CLINICAL PROTOCOL LOXO-BTK-20019

A Phase 3 Open-Label, Randomized Study of LOXO-305 versus Investigator Choice of BTK Inhibitor in Patients with Previously Treated BTK Inhibitor Naïve Mantle Cell Lymphoma (BRUIN-MCL-321)

Investigational Product:	LOXO-305
Protocol Number:	LOXO-BTK-20019
Development Phase:	3
IND #:	139876
EudraCT#:	
Sponsor:	Loxo Oncology, Inc. 281 Tresser Boulevard Stamford, CT 06901
Current Version 1.0	XX XXX XXXX

PROTOCOL APPROVAL PAGE

Protocol Title:	A Phase 3 Open-Label, Randomized Study of LOXO-305 versus Investigator Choice of BTK Inhibitor in Patients with Previously Treated BTK Inhibitor Naïve Mantle Cell Lymphoma (BRUIN-MCL-321)
Protocol Number:	LOXO-BTK-20019
Current Version 1.0	XX X XXXX

The current version of the protocol has been reviewed and approved

_____ _____

Jennifer Kherani, MD Date
Medical Monitor

I have carefully read Protocol LOXO-BTK-20019 entitled "A Phase 3 Open-Label, Randomized Study of LOXO-305 versus Investigator Choice of BTK Inhibitor in Patients with Previously Treated BTK Inhibitor Naïve Mantle Cell Lymphoma (BRUIN-MCL-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 any presentation or publication of study data will be reviewed by Loxo Oncology before release.

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Principal Investigator's Signature Date

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Print Principal Investigator's Name

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A Phase 3 Open-Label, Randomized Study of LOXO-305 versus Investigator Choice of BTK Inhibitor in Patients with Previously Treated BTK Inhibitor Naïve Mantle Cell Lymphoma (BRUIN-MCL-321)

Short Title:

A Phase 3 Trial of LOXO-305 versus Investigator Choice of BTK inhibitor in Previously Treated Mantle Cell Lymphoma

Rationale:

Mantle Cell Lymphoma (MCL) is a rare and aggressive subtype of non-Hodgkin lymphoma (NHL). Young and fit patients typically receive induction chemoimmunotherapy (CIT), followed by high-dose chemotherapy with autologous stem cell salvage, and finally rituximab maintenance. In transplant ineligible patients, induction CIT followed by rituximab maintenance is an accepted alternate approach. Ultimately, none of these approaches are considered curative, and relapse is nearly universal (Dreyling et al. 2017; Lenz et al. 2005; Flinn et al. 2014).

Ibrutinib has received approval in several countries, with additional covalent Bruton's tyrosine kinase (BTK) inhibitors, acalabrutinib and zanubrutinib also approved in select countries, as salvage therapy for patients progressing following upfront CIT, with or without transplant. A pooled analysis from three ibrutinib studies in previously treated MCL involving 370 patients with relapsed MCL reported a mature median progression-free survival (PFS) of 12.5 months (Rule et al. 2019). Comparable outcomes have been reported with the other covalent BTK inhibitors (Song et al 2019, Tam et al. 2019, Wang et al. 2018). The lack of comparative data between these BTK inhibitors is a key evidence gap.

LOXO-305 is an orally available, highly selective, ATP-competitive inhibitor of BTK. LOXO-305 has single digit nanomolar inhibitory activity against wildtype BTK. LOXO-305 is distinct from the approved BTK inhibitors (ibrutinib, acalabrutinib, and zanubrutinib) in several important ways including on the basis of its selectivity, favorable pharmacokinetic (PK) and pharmacologic properties, and non-covalent binding mode (Brandhuber et al. 2018). These features enable LOXO-305 to achieve PK exposures that exceed the BTK IC_{90} at trough and thus deliver tonic BTK target inhibition throughout the dosing period, regardless of the intrinsic rate of BTK turnover. LOXO-305 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.

In a Phase 1/2 study (LOXO-BTK-18001, NCT03740529), LOXO-305 has demonstrated robust and durable anti-tumor activity against a variety of B-cell malignancies including MCL and particularly in patients with previously treated MCL who have received a prior BTK inhibitor. These results provide a basis to believe that the efficacy of LOXO-305 monotherapy in BTK inhibitor naïve, chemotherapy-treated patients should compare favorably with that achieved with existing covalent inhibitors. Given this, the sponsor believes a head to head BTK inhibitor study is warranted. By providing physician-choice for a comparative study, this design consideration should ensure feasibility and broad applicability of the results.

This global study, LOXO-BTK-20019 (BRUIN-MCL-321), will be conducted in patients with pretreated MCL patients who have not received a prior BTK inhibitor and will compare the efficacy and safety of LOXO-305 administered as a continuous monotherapy with investigator choice of continuously administered monotherapy with an approved covalent BTK inhibitor (ibrutinib, acalabrutinib, or zanubrutinib). The study will be conducted globally and investigator's choice of BTK (ICB) options in each country will be based on local availability.

This study will generate important data characterizing the differences in safety, tolerability, and efficacy between LOXO-305 and covalent BTK inhibitors in this patient population.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare progression-free survival (PFS) of LOXO-305 as monotherapy (Arm A) to investigator choice of covalent BTK inhibitor monotherapy (Arm B) in patients with previously treated mantle cell lymphoma (MCL)	Assessed by independent review committee (IRC) • PFS per Lugano criteria
Secondary	
• To compare efficacy of LOXO-305 as monotherapy (Arm A) to investigator choice of covalent BTK inhibitor monotherapy (Arm B) treatment arms	Assessed by both investigator assessment and IRC • overall response rate (ORR) per Lugano criteria • duration of response (DOR) per Lugano criteria Assessed by investigator assessment: • PFS per Lugano criteria • overall survival (OS) • 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 MCL or withdrawal from trial due to toxicity or death, whichever occurs first. • time to treatment failure (TTF), defined as a composite endpoint measuring time from randomization to time when discontinuation criteria met (Section 7). • time to next treatment (TTNT), defined as time from the date of randomization to the date of the next non-protocol-specified therapy for MCL.

Objectives	Endpoints
• To evaluate the safety and tolerability of each treatment arm	• incidence and severity of SAEs, AEs, deaths, and clinical laboratory abnormalities per CTCAE v5.0
• To evaluate the patient-reported outcomes	• comparative tolerability: proportion of time with high side-effect burden • time to worsening (TTW) of MCL-related symptoms

Overall Design

BRUIN-MCL-321 is a Phase 3, global, multicenter, randomized open label study comparing LOXO-305 as continuous monotherapy (Arm A) with investigator's choice of BTK inhibitor monotherapy (Arm B) in patients with previously treated mantle cell lymphoma.

BRUIN-MCL-321 will enroll adult patients with MCL who have previously received any number of prior lines of therapy but must not have been treated with a BTK inhibitor, approved or investigational. Sequential therapy combinations are defined as one line unless separated by disease progression or by a ≥ 6 month treatment free interval. Patients must require treatment as assessed by the investigator. Patients will be randomized 1:1 to either Arm A or Arm B based on the following stratification factors:

- simplified MCL International Prognostic Index (sMIPI) risk group (low/intermediate versus high; Hoster et al. 2008)
- intended comparator BTK inhibitor (ibrutinib versus acalabrutinib/zanubrutinib)
- number of prior lines of therapy (1 versus ≥ 2).

During screening, ICB must be selected from one of the following BTK inhibitors, based on locally available options: ibrutinib, acalabrutinib, or zanubrutinib. Investigators will select the ICB for each patient prior to randomization. Study treatment will be given continuously until progression of disease, unacceptable toxicity, withdrawal of consent, or initiation of a new anticancer therapy. No crossover between treatment arms will be permitted. Upon disease progression (as determined by the investigator) and discontinuation of protocol therapy, all patients will be placed on long-term follow-up (LTFU) every 3 months until death, lost to follow-up, or consent withdrawal. Patients who continue to derive clinical benefit from therapy (as determined by the investigator) at the time of progression may continue to receive therapy if sponsor is notified. Patients who continue therapy beyond investigator assessed disease progression should continue to be followed in accordance with all required on-treatment study procedures, including disease assessments, as outlined herein.

Disclosure Statement:

BRUIN-MCL-321 is a randomized, active treatment study with 2 arms where the participant and investigator will not be blinded.

Number of Patients:

Approximately 500 patients meeting the eligibility criteria will be randomized 1:1 to either Arm A or Arm B.

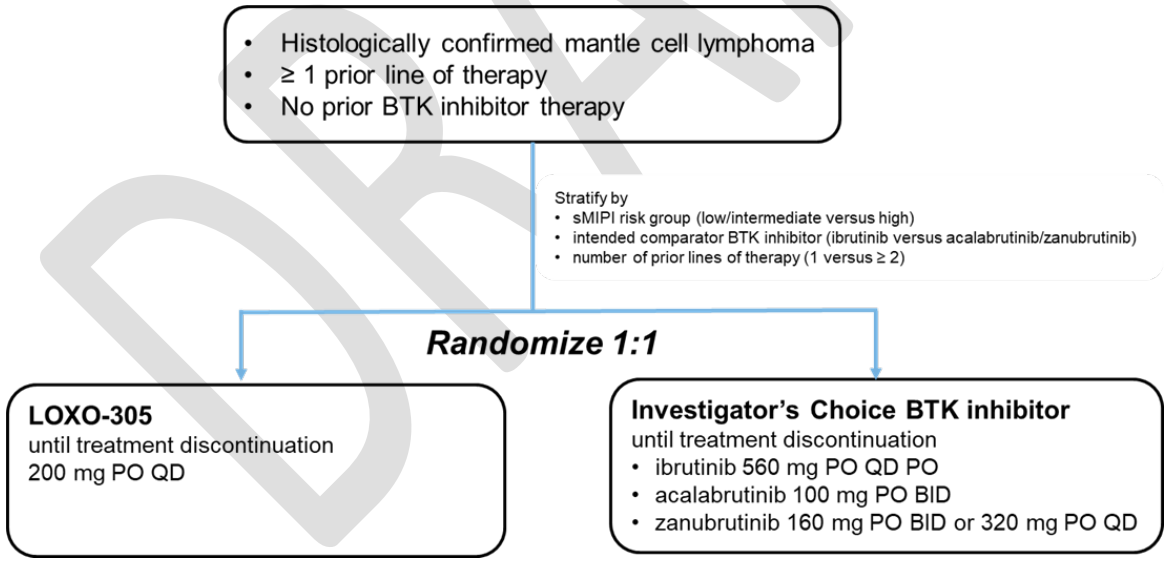
Intervention Groups and Duration:

	Arm A (LOXO-305)	**Arm B (investigator's choice of BTK inhibitor monotherapy)**			
Treatment	LOXO-305	ibrutinib	acalabrutinib	zanubrutinib (investigators pick dose and schedule)	
Dose	200 mg	560 mg	100 mg	160 mg	320 mg
Schedule	QD	QD	BID	BID	QD
Route	oral	oral	oral	oral	

Data Monitoring Committee: A data monitoring committee (DMC) will be utilized to assess aggregate efficacy and safety data for this study. Refer to the DMC charter for further information.

1.2 Schema

LOXO-BTK-20019 Study Design



1.3 Schedule of Activities (SoA)

Schedule of Assessments:

Baseline, On-Study, and Post-Study Treatment Follow-Up SoA for Patients on Arm A and Arm B

Study Period	**Baseline**		**Study Treatment (Cycle = 28 days)**				**Post-Study Treatment Discontinuation**			**Instructions**
Cycle/Visit	**Screening**		**Cycle 1**		**Cycles 2-6**	**Cycles 7+**	**End of Treatment**	**Safety Follow-up[a]**	**Long-Term Follow-up[b]**	
Window	Up to 28 days		D1	±3 days	±7 days	±14 days	+7 days	+7 days	±30 days	
Relative Day within Cycle	≤28	≤14		D8	Day 1	Day 1	after last dose	28 days after last dose	Every 90 days	
Informed consent	X									ICF must be signed before any protocol-specified procedures are performed. See Appendix 1.
Medical history	X									• All conditions ongoing and relevant past surgical and medical history should be collected. • Malignancy history should be collected regarding disease under study, as well as any history of other malignancy
Documentation of histological diagnosis and relevant biomarkers	X									• Anonymized/redacted pathology report(s) confirming histologic diagnosis of MCL (see inclusion criteria and Section 4.1; utilizing t(11;14) status, cyclinD1 expression and B cell markers) required for eligibility. • Reports regarding status of any known MCL relevant biomarkers must also be provided if conducted [e.g. SOX11, TP53 mutation, Ki67% etc.]
Concomitant medication	X		X		X		X			Record prior and current medications at baseline, and all premedication, supportive care, and concomitant medication throughout the study.
Physical examination		X	X	X	X	Q12W starting with Cycle 9	X	X		• Complete PE includes height, weight, basic neurological examination and review of relevant symptoms at screening. • Targeted PE may be performed at other timepoints, include weight and as clinically indicated throughout trial

