receive study supplies from site staff without completion of a full study visit,
- Asking the patient's designee to go to the site and receive study supplies on a patient's behalf, and
- Arranging delivery of study supplies

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of patient's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, patient's home), the Investigator, Sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the patient or designee on the final disposition of any unused or completed study supplies.

10.10.3. Documentation

In source documents, the site should document the patient's verbal understanding and agreement for having visits at an alternative location due to exceptional circumstances. Additionally, the study site should capture in source documents both the alternative visit location and method. Any local laboratory or imaging/diagnostic center used for sample or data collection should comply with local regulations.

Changes to study conduct must be documented as follows:

- Sites will identify and document within source records the details of how patients, visit types, and conducted activities were affected by exceptional circumstances.
- Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source documents generated at a location other than the study site should be part of the Investigator's source documentation and should be transferred to the site in a secure and timely manner.

10.10.4. Tabular Summary of Changes in this Appendix

Visit or Assessment	Protocol	Protocol Addendum 3.0
Study visits	Performed in-person at study site	May be conducted at other (local) healthcare facilities, by home visits or telemedicine (except Screening, C1D1 for patients on Arm A, Cycles 1-6 for patients on Arm B, and crossover [CO]-C1D1).
Physical examination, vital signs, and ECOG PS	Performed at study site during every study visit	After Screening, should be performed at least every other cycle through C7D1. May be conducted at remote (local) healthcare facilities. Home blood pressure, heart rate and temperature monitoring may be performed.
ECGs	Performed at study site at Screening, then as listed on Schedules of Assessments (SoAs) (Section 1.3)	May be conducted at remote (local) healthcare facilities. Patient may take study drug at home and await dose-timed electrocardiogram (ECG) capture to reduce time in clinic.
Blood draws	Performed at study site at Screening, then as listed on SoAs (Section 1.3)	May be conducted at remote (local) or commercial laboratories (except at C1D1 for patients on Arm A, Cycles 1-6 for patients on Arm B, and CO-C1D1).
Serum or urine pregnancy tests (WOCBP only)	Performed at study site at Screening, then as listed on SoAs (Section 1.3)	May be conducted at remote (local) or commercial laboratories.
Urinalysis	Performed at study site at Screening, then as listed on SoAs (Section 1.3)	May be conducted at remote (local) or commercial laboratories at Screening, then may be performed as clinically indicated.
Bone marrow CCI **biopsy**	Collected at study site Screening, at visit days listed on SoAs (Section 1.3), and at End of Treatment (EOT)	Inability to obtain EOT post-progression tumor sample(s) will not be considered a protocol deviation.
CT or MRI radiological imaging	Performed at study site at visit days listed on SoAs (Section 1.3)	May be conducted at remote (local) healthcare facilities at visit days listed on SoAs (Protocol Section 1.3), with provision of ability to provide images to central imaging vendor.
CCI		

Visit or Assessment	Protocol	Protocol Addendum 3.0
Dispense study drug (oral agents only)	No more than 1 cycle is dispensed at study site for Arm A and Arm B patients	May be shipped directly to patients, and more than 1 cycle may be dispensed at a time with Sponsor approval. Note: It is the Investigator's responsibility to determine if the patient is deemed medically fit to receive more than 1 cycle of study drug at a time and/or if drug should be shipped directly to the patient. Once this is determined by the Investigator, sites still need to seek Sponsor approval for the shipment of study drug directly to the patient.

10.10.5. Changes in Protocol Section 1.3: Schedule of Assessments

Visits and assessments may be changed as outlined above in Appendix Section 10.10.2. Additional guidance is provided for remote visits (Appendix Section 10.10.2.1), local laboratory testing (Appendix Section 10.10.2.2), and study intervention and supplies (Appendix Section 10.10.2.3). Changes to study conduct should be documented as described in Appendix Section 10.10.3.

11. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85(5):365-76. doi:10.1093/jnci/85.5.365

Barr PM, Brown JR, Hillmen P, et al. Impact of ibrutinib dose adherence on therapeutic efficacy in patients with previously treated CLL/SLL. *Blood*. 2017;129(19):2612-2615.

Bergmann MA, Goebeler ME, Herold M, et al. Results of a phase I/II study of the German CLL Study Group. *Haematologica*. 2005;90(10):1357-1364.