Study Period	Baseline		Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Cycle/Visit	**Screening**		**Cycle 1**		**Cycles 2-6**	**Cycles 7+**	**End of Treatment**	**Safety Follow-up[a]**	**Long-Term Follow-up[b]**	
Window	Up to 28 days		D1	±3 days	±7 days	±14 days	+7 days	+7 days	±30 days	
Relative Day within Cycle	≤28	≤14		D8	Day 1	Day 1	after last dose	28 days after last dose	Every 90 days	
Vital Signs		X	X	X	X	Q12W starting with Cycle 9	X	X		• Includes systolic and diastolic blood pressure, heart rate, respiratory rate, oxygen saturation and body temperature. • Vital signs assessed at PK time points should be conducted prior to PK blood sampling (up to 4 hours pre-dose, but as close to dosing as possible is preferred)
12-lead ECG		X	X	X	X	Q12W starting with Cycle 9				Obtain ECGs at specified visits and when patients are symptomatic. See Section 8.2.1. ECGs should be collected: • at screening, triplicate ECG • C1D1: single ECG pre-dose (up to 4 hours) and at 2 hours post dose • All other timepoints: single ECG at 2 hours post dose If an unscheduled ECG is done at any time and identifies a new, clinically significant abnormality, an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG testing. If a clinically significant arrhythmia is detected, details must be captured in EDC and/or submitted as requested and required by sponsor.
ECOG performance status		X	X		X	Q12W starting with Cycle 9	X			
sMIPI score		X								
Laboratory Assessments										
Hematology panel		X	X	X	X	Q12W starting with Cycle 9	X	X		• See Section 10.2 Appendix 2

Study Period	**Baseline**		**Study Treatment (Cycle = 28 days)**				**Post-Study Treatment Discontinuation**			**Instructions**
Cycle/Visit	**Screening**		**Cycle 1**		**Cycles 2-6**	**Cycles 7+**	**End of Treatment**	**Safety Follow-up[a]**	**Long-Term Follow-up[b]**	
Window	Up to 28 days		D1	±3 days	±7 days	±14 days	+7 days	+7 days	±30 days	
Relative Day within Cycle	≤28	≤14		D8	Day 1	Day 1	after last dose	28 days after last dose	Every 90 days	
										• If Screening testing is performed within 3 days of C1D1, repeat testing does not need to occur on C1D1. • Additional assessments as clinically indicated.
Chemistry panel		X	X	X	X	Q12W starting with Cycle 9	X	X		• See 10.2 Appendix 2. • If Screening testing is performed within 3 days of C1D1, repeat testing does not need to occur on C1D1. • Additional assessments as clinically indicated.
Coagulation panel		X	As clinically indicated							aPTT and PT (or INR)
Hepatitis B/C screening	X									• HBV and HCV testing to determine if patients have active infection. • Patients who are anti-HBc positive AND hepatitis B PCR positive OR hepatitis C RNA positive are not eligible to participate .
Serum or Urine Pregnancy test (WOCBP only)		X	X		Q12W starting with Cycle 3		X			• See 10.2 Appendix 2 • Perform within 24 hours of the first dose of study treatment, and as indicated in table, or as required per local regulations and/or institutional guidelines.
Urinalysis		X	As clinically indicated							• See Appendix 2 • Dipstick analysis is acceptable
Genetics and Biomarkers										

Study Period	Baseline		Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Cycle/Visit	**Screening**		**Cycle 1**		**Cycles 2-6**	**Cycles 7+**	**End of Treatment**	**Safety Follow-up[a]**	**Long-Term Follow-up[b]**	
Window	Up to 28 days		D1	±3 days	±7 days	±14 days	+7 days	+7 days	±30 days	
Relative Day within Cycle	≤28	≤14		D8	Day 1	Day 1	after last dose	28 days after last dose	Every 90 days	
Archival tumor tissue or fresh biopsy	X									• Must be submitted as described in Section 8.8.1 • Sample must be adequate as outlined in the lab manual. • If archival tissue is not available, a fresh tissue biopsy must be obtained unless there is a moderate to severe safety risk associated with performing or patient does not consent
Saliva Collection	X									• Collect if patient has consented. • Details regarding sample collection and submission can be found in the lab manual.
Blood samples for PK				X	X					Arm A only. Pre-dose sample only
Blood samples for exploratory biomarkers			X (Pre-dose)	X	X	Q12W starting with cycle 9	X			• Details regarding sample type and collection can be found in the lab manual. • For patients who continue to receive therapy beyond progression of disease due to ongoing clinical benefit, sample collection should continue as outlined here, as well as at the time of progression.
Continuous Patient Evaluations										
Survival information							X			• Survival information may be collected by contacting the patient or family directly (e.g., via telephone) if no procedures are required. This information should be collected

Study Period	Baseline		Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Cycle/Visit	**Screening**		**Cycle 1**		**Cycles 2-6**	**Cycles 7+**	**End of Treatment**	**Safety Follow-up[a]**	**Long-Term Follow-up[b]**	
Window	Up to 28 days		D1	±3 days	±7 days	±14 days	+7 days	+7 days	±30 days	
Relative Day within Cycle	≤28	≤14		D8	Day 1	Day 1	after last dose	28 days after last dose	Every 90 days	
										approximately every 90 days after the Safety Follow up visit. See Section 8.1. • Subsequent anticancer therapy information should be collected every 90 days from the end of safety follow up for the first 2 years after discontinuation from study treatment and approximately every 6 months thereafter until death or study completion.
Medical Resource Utilization			X		X	X	X	X		• Hospitalizations, emergency department visits, blood product transfusions, and hematopoietic growth factor use will be collected
Adverse events	X		X		X		X			• Collect SAEs from the time of ICF signing through LTFU as outlined (CTCAE Version 5.0). • Collect AEs from the time of dosing through SFU. • All SAEs (regardless of causality) that occur from the time of consent until ≤ 28 days after the last dose of study drug (or until a new therapy starts) should be reported. After 28 days beyond last dose, only SAEs related to study treatment or protocol procedures are reported.
Patient reported Outcomes via electronic device to patient			→		→	→	→	→		See Table 6.1 for schedule of at home patient questionnaires by electronic device (eCOA)
Patient dosing diary			→		→	→	→			Provide patient diary Day 1. Completed daily by patient. Review at each study visit.
Dispense study drug			X		X	X				See Section 6.1.

Study Period	Baseline		Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Cycle/Visit	**Screening**		**Cycle 1**		**Cycles 2-6**	**Cycles 7+**	**End of Treatment**	**Safety Follow-up[a]**	**Long-Term Follow-up[b]**	
Window	Up to 28 days		D1	±3 days	±7 days	±14 days	+7 days	+7 days	±30 days	
Relative Day within Cycle	≤28	≤14		D8	Day 1	Day 1	after last dose	28 days after last dose	Every 90 days	
Response Assessments										
Radiologic imaging (PET/CT scan, CT scan or MRI)	X				See Instructions Every 12 weeks beginning with C3D1 (± 7 days) through the end of Cycle 24 and then every 24 weeks (± 14 days)		X		See instructions	• Refer to Sections 8.1and 10.7 Appendix 7 for full details and allowances other than PET/CT. • PET/CT with diagnostic quality CT sequences is the preferred method for disease assessment. • Imaging should be obtained until progression, start of a new anticancer therapy, death, or study completion. • If a patient discontinues study treatment for reasons other than PD, death, lost to follow up, or withdrawal of consent, disease assessments should continue every 12 weeks until progression or initiation of another anticancer therapy. • For patients who continue treatment beyond progression due to ongoing clinical benefit, disease assessment imaging should continue as outlined until EOT.
Bone marrow biopsy/aspirate	X				Biopsy required to confirm radiographic CR on study					• Bone marrow biopsy and aspirate required at baseline for all patients and on study to confirm radiographic CR for patients with BM involvement at baseline. Refer to Section 8.1 • Refer to Section 8.8 for full requirements.

Study Period	Baseline		Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Cycle/Visit	**Screening**		**Cycle 1**		**Cycles 2-6**	**Cycles 7+**	**End of Treatment**	**Safety Follow-up[a]**	**Long-Term Follow-up[b]**	
Window	Up to 28 days		D1	±3 days	±7 days	±14 days	+7 days	+7 days	±30 days	
Relative Day within Cycle	≤28	≤14		D8	Day 1	Day 1	after last dose	28 days after last dose	Every 90 days	
Gastrointestinal endoscopy	Required for patients with GI involvement at baseline				Required to confirm radiographic CR on study					• GI endoscopy/biopsy required at baseline for patients with GI involvement on imaging and for patients with negative imaging but clinical suspicion of GI involvement. • GI endoscopy/ biopsy required to confirm CR for patients with known involvement at baseline. • Refer to Sections 8.1and 8.8 for full requirements.
Post-progression tumor biopsy							X			• Obtained prior to the start of next anticancer therapy unless there is a moderate to severe safety risk associated with performing or patient does not consent. • For patients who continue to receive treatment beyond progression due to ongoing clinical benefit, post-progression tumor biopsies should be performed at the time of PD and at EOT (unless events are within 2 cycles of one another) unless there is a moderate to severe safety risk associated with performing or patient does not consent.

Note: Baseline/screening physical examination results and laboratory values drawn within 3 days of C1D1 may be used for both screening/baseline and C1D1 assessments.

a SFU begins when the patient and investigator agree that the patient will no longer continue study treatment. A SFU visit will be conducted 28 (+7) days after last dose of study drug.

b LTFU begins after the SFU visit and continues until death, study withdrawal, or the patient is lost to follow-up. In all cases, no follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

Patient Reported Outcomes (All Treatment Arms)

Instrument	Cycle 1	Weeks 1-12 eCOA at Home				Week 13+ eCOA at Home		End of Treatment	Safety Follow-up	Long-Term Follow-up	Instructions
Visit Window	**Day 1 (In Clinic)**	**Weekly**	**End of Week 4**	**End of Week 8**	**End of Week 12**	**Every 4 Weeks**	**Every 12 Weeks**	**After last dose (+7 Days)**	**28 days after last dose (+ 7 days)**	**Every 12 weeks (± 30 days) for up to 2 years after last dose**	
PRO-CTCAE	X	X				X		X	X		The patient will complete all PRO assessments at home using the provided electronic device, except for baseline (C1D1), EOT, and SFU. PRO assessments administered at clinic must be completed prior to first dose of study drug.
FACT-GP5	X	X				X		X	X		
EORTC QLQ-C30	X				X		X	X	X		
EORTC IL63 (MCL Symptoms Supplement)	X				X		X	X	X		
EORTC IL19 (Physical Function)			X	X		X[a]					
EORTC IL[XX] (MCL Symptom Assessment)			X	X		X[a]					
PGI-S	X		X	X	X	X	X	X	X		
PGI-C			X	X	X	X	X	X	X		
EQ-5D-5L	X				X		X	X	X		

[a] This instrument not administered on weeks where the EORTC QLQ-C30 and EORTC IL63 are administered due to overlapping items.

2 INTRODUCTION

2.1 Study Rationale

LOXO-305 is an orally available, highly selective, ATP-competitive inhibitor of BTK distinct from approved BTK inhibitors (ibrutinib, acalabrutinib, and zanubrutinib) 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), LOXO-305 has demonstrated robust and durable anti-tumor activity against a variety of B-cell malignancies including MCL regardless of prior treatment and including in patients previously treated with covalent BTK inhibitors.

The proposed Phase 3 study is a global, multicenter, randomized open-label study in patients with previously treated MCL. The study will compare LOXO-305, a non-covalent BTK inhibitor versus investigator's choice of covalent BTK inhibitor therapy, evaluating the differences in efficacy, safety and tolerability in this patient population and confirming the activity and safety of LOXO-305 in patients with relapsed MCL.

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 intravenous (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 PI3-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 chronic lymphocytic leukemia (CLL), related to naïve B cells), MCL and marginal zone lymphoma ([MZL], each related to germinal center B cells) and Waldenstrom 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 and acalabrutinib), relapsed/refractory (R/R) MCL (ibrutinib, acalabrutinib, and zanubrutinib), WM (ibrutinib), and MZL (ibrutinib). These agents potently inhibit BTK by binding to the ATP pocket of the enzyme and forming an irreversible, covalent bond with the cysteine residue at position 481 (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 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 to diminished target coverage 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 administration in MCL may be limited by toxicity with up to 25% of patients discontinuing for toxicity (Sharman et al. 2018). 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 and zanubrutinib are both approved for use in the US for relapsed MCL and are more selective than ibrutinib against non-BTK kinase off-targets in preclinical studies. These agents have 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; Song et al. 2019).

While currently available BTK inhibitors are effective in the treatment of MCL, these agents have limitations. New BTK inhibitors that selectively and potently inhibit BTK in susceptible

tumors avoid the toxicities due to inhibition of other kinase and non-kinase off-targets thus expanding the use of BTK both as monotherapy and in future combination approaches.

Treatment of MCL and available BTK inhibitor therapy

MCL is a rare and aggressive subtype of NHL with a median age at diagnosis of 65-70 years. While indolent subtypes of MCL have been characterized, the classical presentation of MCL is typically aggressive and incurable with treatment at diagnosis required for most patients. Young and fit patients typically receive induction CIT, followed by high-dose chemotherapy with autologous stem cell salvage, and finally rituximab maintenance. In transplant ineligible patients, induction (CIT) followed by rituximab maintenance is an accepted alternate approach. Ultimately, none of these approaches are considered curative, and relapse is nearly universal (Dreyling et al. 2017; Lenz et al. 2005; Flinn et al. 2014).