Bonfiglio S, Scarfo L, Gaidano G, et al. Half of chronic lymphocytic leukemia patients relapsing under ibrutinib carry Btk and Plcg2 mutations: A European Research Initiative On Cll (Eric) Real-World Study. European Hematology Association Anuual Meeting 2018 Abstract LB 2601.

Brandhuber B, Gomez E, Smith S, et al. LOXO-305, a next generation reversible BTK inhibitor, for overcoming acquired resistance to irreversible BTK inhibitors. *Clin Lymphoma Myeloma Leuk*. 2018;18: S216.

Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373:2425-2437. doi:10.1056/NEJMoa1509388

Burger JA. Treatment of Chronic Lymphocytic Leukemia. *N Engl J Med.* 2020;383:460-473. doi:10.1056/NEJMra1908213

Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2013;369(1):34-42.

Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016;374(4): 323-332.

Chang BY, Francesco M, De Rooij MFM, et al. Egress of CD191CD51 cells into peripheral blood following treatment with the Bruton tyrosine kinase inhibitor ibrutinib in mantle cell lymphoma patients. *Blood*. 2013;122(14):2412-2424.

Cheson BD, Brugger W, Damaj G, et al. Optimal use of bendamustine in hematologic disorders: treatment recommendations from an International Consensus Panel - An update. *Leuk Lymphoma.* 2016;57(4):766-782.

Cheson BD, Byrd JC, Rai KR et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. *J Clin Oncol.* 2012;30(23):2820-2822.

Chiron D, Di Liberto M, Martin P, et al. Cell-cycle reprogramming for PI3K inhibition overrides a relapse-specific C481S BTK mutation revealed by longitudinal functional genomics in mantle cell lymphoma. *Cancer Discov*. 2014;4(9):1022-1035.

Clinical Trial Facilitation Group (Heads of Medicines Agencies). Recommendations related to contraception and pregnancy testing in clinical trials. 2020; 1.1

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16(1):31-41.

Cuneo A, Follows G, Rigolin GM, et al. Efficacy of bendamustine and rituximab as first salvage treatment in chronic lymphocytic leukemia and indirect comparison with ibrutinib: a GIMEMA, ERIC and UK CLL FORUM study. *Haematologica*. 2018;103(7):1209-1217.

Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2015;26(suppl 5):78-84.

Flinn IW, Hillmen P, Montillo M, et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. *Blood*. 2018;132(23):2446–2455. doi:0.1182/blood-2018-05-850461

Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med*. 2019;380(23): 2225-2236.

Fischer, K, Cramer P, Busch R, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: A multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *J Clin Oncol*. 2011;10;29(26):3559-3566.

Fischer K, Stilgenbauer S, Schweighofer CD, et al. Bendamustine in combination with rituximab (BR) for patients with relapsed chronic lymphocytic leukemia (CLL): A Multicentre Phase II Trial of the German CLL Study Group (GCLLSG). *Blood*. 2008;112(11):330. doi:10.1182/blood.V112.11.330.330

Fraser G, Cramer P, Demirkan F, et al. Updated results from the phase 3 HELIOS study of ibrutinib, bendamustine, and rituximab in relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma. *Leukemia*. 2019;33:969-980. doi:10.1038/s41375-018-0276-9

Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N *Engl J Med.* 2014;370:997-1007.

Hallek, M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018;131(25): 2745-2760.

Hendriks RW, Bredius RG, Pike-Overzet K, Staal FJ. Biology and novel treatment options for XLA, the most common monogenetic immunodeficiency in man. *Expert Opin Ther Targets*. 2011;15(8):1003-1021.

Herishanu Y, Avivi I, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. *Blood*. 2021;137(23):3165-3173. doi:10.1182/blood.2021011568.

Herman SE, Gordon AL, Hertlein A, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765. *Blood*. 2011;117(23)6287-6296.

Hillmen P, Rawstron AC, Brock K, et al. Ibrutinib plus venetoclax in relapsed/refractory chronic lymphocytic leukemia: The CLARITY study. *J Clin Oncol*. 2019;37(30);2722-2729.

Howlader N, Noone AM, Krapcho M, at al. SEER Cancer Statistics Review, 1975-2017, National Cancer Institute. Bethesda, MD. https://seer.cancer.gov/csr/1975_2017/, based on November 2019 SEER data submission, posted to the SEER website, April 2020.