Frontline treatment selection is based on patient characteristics and candidacy for intensive CIT approaches, which yield high response rates including complete responses(CRs) but few long-term remissions (Lenz et al. 2005; Flinn et al. 2014). Overall survival (OS) at diagnosis is estimated at only 4-5 years (Dreyling et al. 2018). After relapse, treatment selection has been shaped by the approval of targeted approaches such as bortezomib (Goy et al. 2009), lenalidomide (Trneny et al. 2016), and temsirolimus (Hess et al. 2009). Response rates with these agents have ranged from 22% with temsirolimus to 40% with lenalidomide, with CRs of generally less than 10% and PFS of less than 7 months. Marketing authorization in select markets for these agents were granted for the treatment of relapsed MCL for bortezomib (Velcade®), for lenalidomide (Revlimid®), and for temsirolomus (Torisel®).

Compared to the activity of these agents, the introduction and availability of BTK inhibitors starting with the approval of ibrutinib in 2014, has permanently altered the standard of care for patients with relapsed MCL. Ibrutinib has received approval in several countries, with additional covalent BTK inhibitors acalabrutinib and zanubrutinib also having approval in select countries, as salvage therapy for patients progressing following upfront CIT, with or without transplant.

Ibrutinib received accelerated US approval for patients with previously treated MCL based on a multi-center, single arm study of 111 patients with a median age of 68 and 3 median prior therapies. The primary endpoint was investigator assessed overall response rate (ORR) using International Working Group Criteria (Cheson 2007) and was reported as 65.8% with a duration of response (DOR) of 17.5 months. Independent review of response demonstrated ORR of 69%. An internationally conducted randomized Phase 3 study showed ibrutinib to be superior to temsirolimus for relapsed MCL leading to approval in Europe (Dreyling 2016). In a recent pooled analysis of 370 patients from three studies in previously treated patients with MCL administered with ibrutinib and followed for 3.5 years, the median PFS was 12.5 months (95% CI 9.8-16.6 months) and median OS 26.7 months (95% CI 22.5-38.4 months) (Rule et al. 2019). Nearly three-quarters of patients (73.2%) had received 2 or more prior lines of therapy (range 1-9) and ORR to ibrutinib monotherapy in this setting was 69.7% with 27% CRs (Rule et al. 2019). The oral administration and demonstrated efficacy of BTK inhibition with

ibrutinib has led to it being the preferred salvage therapy for patients with MCL progressing following prior treatment. Despite the response activity in this setting, ibrutinib is associated with Grade 3 or worse toxicities in patients: atrial fibrillation/flutter 4%, hypertension 8%, infection 21%, neutropenia 23% and bleeding in up to 4% (Imbruvica USPI 2020).

Acalabrutinib is a more selective covalent BTK inhibitor and has received accelerated approval in the US for relapsed MCL based on a single arm Phase 2 study of 124 patients with a median age of 68 years and 2 median prior therapies. For this initial data supporting approval, the primary endpoint was investigator assessed ORR using the Lugano Classification (Cheson et al 2014) and, at a median follow up of 15.2 months, was reported as 81% and with the median PFS and DOR not reached. A response assessment by independent review was conducted as an exploratory endpoint with an ORR of 75%. With prolonged follow up of 26.3 months on study, 40% of patients remained on study, median PFS was 19.5 months and estimated OS rate at 24 months was 72% (Wang et al. 2018). While initial safety at 15.2 months identified neutropenia, anemia and pneumonia as the most common Grade 3 or worse toxicities, with prolonged follow up, cardiac events were identified in 10% of patients with four of these Grade 3 or 4 toxicities (acute coronary syndrome, acute myocardial infarction, cardiopulmonary arrest, coronary artery disease). Overall, acalabrutinib is associated with Grade 3 or worse toxicities in patients: infections (viral, bacterial, or fungal) 19%, hemorrhage 3%, and neutropenia 23%, anemia 8%, thrombocytopenia 7%, and atrial fibrillation/flutter 1.1% (Calquence USPI 2019).

Zanubrutinib was granted US FDA accelerated approval in 2019 for in patients with MCL after receipt of at least one prior therapy. Studies leading to this approval were conducted primarily in the Asia-Pacific region and consisted of 2 single arm trials with enrollment of 118 total previously treated patients with MCL. The median age of patients was 62 with 2 median prior lines of therapy. For both studies, the primary endpoint by independent review using Lugano criteria (Cheson et al. 2014) was an ORR of 84% with a median DOR of 18.5-19.5 months. Major warnings and precautions for use of zanubrutinib are similar to ibrutinib and acalabrutinib and include hemorrhage events, infection, cytopenias, and atrial fibrillation/flutter but are based on safety reported for only the 118 patients treated for MCL (Brukinsa USPI 2019).

The role of BTK inhibitors, especially ibrutinib, is established in the treatment of patients with relapsed MCL and ongoing trials are now investigating these agents compared to CIT in the first-line setting. However, data supporting approval of each BTK inhibitors for treatment of patients with relapsed MCL have been on the basis of single arm trials which enrolled patient populations varied in characteristics. In addition, primary response assessments, by either investigator or independent central committee, used varied response criteria (Cheson 2007 for ibrutinib or Cheson et al. 2014 for acalabrutinib and zanubrutinib). While the primary endpoints of these reported studies suggest similarities in outcomes with any of the 3 agents, the need to extrapolate from cross-trial comparisons is a primary knowledge gap for clinicians. This Phase 3 trial will generate important data characterizing the differences in safety, tolerability, and efficacy in this patient population between LOXO-305 and covalent BTK inhibitors.

2.3 Benefit/Risk Assessment

LOXO-305 has demonstrated clinical activity in the patient population specified for this study. LOXO-BTK-18001 (NCT03740529) is a first in human global Phase 1/ 2 study evaluating the safety and efficacy of LOXO-305 in patients with CLL 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 LOXO-305, assess PK, identify a recommended Phase 2 dose (RP2D) and a maximal tolerated dose (MTD). During Phase 1 dose escalation, LOXO-305 was well tolerated at all dose levels of 25 mg to 300 mg once daily (QD) with no dose-limiting toxicities (DLTs). Given the totality of efficacy, clinical PK, and safety data, the sponsor and Safety Review Committee (SRC) decided that ongoing dose escalation was not medically justified and therefore no MTD was established. A RP2D was identified as 200 mg QD.

PK data show that LOXO-305 is absorbed after oral administration with a median time to maximum plasma concentration (T_{max}) of approximately 2 hours and low clearance. Plasma half-life appears to be approximately 20 hours. Steady-state AUC_{0-24} increases in approximate proportion with daily dose. Following administration of 100 mg QD or higher, mean unbound trough plasma levels of LOXO-305 exceeded the IC_{90} of BTK-wt and BTK C481S in vitro.

Efficacy data from the LOXO-BTK-18001 study show robust and durable anti-tumor activity against a variety of B-cell malignancies including covalent BTK inhibitor pretreated MCL. Enrolled patients have varied prior therapies, including diverse combinations of chemotherapy, anti-CD20 antibodies, autologous stem cell transplant, CAR-T cell therapy, and BTK inhibitors. The vast majority of patients with MCL treated on the LOXO-BTK-18001 study received a prior BTK inhibitor. Anti-tumor activity has been seen regardless of prior treatment including in patients treated with covalent BTK inhibitors. The data of LOXO-305 efficacy in BTK inhibitor pre-treated patients with MCL predicts that LOXO-305 administered in the earlier line setting and to patients not previously treated with a BTK inhibitor as proposed for this Phase 3 study, should compare favourably, and likely surpass, outcomes seen in the current LOXO-BTK-18001 study.

Safety data were available from 172 patients treated in the LOXO-BTK-18001 study as of 09 April 2020, at doses ranging from 25 mg QD to 300 mg QD. The majority of treated patients were patients diagnosed with CLL/SLL (86 patients, 50.0%) or MCL (37 patients, 21.5%). Treatment-emergent adverse events (TEAEs) were reported in 123 patients (71.5%). TEAEs occurring in > 10% (n = 18 or more) of the 172 patients were fatigue (12.8% total, 7.0% related) and diarrhea (10.5% total, 6.4% related). Study drug-related TEAEs occurred in a total of 74 of 172 patients (43.0%). The most frequently reported drug-related TEAEs in > 5% of patients (n = 9 or more) were fatigue (7.0%), diarrhea (6.4%), and contusion (5.2%). All other drug-related TEAEs occurred in < 6 patients each (i.e., 3.5% of patients or less). Thirty-three (33, 19.2%) patients had ≥ Grade 3 TEAEs with 12 (7%) considered to be related to study drug. Three (1.7%) patients have died within 28 days of the last dose of study drug, and no deaths have been attributed to study drug. The safety profile is reflective of the selectivity of LOXO-305. Additional information about the known and expected risks, serious adverse events (SAEs), and

reasonably anticipated AEs of LOXO-305 is provided in the Investigator's Brochure (LOXO-305 IB).

When viewed as a whole, the benefit/risk ratio is favorable for LOXO-305 as monotherapy in the proposed patient population to be evaluated in this study.

More detailed information about the known and expected benefits and risks of ibrutinib, acalabrutinib, and zanubrutinib may be found in the product package insert.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To compare PFS of LOXO-305 as monotherapy (Arm A) to investigator choice of covalent BTK inhibitor monotherapy (Arm B) in patients with previously treated MCL	Assessed by IRC • PFS per Lugano criteria
Secondary	
• To compare efficacy of LOXO-305 as monotherapy (Arm A) to investigator choice of covalent BTK inhibitor monotherapy (Arm B) treatment arms	Assessed by both investigator assessment and IRC: • ORR per Lugano criteria • DOR per Lugano criteria Assessed by investigator assessment • PFS per Lugano criteria • OS • EFS • TTF • TTNT
• To evaluate the safety and tolerability of each treatment arm	• incidence and severity of SAEs, AEs, deaths, and clinical laboratory abnormalities per CTCAE v5.0
• To evaluate the patient reported outcomes	• comparative tolerability: proportion of time with high side-effect burden • TTW of MCL-related symptoms
Exploratory	
• To characterize the PK properties of LOXO-305, explore plasma exposure and selected efficacy and safety outcomes	• Predose concentration (C_{min})
• To evaluate for a correlation between predictive and prognostic biomarkers and clinical outcome to both LOXO-305 and comparator covalent BTK inhibitors.	• Biomarkers assessed from blood, bone marrow or tissue samples, unless precluded by local regulations • Clinical outcomes data
• To evaluate for mechanisms of acquired resistance to both LOXO-305 and comparator covalent BTK inhibitors.	
• To compare pre-treatment and on-treatment biospecimens (peripheral blood and bone marrow) for early predictors of treatment outcome	
• To determine whether pre-treatment co-morbidity scores are predictive of treatment associated toxicity to both LOXO-305 and comparator covalent BTK inhibitors.	
• To assess medical resource utilization	

4 STUDY DESIGN

4.1 Overall Design

LOXO-BTK-20019 (BRUIN MCL-321) is a Phase 3, global, multicenter randomized open label study comparing LOXO-305 as continuous monotherapy (Arm A) with investigator's choice of BTK inhibitor monotherapy (Arm B) in patients with previously treated mantle cell lymphoma. ICB therapy options in each country reflect local availability.

Adult patients will be required to have a documented diagnosis of MCL established locally with histology and molecular markers performed in a Clinical Laboratory Improvement Amendments (CLIA), International Organization for Standardization/Independent Ethics Committee (ISO/IEC), College of American Pathologists (CAP), or other similarly certified laboratory. A confirmed diagnosis will be determined by overexpression of cyclin D1 with at least one B-cell marker (e.g., CD19, CD20, or PAX5) and/or t(11;14), by cytogenetics, florescent in situ hybridization or polymerase chain reaction. Patients may have previously received any number of prior lines of therapy but must not have been treated with a BTK inhibitor, approved or investigational. Sequential therapy combinations are defined as one line unless separated by disease progression or by a ≥ 6-month treatment free interval. Patients must require treatment as assessed by the investigator. Eligible patients will be stratified according to the following factors:

- sMIPI risk group (low/intermediate vs high; Hoster et al. 2008)
- intended comparator BTK inhibitor (ibrutinib versus acalabrutinib/zanubrutinib)
- number of prior lines of therapy (1 versus ≥ 2).

During screening, in countries where ICB therapy consists of more than one option, the investigator will select the ICB comparator for each patient prior to randomization. After confirmation of eligibility, patients will be randomly assigned in a 1:1 ratio to:

- Arm A: LOXO-305 (200 mg QD PO)
- Arm B: investigator's choice of the following BTK inhibitors:
  - ibrutinib (560 mg PO QD)
  - acalabrutinib (100 mg PO BID)
  - zanubrutinib (160 mg PO BID or 320 mg PO QD)

Study treatment will be given continuously until progression of disease (as determined by investigator), unacceptable toxicity, withdrawal of consent, or initiation of a new anticancer treatment. No crossover between arms will be permitted. Patients who continue to clinically benefit from treatment (as determined by investigator) may continue to receive treatment if approved by sponsor. The cycle length will be 28 days for both treatment arms and should be maintained regardless of dose interruptions.

After discontinuation of study treatment, an end of treatment visit should occur within 7 days of last dose of study drug and a safety follow-up (SFU) visit 28 days after last dose of study drug. LTFU will occur every 3 months thereafter until death, lost to follow-up, or consent withdrawal.

Patients who discontinue treatment for any reason other than disease progression, death, lost to follow-up, or withdrawal of consent will be followed for tumor assessment until disease progression, regardless of whether the subject receives a new anticancer treatment. The primary endpoint will be PFS as determined by IRC per Lugano criteria.