Jain P, Keating M, Wierda W, et al. Outcomes of patients with chronic lymphocytic leukemia after discontinuing ibrutinib. *Blood*. 2015;125:2062-2067.

Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res*. 2013;22(7):1717-1727.

Kamel S, Horton L, Ysebaert L, et al. Ibrutinib inhibits collagen-mediated but not ADP-mediated platelet aggregation. *Leukemia*. 2015;29(4): 783-787.

Kater AP, Hillmen P, Eichhorst B, et al. First prospective data on impact of minimal residual disease on long-term clinical outcomes after venetoclax plus rituximab versus bendamustine plus rituximab: Phase III MURANO Study. Presented at: ASH Annual Meeting and Exposition; December 4-8, 2018; San Diego, California. Abstract 695.

Kil LP, de Bruijn MJ, van Hulst JA, Langerak AW, Yuvaraj S, and Hendriks RW. Bruton's tyrosine kinase mediated signaling enhances leukemogenesis in a mouse model for chronic lymphocytic leukemia. *Am J Blood Res*. 2013;3(1):71-83.

Lehman CD, Lamb LR, D'Alessandro HA. Mitigating the impact of coronavirus disease (COVID-19) vaccinations on patients undergoing breast imaging examinations: A pragmatic approach. *Am J Roentgenol*. 2021; 217:1–3. doi.org/10.2214/AJR.21.25688

Mato AR, Shah NN, Jurczak W, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. *Lancet*. 2021;397(10277):892-901. doi: 10.1016/S0140-6736(21)00224-5

Mato AR, Hill BT, Lamanna N, et al. Optimal sequencing of ibrutinib, idelalisib, and venetoclax in chronic lymphocytic leukemia: results from a multicenter study of 683 patients. *Ann Oncol*. 2017;28(5):1050-1056.

Mato AR, Nabhan C, Barr PM, et al. Outcomes of CLL patients treated with sequential kinase inhibitor therapy: a real world experience. *Blood*. 2016;128:2199-2205.

Mato A, Sail K, Yazdy MS, et al. Treatment sequences and outcomes of patients with CLL treated with venetoclax and other novel agents post introduction of novel therapies. Presented at: 61st American Society of Hematology (ASH) Annual Meeting and Exposition 2019; Abstract 1756.

Mato AR, Schuster SJ, Lamanna N, et al. A phase 2 study to assess the safety and efficacy of umbralisib (TGR-1202) in patients with chronic lymphocytic leukemia (CLL) who are intolerant to prior BTK or PI3K Delta inhibitor therapy. European Hematology Association Annual Meeting 2018;Abstract S808.

McMullen JR, Boey EJ, Ooi JY, Seymour JF, Keating MJ, Tam CS. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. *Blood*. 2014;124(25):3829-3830.

Patton DT, Garden OA, Pearce WP, et al. Cutting edge: The phosphoinositide 3-kinase p110δ is critical for the function of CD4+CD25+Foxp3+ regulatory T cells. *J Immunol.* 2006;177(10):6598-6602.

Pound HB, Ho VQ, Bello CM, et al. Bendamustine and rituximab for the treatment of chronic lymphocytic leukemia: The Moffitt Cancer Center Experience. *Blood*. 2011;118(21):4620.

Rawlings DJ, Saffran DC, Tsukada S, et al. Mutation of unique region of Bruton's tyrosine kinase in immunodeficient XID mice. *Science*. 1993;261(5119): 358-361.

Rituxan® (rituximab), United States Prescribing Information, Biogen Idec Inc. and Genentech Inc. 2010, for injection for intravenous use: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103705s5311lbl.pdf

Biosimilar to Rituxan® (rituximab): TRUXIMA® (rituximab-abbs), United States Prescribing Information, Teva Pharmaceuticals USA, Inc, 2018; injection, for intravenous use: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761088s000lbl.pdf

Biosimilar to Rituxan® (rituximab): RUXIENCE™ (rituximab-pvvr), United States Prescribing Information, Pfizer Biosimilars, 2019; injection, for intravenous use: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761103s000lbl.pdf

Biosimilar to Rituxan® (rituximab): RIABNI™ (rituximab-arrx), United States Prescribing Information, Amgen, Inc., 2020; injection, for intravenous use: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761140s000lbl.pdf

Sant M, Allemani C, Tereanu C, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE Project. *Blood*. 2010;116(19):3724-34.