4.2 Scientific Rationale for Study Design

BRUIN-MCL-321 study is a head-to-head comparison of LOXO-305 versus ICB regimen for the treatment in previously treated, BTK inhibitor naïve patients with MCL. The ICB arm consists of ibrutinib, acalabrutinib, or zanubrutinib. The study will be conducted globally and ICB options in each country will be based on local availability.

The preliminary results evaluating LOXO-305 have demonstrated robust and durable anti-tumor activity against a variety of B-cell malignancies including MCL and particularly in previously treated MCL who have received a prior BTK inhibitor. Response rates and duration of therapy compare favorably to standard of care (SOC) therapies. These results support a comparative trial of LOXO-305 versus ICB.

BRUIN-MCL-321 study will generate important data characterizing the differences in safety, tolerability, and efficacy in this patient population between LOXO-305 and covalent BTK inhibitors.

4.3 Justification for Dose

LOXO-305

Preclinical data supporting the selection of the starting dose of LOXO-305 for the first-in-human Phase 1/2 study of LOXO-305 (LOXO-BTK-18001) can be found in the IB. During Phase 1 dose escalation, LOXO-305 has been administered at doses ranging from 25 mg QD to 300 mg QD. Responses were seen at all dose levels including 25 mg QD and across tumor types. PK data obtained during dose escalation demonstrated that at doses of 100 mg QD or higher, mean trough plasma levels of LOXO-305 exceeded the concentration required for 90% inhibition (IC_{90} = 825 ng/mL) of BTK in vitro. During Phase 1, additional patients were enrolled to dose levels cleared for safety to confirm safety and evaluate additional preliminary efficacy. As of 09 April 2020, 172 patients had been dosed with LOXO-305 with 87 patients (50.6%) receiving a starting dose of 200 mg QD. Based on the totality of efficacy, clinical PK, and safety data of all enrolled patients, the sponsor and SRC determined that the recommended Phase 2 dose of LOXO-305 is 200 mg QD.

4.4 End of Study Definition

The end of the study is estimated at approximately 48 months from the first subject randomized to allow at least 2 years follow up on all enrolled patients (assuming approximately 20 months recruitment).

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 the following criteria apply:

Age

1. At least 18 years of age

Type of Patient and Disease Characteristics

2. Confirmed diagnosis by local laboratory of mantle cell lymphoma with documentation of overexpression of cyclin D1 with at least one B-cell marker (e.g., CD19, CD20, or PAX5) and/or t (11;14), by cytogenetics, fluorescent in situ hybridization (FISH) or polymerase chain reaction.
   - availability of adequate archival tissue or fresh biopsy sample
   - if archival tissue is not available, a fresh tissue biopsy must be obtained unless there is a moderate to severe safety risk associated with performing and/ or consent is not obtained (Section 8.7.2)
3. Previously treated with at least one prior line of systemic therapy (See Section 4.1) for mantle cell lymphoma.
4. Measurable disease on radiologic assessment as defined by Lugano criteria: at least one nodal lesion (> 1.5 cm in long axis) or extra-nodal lesion (> 1.0 cm in long axis) measurable in 2 dimensions, not previously radiated (unless progression has been radiographically documented following radiation therapy).
5. Documented evidence of radiographically and/or histologically confirmed disease progression on the most recent line of therapy or relapse prior to study enrollment.
6. ECOG 0-2.
7. Adequate organ function

System	Laboratory Value
Hepatic	
ALT or AST	≤ 3 × the ULN or ≤ 5 × ULN with documented liver involvement
Total bilirubin	≤ 1.5 × ULN or ≤ 3 × ULN with documented liver involvement and/or Gilbert's Disease
Renal	
Serum creatinine	Calculated creatinine clearance ≥ 30ml/min according to Cockcroft/Gault Formula: $\frac{(140 - \text{age}) \times \text{body weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72} \times 0.85$ (if female)
Hematologic	
Hemoglobin	≥ 8 g/dL (≥ 80 g/L)
ANC	≥ 0.75 × 10^9/L
Platelets	≥ 50 × 10^9/L
Notes: Hgb and platelets: independent of transfusions within 7 days of screening assessment. ANC: independent of growth factor support within 7 days of screening assessment.	

8. Willingness to undergo confirmatory procedures for assessment of disease status as required by protocol; including BM biopsy and GI endoscopy when appropriate and medically feasible.
9. Patients are required to have the following washout periods prior to planned Cycle 1 Day 1 (C1D1). In addition, prior treatment-related AEs must have recovered to Grade ≤ 1 with the exception of alopecia.
   - targeted agents, investigational agents, therapeutic monoclonal antibodies or cytotoxic chemotherapy: 5 half-lives or 2 weeks, whichever is shorter
   - immunoconjugated antibody treatment within 10 weeks prior to randomization
   - broad field radiation (≥ 30% of the bone marrow or whole brain radiotherapy): 14 days
   - palliative limited field radiation: 7 days
10. Must have life expectancy of at least 3 months

Contraception

11. Willingness of men and women of reproductive potential to observe conventional and highly effective or acceptable birth control methods for the duration of treatment and for 6 months following the last dose of study treatment (see Section 10.3 Appendix 3).

Informed Consent

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

Other Inclusions

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

5.2 Exclusion Criteria

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

Medical Conditions

1. Current suspected or confirmed active CNS involvement with MCL or previous CNS involvement
2. Prior treatment with an approved or investigational BTK inhibitor
3. Major surgery within 4 weeks prior to randomization
4. History of bleeding diathesis
5. History of stroke or intracranial hemorrhage within 6 months of randomization

6. History of allogeneic or autologous stem cell transplant (SCT) or chimeric antigen receptor-modified T-cell (CAR-T) therapy within 60 days of randomization or presence of any of the following, regardless of prior SCT and/or CAR-T therapy timing:
   - active graft versus host disease (GVHD);
   - cytopenia from incomplete blood cell count recovery post-transplant;
   - need for anti-cytokine therapy for toxicity from CAR-T therapy; residual symptoms of neurotoxicity > Grade 1 from CAR-T therapy;
   - ongoing immunosuppressive therapy (> 20 mg prednisone or equivalent daily).

7. Significant cardiovascular disease defined as:
   - unstable angina or acute coronary syndrome within the past 2 months prior to randomization
   - history of myocardial infarction within 3 months prior to randomization or
   - documented LVEF by any method of ≤ 40% in the 12 months prior to randomization
   - ≥ Grade 3 NYHA functional classification system of heart failure, uncontrolled or symptomatic arrhythmias
8. Prolongation of the QT interval corrected for heart rate (QTcF) > 470 msec on at least 2/3 consecutive electrocardiograms (ECGs), and mean QTcF > 470 msec on all 3 ECGs, during Screening. QTcF is calculated using Fridericia's Formula (QTcF): $QTcF = QT/(RR^{0.33})$.
   - Correction of suspected drug-induced QTcF prolongation 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.
   - Correction for underlying bundle branch block (BBB) allowed.
9. Known human immunodeficiency virus (HIV) infection, regardless of CD4 count. Unknown or negative status are eligible.
10. Known active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection based on criteria below:
    - HBV: defined by positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (anti-HBc). If anti-HBc positive or surface antigen negative result, patient will need to have a negative result for hepatitis B DNA before randomization. Patients who are anti-HBc positive and hepatitis B PCR positive will be excluded.
    - HCV: defined by positive hepatitis C antibody. If positive hepatitis C antibody result, patient will need to have a negative result for hepatitis C RNA before randomization. Patients who are hepatitis C RNA positive will be excluded.
11. Known active cytomegalovirus **(**CMV) infection. Unknown or negative status are eligible.
12. Pregnancy, lactation or plan to breastfeed during the study or within 30 days of the last dose of study treatment.
13. Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal (GI) absorption of the study drug.

14. Evidence of other clinically significant uncontrolled condition(s) including but not limited to, uncontrolled systemic bacterial, viral, fungal or parasitic infection (except for fungal nail infection), 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. History of second malignancy unless in remission for at least 2 years; in-situ carcinomas not requiring treatment intervention and non-metastatic breast or prostate cancer where hormonal therapy is being continued as standard of care are allowed.

Prior/Concomitant Therapy

16. Current treatment with strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers and/or strong P-gp inhibitors.
    Because of their effect on CYP3A4, use of any of the following within 3 days of study therapy start or planned use during study participation is prohibited,
    a. grapefruit or grapefruit products
    b. Seville oranges or products from Seville oranges
    c. star fruit
17. Steroid use with anti-neoplastic intent within 7 days of study drug initiation.
18. Patients requiring therapeutic anticoagulation with warfarin or another vitamin K antagonist.
19. Vaccination with live vaccine within 28 days prior to randomization

Prior/Concurrent Clinical Study Experience

20. Concurrent treatment with an investigational agent or anticancer therapy, unless noted in Section 6.5.

Other Exclusions

21. Have a known hypersensitivity to any of the excipients of LOXO-305 or to the intended covalent BTK inhibitor if randomized to control arm.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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 study treatment until after the final dose.

No food or drink restrictions are required for administration of LOXO-305. LOXO-305 tablets should be swallowed whole.

Refer to locally approved label for pertinent information regarding the intended covalent BTK inhibitor if randomized to control arm.

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized to study treatment due to inability to complete or meet the criteria for participation (Section 5.1 and 5.2). Re-screened patients will be provided a new patient number with each rescreening. Repeat of laboratory tests during the screening period or repeating screening tests to comply with the protocol-designated 28-day screening period does not reconstitute rescreening.

6 STUDY INTERVENTION

Study intervention is defined as any investigational treatment or marketed product(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

Intervention Groups and Duration:

	Arm A (LOXO-305)	**Arm B (investigator's choice of BTK inhibitor monotherapy)**			
Treatment	LOXO-305	ibrutinib	acalabrutinib	zanubrutinib (investigators pick dose and schedule)	
Dose	200 mg	560 mg	100 mg	160 mg or	320 mg
Schedule	QD	QD	BID	BID or	QD
Route	oral	oral	oral	oral	

Selection of ICB for each patient will be determined by the investigator prior to randomization. Dosing and administration of ICB will be based on local product labels which provide complete prescribing information including method of administration and dose modification, warnings, precautions, contraindications, and anticipated adverse reactions. Investigators should follow institutional procedures for administration of the ICB, where applicable.

Dosing of all agents will be fixed and not based on body-surface area or weight.

6.1.1 Selection and Timing of Doses

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

Patients will begin dosing assigned treatment on C1D1. Treatment will continue until progression, unacceptable toxicity, or other reason for treatment discontinuation. Patients with documented PD 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 sponsor is notified of the continuation of treatment is approved by the sponsor.

A delay of a cycle due to holiday, weekend, bad weather, or other unforeseen circumstances will be permitted for a maximum of an additional 7 days and not counted as a protocol deviation.

Arm A: LOXO-305 should be taken at a consistent time on each day.

All patients taking LOXO-305 should not consume grapefruit or grapefruit products, Seville oranges or Seville orange products, or star fruit or star fruit products from the 3 days prior to start of study therapy until therapy is stopped. LOXO-305 may be taken with food or drink but should be taken as consistently as possible. No fasting is required for LOXO-305. Refer to Sections 6.5 and 10.5 Appendix 5 for concomitant medication considerations.

Patients randomized to LOXO-305 treatment must keep a daily diary to record dosing compliance, 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 be skipped and recorded in the dosing diary as missed. Completely missed doses should not be made up but should be recorded as missed in the daily diary. 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.

Arm B: ICB inhibitor (ibrutinib, acalabrutinib, or zanubrutinib) should be taken at approximately the same time(s) on each day, with BID dosing separated by approximately 12 hours (a minimum of 6 hours between consecutive doses).

Participants randomized to ICB treatment must keep a daily diary to record dosing compliance, which will also be assessed at each clinic visit by means of a capsule count in the returned bottle(s). Dose timing, allowable concomitant medications and drug holds should follow recommended guidance as outlined in the local product package insert.

6.2 Preparation/Handling/Storage/Accountability

Refer to the Pharmacy Manual for accountability.

6.2.1 LOXO-305

LOXO-305 tablets are available at strengths of 25 mg, 50 mg 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 Investigator's Choice of BTK Inhibitor

Ibrutinib
Ibrutinib tablets or capsules will be stored according to instructions provided in the locally approved product package insert.

Acalabrutinib
Acalabrutinib capsules will be stored according to instructions provided in the locally approved product package insert.

Zanubrutinib
Zanubrutinib capsules will be stored according to instructions provided in the locally approved product package insert.

6.3 Measures to Minimize Bias: Randomization and Blinding

This is an open-label study.

This study will use an interactive voice/web response system (IXRS) for randomization. Randomization will be used to minimize bias in the assignment of patients to treatment groups, to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced, and to enhance the validity of statistical comparisons across treatment groups.

Patients will be randomized 1:1 into 2 treatments arms, with randomization stratified by sMIPI risk group, intended comparator BTK inhibitor, and number of prior lines of therapy in order to minimize bias in the assignment of patients.

6.4 Study Intervention Compliance

For patients in both treatment arms, compliance with study treatment will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned capsules, 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 for any assigned study drug in a cycle for any reason other than toxicity. 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 study treatment.

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 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. Concomitant use of myeloid growth factors (and all concomitant medications) should be captured in the eCRF with accurate dates of receipt to provide documentation of the temporal relationship with regard to PET imaging. Excluded medications for eligibility are indicated in the Exclusion Criteria (Section 5.2).

6.5.1 Allowed Concomitant Medication and Supportive Care

Standard supportive medications may 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 (ASCO) or European Society for Medical Oncology (ESMO) guidelines
- red blood cell and platelet transfusions

- anti-emetic, analgesic, and antidiarrheal medications
- electrolyte repletion (e.g., calcium and magnesium) to correct low electrolyte levels
- glucocorticoid use on study (less than 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.
- thyroid replacement therapy for hypothyroidism
- bisphosphonates, denosumab, and other medications for the treatment of osteoporosis, prevention of skeletal-related events from bone metastases, and/or hypoparathyroidism.

Continuation of medications that the patient has been on for the previous 28 days is allowed, provided they are not on the list of prohibited concomitant medications (refer to Section 10.5 Appendix 5). Such therapy may include hormonal therapy for patients with prior

- prostate cancer (e.g., gonadotropin-releasing hormone [GnRH] or luteinizing hormone-releasing hormone [LHRH] agonists), or
- breast cancer (e.g., GnRH/LHRH agonists, aromatase inhibitors, selective estrogen receptor modulators, or degraders).

Local treatment while receiving study treatment (e.g., palliative radiation therapy or surgery for bone metastases) 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 are other target lesions that can be followed for response assessment. If study drug is held, patients should have recovered from the acute effects of radiation or surgery prior to restarting study treatment. For patients on Arm A, the sponsor recommends holding LOXO-305 for approximately 3 to 5 half-lives (approximately 3 to 5 days) before and after surgery. For patients on Arm B, the sponsor recommends following guidance as outlined in the product package insert. Study drug may be held for radiation at the discretion of the investigator. All procedures and radiation therapy received on study must be documented in the eCRF.

6.5.2 Prohibited Concomitant Therapy for Arm A and Arm B

- For Arm A: LOXO-305 is a substrate of CYP3A4. Patients should not take strong inhibitors or inducers of CYP3A4 (refer to Section 10.5 Appendix 5) as they could alter the drug's PK. If patients discontinue a strong CYP3A4 inducer, at least 5 days should lapse before LOXO-305 is administered. If during the study, patients require initiation of treatment with strong inhibitors or inducers of CYP3A4, for clinical reasons, the sponsor should be consulted to determine whether LOXO-305 should be stopped, and therefore whether the patient should be removed from the study.
    - This restriction includes herbal products, such as St John's wort, which may decrease the drug levels of LOXO-305.

- Moderate inhibitors or inducers of CYP3A4 should be taken with caution. Any exceptions to the above must be approved by the Sponsor.

- For Arm A and Arm B: Grapefruit, grapefruit products, Seville oranges, Seville orange products, star fruit, and star fruit products should be avoided for the duration of treatment.
- For Arm A and Arm B: Except as indicated in Section 6.5.1, patients are not allowed to receive concomitant systemic anti-cancer agents, hematopoietic growth factors for prophylaxis in Cycle 1, 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.
- For Arm A and Arm B: Live vaccines should not be administered while on study treatment or within 90 days after the last dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, H1N1 flu, rabies, bacillus Calmette-Guérin, and typhoid. Seasonal flu vaccines that do not contain live virus are permitted.

6.5.2.1 Concomitant Therapy Considerations for Arm A

LOXO-305 inhibits P-glycoprotein (P-gp) in vitro and is a time dependent inhibitor of CYP3A4. The consequences of the noted interactions in the clinic are not yet known. Therefore, if sensitive CYP3A4 substrates or P-gp substrates are given as concomitant medications with LOXO-305, monitor patients for increased adverse reactions of these co-administered concomitant medications and adjust their dose according to their prescribing information (refer to Section 10.5 Appendix 5).

See LOXO-305 IB for full detailed information.

6.5.2.2 Concomitant Therapy Considerations for Arm B

Permitted and prohibited concomitant medications, and concurrent medication administration should follow recommended guidance as outlined in the local product package insert.

6.6 Dose Modification Guidelines

Dose modifications are allowed for management of study therapy related toxicities. If dose modification of study therapy is required for any adverse event (AE) not related to study therapy, 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, hypothyroidism, or hypertension).

For Arm A and Arm B the following rules should guide dosing:

- If a dose reduction is required, the dose may be re-escalated for Arm A. For Arm B, follow the local package insert for dose modification guidance. For suggested dose modification guidelines, follow Table 6.1. If discontinuation instructions differ based upon the local product package insert, the product package insert guidance should be utilized.
- Potential dose interruption duration,
    - Study drug may be withheld for up to 28 days from the last dose to allow time to recover from toxicity with resumption of therapy as outlined in Sections 6.6.1 and 6.6.2.
    - In exceptional circumstances, a longer delay is permitted upon agreement between the investigator and the sponsor.

Dose reductions should be made according to the following table. If the locally approved product package insert guidance differs from Table 6.1, the label should be followed preferentially. In addition, the dose can be delayed or adjusted at the investigator's discretion as clinically indicated to ensure patient safety.

Table 6.1 Dose Reduction for Study Treatments:

	Arm A (LOXO-305)	**Arm B* (investigator's choice of BTK inhibitor monotherapy)**			
AE	**LOXO-305**	**ibrutinib**	**acalabrutinib**	**zanubrutinib**	
Dose Level 0 (Starting Dose)	200 mg QD	560 mg QD	100 mg BID	160mg BID or	320mg QD
1st occurrence	No change	No change	No change	No change	No change
2nd occurrence	150 mg QD	420mg QD	No change	80mg BID	160mg QD
3rd occurrence	100 mg QD	280mg QD	100mg QD	80mg QD	80mg QD
4th occurrence	50 mg QD	Discontinue	Discontinue	Discontinue	Discontinue
5th occurrence	Discontinue	-	-	-	-

*Refer to individual ICB product package inserts for specific dose modification recommendations

6.6.1 Dose Modifications and Toxicity Management Guidelines for Arm A

Cycles are 28 days in duration regardless of dose interruption. A patient who experiences a clinically significant AE may have LOXO-305 dosing withheld to evaluate the AE and to allow for recovery (to Grade 1 or baseline level). Upon recovery, the patient may restart therapy as outlined in Table 6.1 if it is considered in his/her best interest to continue therapy. If the dose is reduced, it may be re-escalated.

6.6.2 Dose Modification and Toxicity Management Guidelines for Arm B

Refer to the local product package insert for the current dose modification and toxicity management guidelines for ibrutinib, acalabrutinib, and zanubrutinib. If a dose reduction for toxicity occurs with any agent, dose re-escalation may be considered as directed in local product

package insert instructions. The following information provides recommendations for dose adjustments. These serve as a guide and do not replace investigator judgment and applicable local product package insert recommendations.

6.6.2.1 Dose Modification for Ibrutinib

The following information provides summary of safety and dose modification from the product package insert for ibrutinib. These serve as a guide and do not replace investigator judgment and applicable local product package insert recommendations. Refer to the local product package insert for the current safety information, toxicity management and dose modification guidelines for ibrutinib.

Treatment with ibrutinib has been associated with AEs of hemorrhage, infections, cytopenias, atrial fibrillation, secondary primary malignancies, tumor lysis syndrome (TLS. Patients should be monitored for signs and symptoms of bleeding as well as fever. Patients should be evaluated with monthly blood counts and periodic ECG surveillance and for development of arrhythmic symptoms (e.g., palpitations, light headedness). Additionally, patients at high risk for developing TLS (e.g., high tumor burden) should be monitored closely. Monitor for skin cancers and advise protection from sun exposure.

6.6.2.2 Dose Modification for Acalabrutinib

The following information provides summary of safety and dose modification from the product package insert for acalabrutinib. These serve as a guide and do not replace investigator judgment and applicable local product package insert recommendations. Refer to the local product package insert for the current safety information, toxicity management and dose modification guidelines for acalabrutinib.

Treatment with acalabrutinib has been associated with AEs of hemorrhage, serious and opportunistic infections (most commonly respiratory; e.g., hepatitis B reactivation, fungal pneumonia, and *pneumocystis jiroveci)*, cytopenias, atrial fibrillation, and secondary primary malignancies. Patients should be monitored for signs and symptoms of bleeding as well as fever and opportunistic infection. Prophylactic treatment should be considered in patients at high risk for opportunistic infections. Patients should be evaluated regularly for blood counts and undergo periodic ECG surveillance as well and when they develop arrhythmic symptoms (e.g., palpitations, light headedness). Additionally, patients should be monitored for skin cancers and advise protection from sun exposure.

6.6.2.3 Dose Modification for Zanubrutinib

The following information provides summary of safety and dose modification from the product package insert for zanubrutinib. These serve as a guide and do not replace investigator judgment and applicable local product package insert recommendations. Refer to the local product package insert for the current safety information, toxicity management and dose modification guidelines for zanubrutinib.

Treatment with zanubrutinib has been associated with AEs of hemorrhage, cytopenias, cardiac arrhythmias, serious and opportunistic infections (most commonly respiratory; e.g., hepatitis B reactivation, herpes simplex virus and *pneumocystis* jiroveci) and embryo-fetal toxicity. Patients should be monitored for signs and symptoms of bleeding as well as fever and opportunistic infection. Prophylactic treatment should be considered in patients at high risk for opportunistic infections. Patients should be evaluated regularly for blood counts and undergo periodic ECG surveillance as well and when they develop arrhythmic symptoms (e.g., palpitations, light headedness). Additionally, patients should be monitored for skin cancers and advise protection from sun exposure.

6.7 Intervention after the End of the Study

The end of study is defined in Section 4.4. Investigators will continue to follow the SoA provided in Section 1.3 until notified by 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 LOXO-305 until the patient is able to obtain commercially available LOXO-305 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 LOXO-305 once the regulatory requirements are satisfied. These may include, but are not limited to a rollover trial, patient assistance (should the patient qualify), or commercial LOXO-305. The study may be terminated if LOXO-305 does not obtain marketing approval or the development of LOXO-305 is no longer being pursued by the sponsor.

For patients randomized to Arm B: As study drug options used in Arm B are all locally approved, 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 End of Treatment

The EOT assessments and procedures for all patients will be conducted in accordance with the SoA (Section 1.3). These EOT assessments include post-progression biopsy which may consist of bone marrow aspirate and biopsy from patients who experience PD if the patient provides informed consent, and if the tissue can be safely obtained.

Patients who discontinue treatment for reasons other than PD should remain on study and continue to have disease assessments performed per protocol.

6.7.3 Safety Follow-up

The SFU assessments will be conducted in accordance with the SoA (Section 1.3). The SFU procedures may be performed as part of the EOT visit if the latter was performed at least 28 days (± 7 days) after final dose of the last cycle.

A SFU Visit 28 days (± 7 days) after the EOT visit should be performed if EOT occurred for AE to determine the status of any unresolved AEs.

6.7.4 Long-Term Follow-up

The LTFU assessments and procedures will be conducted in accordance with the SoA (Section 1.3). After treatment discontinuation, LTFU will occur approximately every 90 days (± 30 days) for up to 2 years, 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 is required to undergo disease assessment as specified in Section 10.7 Appendix 7.

LTFU may be conducted by phone when response assessment is not scheduled. Unscheduled interactions which may also constitute a LTFU 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 PARTICIPANT 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 Section 6.7.4). 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 Lugano criteria (Cheson et al. 2014)

  Exception: Patients with documented PD who are tolerating treatment and, in the opinion of the investigator, are deriving clinical benefit from continuing study treatment, may continue treatment with prior sponsor approval.
- Unacceptable toxicity
- Intercurrent illness compromising ability to fulfill protocol requirements
- 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 dose delay > 28 days for unacceptable toxicity, unless a clinical need for prolonged delay has been determined by the investigator with documented sponsor notification.
- 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 therapy 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 6.7.2. Patients will enter LTFU where they may be required to undergo disease assessments (refer to Section 6.7.4).

7.2 Participant 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 good clinical practice (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 participant 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 SoA (Section 1.3), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments).

7.3 Lost to Follow up

A participant 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 10.1.10.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). 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 participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- 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. The sponsor (or designee) will confirm eligibility prior to patient dosing.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count, scans, ECG) 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 SoA (Section 1.3).

8.1 Efficacy Assessments

8.1.1 Response Assessments

Response will be assessed by the investigator and the IRC as described using the Lugano response criteria (Section 10.7 Appendix 7). All patients must have clinical examination and response assessments during the course of treatment, while on study, and during follow up as indicated in the SoA (Section 1.3). For patients with clinical signs and symptoms of disease progression, confirmation via imaging assessment as outlined in Lugano criteria (Section 10.7; Appendix 7) should be conducted.

With approved BTK inhibitors, lymphocytosis and leukocytosis are well-documented on-target effects that occur early during administration study therapy. 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 are not considered PD.

All measurable disease must be documented at screening and reassessed at scheduled timepoints indicated in the SoA for response assessment. Disease progression will be assessed by the investigator. Patients who continue to clinically benefit at the time of disease progression and remain on therapy beyond PD, assessments as outlined in the SoA (Section 1.3) must continue to be obtained and submitted to the IRC.