Seymour JF, Kipps TJ, Eichhorst B. Venetoclax–rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med*. 2018;378:1107-1120.

Schenkel B, Rider A, Macomson B, Hallworth P. Real-world treatment patterns and characteristics in patients with chronic lymphocytic leukemia. *J Clin Oncol*. 2017;35(8):65-65.

Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib–rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med*. 2019;381:432-443.

Sharman JP; Coutre SE; Furman RR; Final results of a randomized, phase III study of rituximab with or without idelalisib followed by open-label idelalisib in patients with relapsed chronic lymphocytic leukemia. *J Clin Oncol*. 2019;37(16)1391-1402.

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA*. 2020;70(1)7-30. https://doi.org/10.3322/caac.21590.

Tam C, Grigg AP, Opat S, et al. The BTK inhibitor, Bgb-3111, is safe, tolerable, and highly active in patients with relapsed/refractory B-cell malignancies: Initial report of a phase 1 first-in-human trial. *Blood*. 2015;126(23):832-883.

Thomas JD, Sideras P, Smith CI, Vorechovsky I, Chapman V, Paul WE. Colocalization of X-linked agammaglobulinemia and X-linked immunodeficiency genes. *Science*. 1993;261(5119): 355-358.

Treanda® (bendamustine), United States Prescribing Information, Cephalon Inc. 2008, for (bendamustine hydrochloride) for injection, for intravenous infusion: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/022303lbl.pdf

Tu W, Gierada DS, Joe BN. COVID-19 vaccination-related lymphadenopathy: What to be aware of. *Radiology: Imaging Cancer*. 2021;3(3). doi.org/10.1148/rycan.2021210038.

Turtle CJ, Hay KA, Hanafi L-A, et al. Durable molecular remissions in chronic lymphocytic leukemia treated with CD19-specific chimeric antigen receptor–modified T cells after failure of ibrutinib. *J Clin Oncol*. 2017;35(26):3010-3020.

Vetrie DI, Vorechovsky P, Sideras J, et al. The gene involved in X-linked agammaglobulinaemia is a member of the src family of protein-tyrosine kinases. *Nature*. 1993;361(6409):226-233.

Watson L, Wyld P, Catovsky D. Disease burden of chronic lymphocytic leukaemia within the european union. *Eur J Haematol*. 2008;81(4):253-258.

WHO: 2014 Review of Cancer Medicines on the World Health Organization [WHO] List of Essential Medicines.
https://www.who.int/selection_medicines/committees/expert/20/applications/CLL.pdf

Wierda WG, Byrd JC, Abramson JS, et al. Chronic lymphocytic leukemia/small lymphocytic lymphoma, Version 4, NCCN Clinical Practice Guidelines in Oncology. JNCCN 2020;18(2):185-217.

Woyach JA, Ruppert AS, Guinn D, et al. BTK(C481S-mediated resistance to ibrutinib in chronic lymphocytic leukemia. *J Clin Oncol*. 2017; 35(13): 1437-1443.

Woyach, JA, Ruppert AS, Heerema D, Zhao W, Booth J, Ding AM, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. *N Engl J Med*. 2018;379(26):2517-2528.

Woyach JA, Huang Y, Rogers K., et al. Resistance to acalabrutinib in CLL is mediated primarily by BTK mutations. *Blood*. 2019;134(Supplement_1):504.

Xu L, Tsakmaklis N, Yang G, et al. Acquired mutations associated with ibrutinib resistance in Waldenstrom macroglobulinemia. *Blood*. 2017;129(18): 2519-2525.

Yang G, Zhou Y, Liu X, et al. A mutation in MYD88 (L265P) supports the survival of lymphoplasmacytic cells by activation of Bruton tyrosine kinase in Waldenström macroglobulinemia. *Blood*. 2013;122(7): 1222-1232.

Zydelig® (idelalisib), United States Prescribing Information, Gilead Sciences Inc. Approved 2014, Revised 2020, Revised 2022, for (idelalisib) tablets, for oral use: https://www.gilead.com/-/media/files/pdfs/medicines/oncology/zydelig/zydelig_pi.pdf.

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