8.1.2 Imaging

The preferred imaging is fluorodeoxyglucose (FDG)-positron-emission computed tomography (PET/CT) scan for all assessments with a contrast (oral and IV) enhanced CT of diagnostic quality to facilitate accurate tumor measurement. If PET/CT is unavailable, contrast (IV and oral) enhanced computed tomography (CT) scans, including spiral CT, are the preferred

alternative imaging method (CT scan thickness recommended to be ≤5 mm). Imaging should include chest, abdomen, and pelvis, and other areas (such as the neck, head and extremities) with disease involvement. Magnetic resonance imaging (MRI) is also acceptable in certain situations, such as when there is a concern about radiation exposure and/ or allergies associated with CT. Intravenous and oral contrast is required unless medically contraindicated.

If routine PET imaging is unavailable for ongoing disease assessments throughout the course of the clinical trial, obtaining PET imaging in addition to the collected CT scans (as outlined above) at a minimum of baseline and to confirm CR is preferred whenever possible.

The radiographic method of tumor assessment used at baseline must be used consistently throughout the study. Further studies (e.g. bone marrow biopsy and/ or GI endoscopy) will be required for confirmation of CR as outlined in Lugano criteria (see Section 10.7 Appendix 7) and herein.

Tumor assessments will be performed for each patient at the times shown in the SoA (Section 1.3) and whenever clinically indicated. Radiologic assessments obtained previously as part of routine clinical care and obtained prior to consent may be used as baseline assessment, provided they are of the diagnostic quality outlined here and were done no more than 28 days before the first dose of study drug.

Imaging should be obtained: Every 12 weeks beginning C3D1 (± 1 week) through the end of Cycle 24 and every 24 weeks (± 2 weeks) thereafter until progression, start of a new anticancer therapy, death, or study completion.

Investigators may conduct an initial tumor evaluation on C2D1 (± 7 days) and a confirmatory tumor evaluation a minimum of 4 weeks after the first tumor evaluation that shows a CR or PR by disease-specific criteria, if consistent with local regulatory authority requirements.

See the site imaging manual for guidelines on how the various imaging studies should be performed and transmitted for central review. All imaging should be submitted for central review by completion of the cycle during which it was collected if possible. If imaging is unscheduled, submission should be completed within 28 days of collection if possible. Redacted bone marrow biopsy and/or endoscopy pathology reports must also be submitted. For patients who continue to receive therapy beyond PD, IRC submissions must continue.

8.1.3 Procedures to Confirm Complete Response

Patients with bone marrow tumor involvement at baseline on PET/ CT and/ or biopsy will be required to undergo a bone marrow biopsy and aspiration for confirmation of CR.

Additionally, for any subject with documented gastrointestinal tumor involvement at baseline, a GI esophagogastroduodenoscopy and colonoscopy with random segmental biopsies are required for confirmation of CR.

8.2 Safety Assessments

8.2.1 Electrocardiograms

Electrocardiogram (ECG) monitoring should be performed as outlined in the SoA (Section 1.3). 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. When ECGs coincide with PK draw days, ECGs should be performed before the PK blood draw. 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 10.9 Appendix 9) and this value should be entered into the eCRF.
- If an unscheduled ECG is done at any time and found to have a new abnormality, 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 CTCAE v5.0 criteria, ECGs should be collected 1 minute apart.
- 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/or sponsor required documentation and provided as requested by the sponsor.

8.2.2 Clinical Safety Laboratory Assessments

Refer to Section 10.2 Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency. All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and the SoA (Section 1.3). Any additional safety monitoring for ibrutinib, acalabrutinib, and zanubrutinib should be conducted according to instructions provided in the local product package insert for the individual product.

If there is a clinically significant abnormal laboratory (e.g., a result that requires a change in study treatment or requires medical intervention) and it is not known to be related to a pre-existing diagnosis (or is worse than the expected/ known baseline severity for that pre-existing diagnosis), this should be reported into the eCRF as an AE.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

The investigator must review laboratory reports, 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 participant management or are considered clinically significant by the investigator especially if resulting in study therapy management (e.g., dose modification), reporting of the abnormality (e.g., AE or SAE) should be performed and recorded in the eCRF.

Discrepancies from the standard laboratory panels as outlined in Section 10.2 Appendix 2 due to local differing laboratory practices and reporting (e.g., local usage of urea rather than BUN, omission of urinalysis parameters, etc.), this alteration is not considered a protocol deviation providing there is no impact to patient safety and/or data integrity/interpretability required to evaluate study drug as outlined in the protocol (as assessed by investigator and approved by sponsor). The local values will be recorded in the eCRF as able (if physiologically equivalent) or omitted when unavailable.

Enrollment and treatment decisions may be based upon local laboratory results. Local laboratories will be utilized for routine laboratory tests and safety follow-up, (e.g., blood chemistries from serum or plasma, hematology, and urinalysis). Special assessments such as PK

studies, will be performed centrally. Additional guidance regarding testing and handling and processing of samples for central assessment is provided in the laboratory manual.

8.2.2.1 Hematology

Hematology should be assessed locally in accordance with the SoA (Section 1.3) and should include components as outlined in Section 10.2 Appendix 2.

8.2.2.2 Blood Chemistry

Blood chemistry from serum or plasma should be assessed locally in accordance with the SoA (Section 1.3) and should include components as outlined in Section 10.2 Appendix 2.

If an unscheduled ECG is done at any time and found to have a new abnormality, then an electrolyte panel (i.e., calcium, magnesium and potassium) should be done to coincide with the ECG testing if clinically feasible.

8.2.2.3 Coagulation

The coagulation panel should include aPTT and PT or INR and should be assessed locally at baseline (as indicated on the SoA in Section 1.3) and as clinically indicated (e.g., if a significant bleeding event should occur).

8.2.2.4 Urinalysis

Urinalysis should be assessed locally in accordance with the SoA (Section 1.3) and should include components as outlined in Section 10.2 Appendix 2.

8.2.2.5 Pregnancy Testing

For WOCBP: Pregnancy testing (serum or urine) must be conducted in accordance with the SoA (Section 1.3). Pregnancy reporting information is provided in Section 8.3.5. All women which is defined as following menarche and who are not postmenopausal (and 2 years of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening. In addition, for women of childbearing potential, a serum or urine pregnancy test must be performed at screening and monthly thereafter or as required per local regulations and/or institutional guidelines during study treatment. 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.

8.2.2.6 Viral testing

Hepatitis testing should be assessed at baseline 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. 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, CMV-DNA). Patients with evidence of active hepatitis B and/or hepatitis C infection (as defined in the exclusion criteria, Section 5.2) 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 anti-retroviral medications and LOXO-305 and risk of opportunistic infections with both HIV and approved BTK inhibitors.

8.2.2.7 Hepatic Safety Monitoring

Hepatic laboratory studies should be assessed locally in accordance with the SoA (Section 1.3) and should include components as outlined in Section 10.2 Appendix 2. Reference hepatic laboratory parameters that may be necessary to evaluate hepatic events are outlined in Section 10.4 Appendix 4. The sponsor should be notified if a patient experiences elevated AST/ALT and bilirubin that meet the following criteria:

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

8.3 Adverse Events and Serious 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 unless the AE develops or worsens due to study related procedures. All SAEs, regardless of causality, that occurred from time of informed consent to SFU (28 days [+ 7 days] after last dose of study drug), are to be recorded on the appropriate eCRF. 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 AE. 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.

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.

8.3.1 Grading and Intensity of Adverse Events

The investigator will grade the severity of each AE using, when applicable, the NCI CTCAE, version 5. 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. interfering with normal activities.
- 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 CTCAE severity based on numeric value may not necessarily meet life-threatening criteria.

8.3.2 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 8.3.1 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 LOXO-305 IB or local labels for ibrutinib, acalabrutinb, or zanubrutinib.

8.3.3 Serious Adverse Event Reporting

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 judgment 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 should also be considered serious.

Any hospital admission with at least one 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.

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.

8.3.3.1 Serious Adverse Reporting – Procedures for Investigators: Initial Report

All SAEs occurring from the time informed consent is signed through 28 days after the last dose 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.

To report the SAE, complete the paper SAE form located in the study manual. Fax or email the completed paper SAE form to Clinical Safety (the fax number and email address is listed below) within 24 hours of awareness.

Safety Contact Information

XX Clinical Safety

XX SAE Reporting – USA

Fax: +1-888-XXX-XXXX

e-mail: globalSAEinbox@XX.com

XX SAE Reporting – Rest of World

Fax: + 00 800-XXX-XXXX

e-mail: globalSAEinbox@XX.com

The investigator will be requested to supply detailed information regarding the event. SAEs must also be reported to the institutional review board/ independent ethics committee (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 (see Section 8.3.5).

8.3.4 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.

8.3.5 Pregnancy Reporting

If the patient or partner of a patient participating in the study becomes pregnant during the study or within 28 days of discontinuing study drug, 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.

8.4 Treatment Overdose

For Arm A, refer to the LOXO-305 IB for further information, recommendations and guidance.

For Arm B, refer to the local product package insert for ibrutinib, acalabrutinib and zanubrutinib for available information on the signs, symptoms, and treatment of overdose.

8.5 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 LOXO-305 in Arm A only.

Blood for PK assessment will be collected on C1D8, and at the first day of each consecutive cycle up to Cycle 6. Samples are to be drawn within 1 hour prior to dose, and exact time of sample collection should be recorded. In addition, time of previous dose should be recorded. Additional PK may also be assessed in patients when considered necessary by the investigator to understand exposure in relationship to possible safety.

Bioanalytical samples collected to measure investigational product concentration and metabolism and/or protein binding will be retained for a maximum of 2 years following last patient visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses, such as metabolism, transport and/or protein binding work. See the laboratory manual for details regarding sampling and submission.

8.6 Pharmacodynamics

Not applicable.

8.7 Genetics

8.7.1 Blood Samples for Exploratory Biomarkers Research

Whole blood for correlative exploratory research studies must be collected in accordance with the SoA (Section 1.3). The primary purposes for this analysis may include but not limited to identification of early indicators of treatment efficacy, to investigate somatic or germline genetic variants thought to play a role in MCL, and to identify potential mechanisms of resistance after treatment in cfDNA and circulating tumor cells. Assessment of variable response may include evaluation of AEs or differences in efficacy. Refer to the laboratory manual for specific information regarding testing and sampling details. Samples will not be used to conduct unspecified disease or population genetic research either now or in the future.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.

Samples will be retained at a facility selected by sponsor for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and IRB/IECs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LOXO-305 or after LOXO-305 becomes commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome and exome sequencing, genome-wide association studies, and candidate gene studies. Regardless of technology utilized, data generated will be used only for the specific research scope described in this section. See the laboratory manual for details regarding sampling and submission.

8.7.2 Central Tumor Sample Submission

Adequate tissue samples at screening and at progression are required. If an archived sample is not available, a fresh sample should be obtained unless biopsy procedure is considered associated with moderate to high risks of complication or consent is not obtained. For patients who continue to receive therapy beyond progression, an additional biopsy will be required unless PD and EOT are within 2 cycles of one another (unless associated with a moderate to high safety risk or consent not obtained). Patients with inadequate archived and/or fresh tissue sample availability at screening may still be considered for enrollment upon review with documented Sponsor approval. Nodal tissue is preferred and must include at least 11 unstained slides (or representative sections of archived paraffin block). However, it is strongly recommended that 20 FFPE slides be submitted. Preferably, each section should be approximately 5 µm thick. In certain circumstances fewer slides may be acceptable with prior sponsor approval (i.e., where

it can be demonstrated by the site that fewer slides will provide a sample of sufficient quantity for retrospective central analysis of MTC diagnosis).

For tumor sample is being submitted at screening, the sample should be of sufficient quality and quantity to allow molecular analysis. Refer to the laboratory manual for tumor sample requirements and for details regarding sampling and submission.

8.7.3 Minimal Residual Disease

MRD peripheral blood and bone marrow aspirate samples for analysis should be collected in accordance with the SoA (Section 1.3). Tumor tissue specimens submitted at baseline may also be used to inform MRD assessment. See the laboratory manual for details regarding sampling and submission.

8.7.4 Saliva for Germline DNA

Saliva for germline DNA should be collected during Screening unless the patient does not consent. This sample may be used to determine the somatic or germline origin of mutations identified from analysis of archival or fresh tumor samples. See the laboratory manual for details regarding sampling and submission.

8.8 Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, resistance mechanisms, variability of participant response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including but not limited to deoxyribonucleic acid (DNA), cell free DNA, RNA, proteins, lipids, and other cellular elements.

Blood and tissue samples for biomarker research will be collected at the times specified in the SoA (Section 1.3) where local regulations allow. It is possible that biomarker data for patients in the study have already been generated from samples that were collected and analyzed prior to enrolling in this study. This may include pathology reports and data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in Sections 8.7 and 8.8.

Samples will be used for research on the drug target, disease process, variable response to LOXO-305, pathways associated with MCL and the mechanism of action of LOXO-305. These samples may also be used to develop related research methods or to validate diagnostic tools or assays.

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigator site personnel.

An optional tissue biopsy may be collected at the time of progression if it can be safely performed and patient or legal representative/ guardian provides consent.

Loxo has a right to retain a portion of the submitted tissue. Archival blocks will be sectioned and returned to the study site if requested. Slides and tissue samples collected on-study will not be returned. For biopsies performed in the setting of disease progression, the sponsor should be contacted to inform them of the planned biopsy.

Samples will be retained at a facility selected by Loxo for a maximum 15 years after the last participant visit for the study, or for a shorter period if local regulations and IRB/IECs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LOXO-305 or after LOXO-305 becomes commercially available. Technologies are expected to improve during the 15-year storage period and, therefore, cannot be specifically named. Existing approaches, including mutation profiling, copy number variability analysis, gene expression assays, multiplex assays, whole genome sequencing, whole exome sequencing, RNA sequencing, and/or immunohistochemistry may be performed on these tissue samples to assess potential associations between these biomarkers and clinical outcomes. See the laboratory manual for details regarding sampling and submission.

8.8.1 Samples Required for Eligibility and Ongoing Assessment

Tumor Tissue Diagnosis

De-identified surgical pathology reports of the patient's histologic diagnosis of lymphoma, relevant biomarkers as well as ancillary studies such as flow cytometry, immunohistochemistry, FISH, cytogenetics, or molecular studies which were used to establish and inform the diagnosis are also required at screening (e.g., p53, SOX-11 and/or Ki67 staining). Redacted documentation of Cyclin D1 overexpression, t(11;14) and/or B cell marker status as outlined in the overall design and inclusion criteria (Sections 4.1 and 5.1) must be provided either from any time in the patient's history or from current biopsy studies in order for enrollment to proceed. Status determined after most recent treatment is preferred. Confirmation of MCL diagnosis (as outlined in Sections 4.1 and 5.1) must be determined in a laboratory with certification by CLIA, ISO/IEC, CAP, or equivalent. Redacted reports must be submitted to the sponsor or designee.

8.8.2 Bone Marrow Aspirate and Biopsy

A bone marrow biopsy and aspirate will be required at baseline for all patients as outlined in the SoA Section 1.3. Additionally, repeat bone marrow biopsy and aspirate is required for confirmation of CR for patients with BM involvement at baseline. See the laboratory manual for details regarding sampling and submission.

8.8.3 Gastrointestinal Endoscopy

For enrolled patients with suspected GI involvement on baseline imaging or by clinical symptomatology, esophagogastroduodenoscopy and/or colonoscopy (as clinically appropriate)

with random segmental biopsies must be performed during screening, if it is clinically safe to do so.

If GI involvement is not observed radiographically or suspected clinically at baseline, an esophagogastroduodenoscopy and colonoscopy with random segmental biopsies at baseline is not required.

For all patients with confirmed GI involvement by biopsy at baseline achieving radiographic CR, an esophagogastroduodenoscopy and/or colonoscopy, as clinically appropriate, with random segmental biopsies is required to confirm CR. See the laboratory manual for details regarding sampling and submission.

8.9 Immunogenicity Assessments

Not applicable.

8.10 Medical Resources Utilization and Health Economics

8.10.1 Patient-Reported Outcomes and Medical Resource Utilization

Patient-reported questionnaires will be administered electronically according to the SoA (Section 1.3) in countries where the questionnaires have been translated into the native language of the region and linguistically validated. The patient-reported outcomes will be used to compare changes in MCL symptoms, physical function, bothersome side effects, and other health-related quality of life (HRQoL) outcomes between treatment arms, and generate health utility data. Questionnaires will be administered electronically using a provisioned electronic patient-reported outcome (ePRO) device to the patient. Patients will complete the specified baseline assessments electronically at C1D1 clinic visit prior to their first dose of study drug. Subsequent assessments will be completed at home according to the SoA to minimize the number of activities required during clinic visits, with the exception of EOT and SFU. At these visits, 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 receipt of treatments.

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

PRO-CTCAE

These items have been developed to assess select symptomatic AEs from the patient perspective associated with cancer therapy, to complement the CTCAE data collected at the site level (Basch et al. 2014; Bennet et al. 2016).

The reported outcome-CTCAE will be administered electronically directly to the patient via the electronic device provided on a weekly basis for the first 12 weeks and then per cycle afterward. Sites will not administer this instrument.

FACT-GP5

This is a single item from the Functional Assessment of Cancer Therapy-Side Effects general scale to assess the overall burden of the items reported via the PRO-CTCAE. This item will be administered electronically directly to the patient via the electronic device provided thru the SoA. Sites will not administer this instrument.

EORTC QLQ-C30

Health-related quality of life will be assessed using the European Organization 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 cover 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)

Electronic versions of the questionnaires will be used and will be available to the patient on the provided electronic device. The full scale will be completed electronically on Day 1 of each cycle at the clinic site prior to receiving study treatment, whereas items 1 to 5 of this scale (EORTC QLQ-C30 patient functioning [PF]) will be completed weekly by the patient on the device provided (not at the clinic site).

EORTC IL63: MCL Symptom Assessment - Supplement

At timepoints where the EORTC QLQ-C30 is being administered, patients will complete the EORTC IL63, a supplemental set of 6 symptom items associated with MCL: Fatigue, Night sweats, Fever/Chills, and Bloating as experienced in the last 7 days.

EORTC IL[XX]: MCL Symptom Assessment

The EORTC IL[XX] consists of 14 symptom items associated with MCL that are drawn from the EORTC QLQ-C30 (8 items: appetite loss, fatigue, pain, nausea, dyspnea, sleep problems) and EORTC IL63 (6 items: Night sweats, Fever/Chills, Fatigue, and Bloating) into a single

assessment for completion by the patient at home at time-points in between administration of the full EORTC QLQ-C30 and EORTC IL63 in order to minimize patient burden.

The item library number will be added upon approval by EORTC.

EORTC IL19: Physical Function

The EORTC IL19 consists of five 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 home at time-points in between administration of the full EORTC QLQ-C30 in order to minimize patient burden.

PGIS (PATIENT'S GLOBAL IMPRESSION OF SEVERITY) Cancer Symptoms

The PGIS-Cancer Symptoms is a single-item assessment whereby patients are asked to report the overall severity of their cancer-related symptoms in the past 7 days using a 5-level response scale ranging from "No Symptoms" to "Very Severe".

PGIC (PATIENT GLOBAL IMPRESSION OF CHANGE) Cancer Symptoms

The PGIC-Cancer Symptoms is a single-item assessment whereby patients are asked to report how their cancer-related symptoms are now, compared to before they started taking the study medication using a 5-level response scale ranging from "Much Better" to "Much Worse".

EQ-5D-5L

Health status will be assessed using the 5-level-EuroQol (EQ-5D-5L) (Herdman et al. 2011). 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 on Day 1 of each cycle prior to receiving study treatment. EQ-5D-5L responses may be incorporated into cost utility analyses but is not intended to be included in the clinical study report (CSR).

Medical Resource Utilization

Health care 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 (granulocyte-colony-stimulating factor [G-CSF] use and transfusions).

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

Treatment with LOXO-305 will provide a clinically meaningful increase in PFS over treatment with ICB inhibitor monotherapy in patients with previously treated MCL.

9.2 Sample Size Determination

The study is expected to enroll approximately 500 patients. Patients will be randomized at 1:1 ratio between LOXO-305 (Arm A) and comparator (Arm B). The study is sized to achieve approximately 80% power to detect a targeted hazard ratio (HR) of 0.73 in PFS which, under the model assumptions, translates into a 37% relative improvement in median PFS comparing LOXO-305 arm to the comparator arm, at the 2-sided significance level of 0.05.

This sample size calculation was based on a median PFS of 16 months in the comparator arm versus a median PFS of 21.9 months in LOXO-305 arm. The accrual period is assumed to be 20 months, and a 10% of dropout rate is assumed by the time of the final PFS analysis.

9.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

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”).

9.4 Statistical Analyses

One interim analysis and a final analysis of PFS are planned. The interim analysis is planned when approximately 216 IRC-assessed events have been observed, which is expected to occur approximately 28 months after the first patient has been randomized. The final analysis is planned when approximately 322 IRC-assessed events have been observed, which is expected to occur approximately 42 months after the first patient has been randomized.

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 2-sided alpha level of 0.05, 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.

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 Statistical Analysis Plan (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 and exploratory 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 intention-to-treat (ITT) population. Baseline disease characteristics, prior anticancer therapies, historical illness, and preexisting conditions will also be summarized.

9.4.3.3 Concomitant Therapy

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

9.4.3.4 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.

9.4.4 Efficacy Analyses

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

9.4.4.1 Primary Analysis

The primary efficacy endpoint of PFS is defined as the time from the date of randomization until disease progression (assessed by the IRC per Lugano criteria) 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.

A log-rank test, stratified by the randomization strata, will be used for the primary comparison of PFS. The HR and its 95% CI will be computed from a stratified Cox regression model. In addition, median PFS and its 95% CI, as well as PFS rates and associated 95% CI at selected timepoints, will be provided. Sensitivity analyses for PFS will be described in the SAP.

Superiority for final analyses are anticipated to be assessed at 2-sided alpha level 0.046 (HR = 0.80). An efficacy interim analysis is planned and the Details are provided in Section 9.5.

9.4.4.2 Secondary Analyses

PFS per investigator assessment is defined as the time from the date of randomization until disease progression (per Lugano criteria) 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 number of patients who achieve a BOR of CR or PR divided by the total number of patients randomized to each treatment arm. The ORR, with 95% CI, will be summarized by treatment arm. ORR will be compared between Arm A and Arm B using a Cochran-Mantel-Haenszel test stratified by the randomization strata. The ORR according to both IRC and investigator-assessment will be evaluated.

DOR is defined as the time from the date of the first documented response to the earlier of the documentation of definitive PD (per Lugano criteria) or death from any cause. Patients who are alive and without documented disease progression as of a data analysis cutoff date will be censored. The same censoring rules and analysis methods will be applied as described for PFS. The DOR according to both IRC and investigator-assessment will be evaluated.

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 at the last date the patient is known to be alive.

EFS is defined as the time from date of randomization to the date of disease progression or start of new treatment for MCL or withdrawal from trial due to toxicity or death, whichever occurs first.

TTF is defined as a composite endpoint measuring time from randomization to discontinuation of treatment for any reason.

TTNT is defined as time from the date of randomization to the date of the next non-protocol-specified therapy for progressive MCL.

The analysis methods for OS, EFS, TTF and TTNT 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.

AEs will be graded by the investigator according to the National Cancer Institute (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.

Summaries by treatment arm will be provided for the following:

- Grade 3 or Grade 4 TEAEs
- TEAEs leading to permanent study treatment discontinuation
- TEAEs leading to dose modification
- serious TEAEs, and
- TEAEs resulting in death.

9.4.6 Pharmacokinetic/Pharmacodynamic Analyses

LOXO-305 plasma concentrations will be summarized by descriptive statistics. Additional analysis utilizing the population PK approach may also be conducted if deemed appropriate.

The relationship between LOXO-305 plasma exposure and selected efficacy and safety outcomes may be explored.

9.4.7 Other Analyses

9.4.7.1 Patient-Reported Outcomes and Medical Resource Utilization

For each 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.

TTW of MCL-symptoms will be described using the method of Kaplan-Meier and a comparative analysis between the 2 arms using a log-rank test. Further details will be provided in the SAP.

Proportion of time with high side-effect burden will be specified in a future SAP specific to this PRO endpoint. The SAP for PRO endpoints will include further details for each PRO assessment, the patient dimension studied, as well as those analyses intended to evaluate the performance and measurement properties of each assessment, including the reliability and validation of the relationship between patient-reported outcomes and other study outcomes.

Frequency counts of hospitalizations, emergency room visits, G-CSF use, and transfusions will be reported descriptively for each treatment arm by cycle.

9.4.7.2 Subgroup Analyses

Details of subgroup analysis will be provided in SAP.

9.4.7.3 Biomarker Analysis

Biomarker results will be summarized and may be analyzed for correlations with clinical outcomes, if feasible.

9.5 Interim Analyses

One interim analysis will be conducted. The stopping rule is based on the primary efficacy endpoint, IRC-assessed PFS using Lan-DeMets alpha-spending function with the O'Brien-Fleming boundary (Lan and DeMets 1983, O'Brien and Fleming 1979). The interim analysis will occur when approximately 216 PFS events (67% of the event goal) have been observed. Superiority for interim analysis is anticipated to be assessed at 2-sided alpha level of 0.012 (HR = 0.71). The nominal alpha levels for the interim and final analyses will be determined based on the actual number of PFS events observed at the time of the analyses.

The SAP will describe the planned interim analyses in greater detail.

9.6 Data Monitoring Committee

The DMC will review the safety data periodically and the results of the interim analysis and provide recommendations according to the DMC charter.

The first safety data review will be performed by the DMC after approximately 50 patients have been randomized and had the opportunity to be treated for approximately 8 weeks. After the first review meeting, the DMC will meet and review data approximately every 6 months. Detailed information on the role of the DMC and frequency of meetings will be provided in the DMC charter separate from this protocol.

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 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

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 and initiated 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.
- 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

The sponsor or its representative is required to report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system according to Directive 2001/20/EC, and to all country regulatory authorities where the study is being conducted, according to local applicable regulations.

The following describes the safety reporting timeline requirements for SUSARs and other reportable events:

Immediately and within 7 calendar days:

- Any suspected AE that is associated with the use of the study drug, unexpected, and fatal or life-threatening. Follow-up information must be reported in the following 8 days.

Immediately and within 15 calendar days:

- Any suspected AE that is associated with the use of the study drug, unexpected, and serious, but not fatal or life-threatening, and there is evidence to suggest a causal relationship between the study drug and the event.

- Any finding from tests in laboratory animals that suggest a significant risk for human patients, including reports of mutagenicity, teratogenicity, or carcinogenicity.

- Any event in connection with the conduct of the study or the development of the study drug that may affect the safety of the study patients. In addition, periodic safety reporting to regulatory authorities will be performed by the sponsor or its representative according to national and local regulations.

10.1.5 Data Protection

- Patients will be assigned a unique identifier by the sponsor. Any patient 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 his/her 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 patients.
- The patient must be informed that his/her 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. Blinded independent review committee will consist of independent radiologists to perform response assessments and determination of disease progression per Lugano criteria (Section 10.7 Appendix 7).

10.1.7 Dissemination of Clinical Study Data

Dissemination of study data will be performed according to all applicable regulations and international policies.

10.1.8 Data Quality Assurance

- All patient data relating to the study will be recorded on printed or 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 CRF 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.
- The sponsor or its representatives will do the following to ensure accurate, complete, and reliable data:
    - 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, 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 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 IRB/IECs with direct access to original source documents.

Data Capture System

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

An electronic data capture (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, electronic Patient Reported Outcomes (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.

10.1.9 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 reported on the CRF or 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.

10.1.10 Study and Site Start and Closure

The sponsor designee 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.

10.1.10.1 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.

10.1.10.2 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: Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology – Local laboratory	
Leukocytes (WBC)	Basophils
Neutrophils	Erythrocytes (RBC)
Lymphocytes	Hemoglobin (HGB)
Monocytes	Hematocrit (HCT)
Eosinophils	Platelets (PLT)
Coagulation – Local laboratory	
PT/INR	PTT/aPTT
Clinical chemistry – Local laboratory	
Serum concentrations of:	
Sodium	
Chloride	
Albumin	
Glucose (random)	
Magnesium	
Potassium	
Protein	
Blood urea nitrogen (BUN) or blood urea	
Calcium	
Creatinine	
Lactate dehydrogenase (LDH)	
Hepatic monitoring – Local laboratory	
Alanine aminotransferase (ALT)	Bilirubin, direct
Aspartate aminotransferase (AST)	Bilirubin, total
Alkaline phosphatase	
Urinalysis – Local laboratory	
Blood	Protein
Glucose	Specific gravity
Ketones	Urine leukocyte esterase[a]
pH	
Pregnancy Test[b] – Local laboratory	
Urine pregnancy test	Serum pregnancy test
Thyroid panel - Local laboratory	
Free Triiodothyronine (T3)	Thyroid-stimulating hormone (TSH)
Free Thyroxine (T4)	

Note: Neutrophils reported by automated differential hematology instruments include both segmented and band forms. When a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and reported on the CRF, unless the CRF specifically provides an entry field for bands.

[a] Urine microscopy may be used in the place of the urine leukocyte esterase assessment to test for the presence of WBCs.

[b] For female patients of childbearing potential.

10.3 Appendix 3: Contraceptive Guidance

Willingness of men and women of reproductive potential to observe conventional and highly effective or acceptable birth control methods for the duration of treatment and for 6 months following the last dose of study treatment. Women of reproductive potential are defined as following menarche and who are not postmenopausal (and 2 years of non-therapy-induced amenorrhea) or surgically sterile). For male patients with a non-pregnant female partner of child-bearing potential and a woman of child-bearing potential one of the following

Highly effective birth control methods with a failure rate of less than 1% per year when used consistently and correctly are recommended (CTFG 2014):

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.

Note:
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.

Acceptable birth control methods with a failure rate of more than 1% per year when used consistently and correctly include (CTFG 2014):

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)

Note:
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.

Birth control methods unacceptable for this clinical trial are:

a. periodic abstinence (calendar, symptothermal, or post-ovulation methods)
b. withdrawal (coitus interruptus)
c. spermicide only
d. lactational amenorrhea method

Sperm donation is prohibited during the duration of participation on this protocol and for 6 months after the last dose of study drug.

10.4 Appendix 4: Liver Safety

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 sponsor when appropriate.

Hepatic Monitoring Tests	
Hepatic Hematology	**Haptoglobin**
HGB	
HCT	**Hepatic Coagulation**
Erythrocytes (RBC)	Prothrombin time
Leukocytes (WBC)	Prothrombin time, 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	
AST	**Other Serology Testing**
GGT	CMV/EBV testing (antibody and/or DNA)
CPK	**Recommended Autoimmune Serology**
	Anti-nuclear antibody [a]
	Anti-smooth muscle antibody [a]

Note: Neutrophils reported by automated differential hematology instruments include both segmented and bad forms. Whenever a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

10.5 Appendix 5: Restricted and Prohibited Concomitant Medication

The following table(s) describes 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. See Section 6.5 for additional information.

This is not an all-inclusive list.

Note: Nonsystemic (e.g., topical creams, eye drops, mouthwashes, etc.) applications of the following are permissible.

Inhibitors of CYP3A4	
Strong inhibitors [a]	**Moderate inhibitors** [b]
boceprevir	amprenavir
clarithromycin	aprepitant
conivaptan	atazanavir
grapefruit juice	ciprofloxacin
indinavir	darunavir
itraconazole	diltiazem
ketoconazole	erythromycin
lopinavir	fluconazole
mibefradil	fosamprenavir
nefazodone	imatinib
nelfinavir	verapamil
posaconazole	
ritonavir	
saquinavir	
telaprevir	
telithromycin	
voriconazole	
Star fruit	
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 above lists are not exhaustive. Additional information refer to: http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm.

Inducers of CYP3A4

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

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

CYP3A Sensitive Substrates

abemaciclib	darunavir	lopinavir	simvastatin
acalabrutinib	dasatinib	lovastatin	sirolimus
alectinib	dronedarone	lumefantrine	tacrolimus
alfentanil	ebastine (OUS only)	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 14May2020.

Examples of Strong P-gp Inhibitors	
amiodarone	quinidine
carvedilol	ranolazine
clarithromycin	ritonavir
dronedarone	saquinavir and ritonavir
itraconazole	telaprevir
lapatinib	tipranavir and ritonavir
lopinavir and ritonavir	verapamil
propafenone	

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.

Examples of P-gp Substrates	
dabigatran	loperamide
digoxin	verapimil

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.

10.6 Appendix 6: Creatinine Clearance Formula

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

For serum creatinine concentration in mg/dL:

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

[a] Age in years, weight (wt) in kilograms.

Source: Cockcroft and Gault 1976.

10.7 Appendix 7: Lugano Classification of Response in Non-Hodgkin Lymphoma

Lugano Classification of Response

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	**Complete metabolic response**	**Complete radiologic response (all of the following)**
Lymph nodes and extra lymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial metabolic response**	**Partial remission (all of the following):**
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow, but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	**Progressive metabolic disease**	**Progressive disease requires at least 1 of the following PPD progression:**
Individual target nodes/nodal masses Extranodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end of treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly New or clear progression of preexisting nonmeasured lesions
Nonmeasured lesions	None	Regrowth of previously resolved lesions

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; GI = gastrointestinal; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

Footnotes:

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).

Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation.

Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability, but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging.

In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤mediastinum; 3, uptake > mediastinum, but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Source: (Cheson et al. 2014).

10.8 Appendix 8: Guidelines for Patient Sample Collection for Central Analysis

Select patient samples from bone marrow, GI endoscopy biopsy and/or nodal/extranodal sites will be collected during the conduct of this study for central assessment. The following table is meant to be a guide; refer to the laboratory manual for additional details.

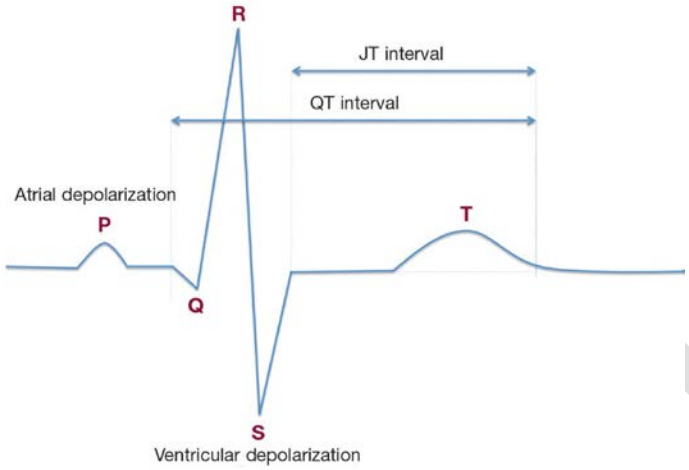
Guidelines for Patient Sample Collection for Analysis

Time Point	GI Endoscopy	Bone Marrow	Lymph Node/Tumor Tissue
Baseline	Required at baseline for patients with suspected GI involvement on imaging and/ or clinical suspicion of GI involvement	Required at baseline for all patients	Required archived or fresh at baseline unless considered unsafe or patient does not consent
Response time points	Required at CR for patients with involvement at baseline	Required at CR for patients with involvement at baseline	-
Progression	-	-	Required for all patients unless considered unsafe or patient does not consent
EOT[a]	-	-	Required for all patients unless considered unsafe or patient does not consent

a if PD + EOT are at same time, singular sample is required. For patients who continue beyond PD due to ongoing clinical benefit, samples at both timepoints should be collected as safe/able.

10.9 Appendix 9: QTcF Measurement Adjustment in Patients with a Widened QRS Complex > 110 ms

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 subjects with normal QRS durations, without BBB or intra-ventricular 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 subjects 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].

10.10 Appendix 10: Abbreviations

Abbreviation or Term	Definition
AE	adverse event
ADL	activities of daily living
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
AUC_{0-24}	area under the concentration versus time curve from time 0 to 24 hours
BCR	B cell receptor
BID	twice daily
BUN	blood urea nitrogen
BTK	Bruton's tyrosine kinase
C	cycle
C1D1	Cycle 1 Day 1
CAP	College of American Pathologists
CAR-T	chimeric antigen receptor-modified T cells
cfDNA	circulating free tumor deoxyribonucleic acid
CIT	chemoimmunotherapy
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CLL	chronic lymphocytic leukemia
C_{min}	minimum drug concentration
CMV	cytomegalovirus
CMV-DNA	cytomegalovirus DNA
CNS	central nervous system
CR	complete response
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DAG	diacyl glycerol
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
eCOA	electronic Clinical Outcomes Assessments
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture

Abbreviation or Term	Definition
EORTC IL19	European Organisation for Research and Treatment Item Library 19
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0
EOT	End of Treatment
FACT-GP5	Functional Assessment of Cancer Therapy-Side Effects
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GI	gastrointestinal
GLP	Good Laboratory Practice
GnRH	gonadotropin-releasing hormone
GVHD	graft versus host disease
HBV-DNA	hepatitis B virus DNA
HCV-RNA	hepatitis C virus RNA
HIV	Human Immunodeficiency Virus
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
IC_{90}	90% inhibitory concentration
ICB	investigator's choice of BTK
ICF	informed consent form
ICH	International Council for Harmonisation
ICH GCP	International Council for Harmonisation-Good Clinical Practices
IEC	Independent Ethics Committee
INR	international normalized ratio
IP3	inositol 3-phosphate
IRB	Institutional Review Board
IRC	Independent Review Committee
ISO/IEC	International Organization for Standardization/ Independent Ethics Committee
ITP	idiopathic thrombocytopenic purpura
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	Intravenous
K_m	Michaelis constant
LDH	lactate dehydrogenase
LDi	longest diameter
LHRH	luteinizing hormone-releasing hormone
LMA	locomotor activity
LOXO-305	investigational product
LTFU	Long-term Follow-up
MCL	mantle cell lymphoma

Abbreviation or Term	Definition
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MR	minor response
MRD	minimal residual disease
MRI	magnetic resonance imaging
MRSD	maximum recommended starting dose
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NHL	non-Hodgkin lymphoma
NOAEL	no-observable-adverse-effect-level
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PGIC	Patient Global Impression of Change – Cancer Symptoms
PGIS	Patient's Global Impression of Severity – Cancer Symptoms
P-gp	p-glycoprotein
PI3K	PI3-kinase
PIP3	phosphatidylinositol 3-phosphate
PK	pharmacokinetic
PLCg2	phospholipase C gamma 2
PO	per os (oral)
PP	Per-protocol Analysis Set
PPI	proton pump inhibitors
PR	partial response
PRO-CTCAE	patient-reported outcome Common Terminology Criteria for Adverse Events
PT	prothrombin time
QD	once daily
QTcF	QT interval corrected for heart rate (Fridericia's formula)
RBC	red blood cell
REB	Research Ethics Board
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
R/R	relapsed/refractory
RT	Richter's Transformation
SAE	serious adverse event

Abbreviation or Term	Definition
SAP	Statistical Analysis Plan
SC	Subcutaneous
SCT	stem cell transplant
SD	stable disease
SDD	spray-dried dispersion
SERDs	selective estrogen receptor degraders
SERMs	selective estrogen receptor modulators
SFU	Safety Follow-up
SLL	Small Lymphocytic Lymphoma
SPD	sum of product diameters
SRC	Safety Review Committee
STD 10	severely toxic dose in 10% of the animals
SUSARs	suspected unexpected serious adverse reactions
$T_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
TEC	Tec kinase
TID	thrice daily
T_{max}	time to maximum plasma concentration
ULN	upper limit of normal
US	United States
VGPR	very good partial response
V_z/F	apparent volume of distribution
WBC	white blood cell
WM	Waldenstrom macroglobulinemia
Xid	X-linked immunodeficiency
XLA	X-linked agammaglobulinemia
Y551	tyrosine residue 551

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