Protocol J2N-MC-JZNJ (b)

A Phase 2 Study of Oral LOXO-305 in Patients with Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) or Non-Hodgkin Lymphoma (NHL)

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LOXO-305 (LY3527727)

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Approval Date: 16-Jul-2021 GMT

SYNOPSIS

TITLE:

A Phase 2 Study of Oral LOXO-305 in Patients with Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) or Non-Hodgkin Lymphoma (NHL)

PROTOCOL NUMBER:

J2N-MC-JZNJ

STUDY SITES:

Approximately 20 to 25 institutions in China are planned for participation in this study.

PHASE:

Phase 2

OBJECTIVES AND ENDPOINTS:

Objectives	Endpoints
Primary • To assess the anti-tumor activity of LOXO-305 based on ORR according to Lugano Treatment Response Criteria for MCL and other NHL (Appendix A), International Workshop Guidelines for CLL/SLL (IWCLL 2018, Appendix B) and WM (IWWM, Appendix C), or other criteria as appropriate to tumor type, as assessed by an IRC	• ORR by IRC
Secondary • To assess, for each cohort, the anti-tumor activity of LOXO-305	• ORR (by investigator) • BOR (by investigator and IRC) • DOR (by investigator and IRC) • PFS (by investigator and IRC) • OS
• To determine the safety profile and tolerability of LOXO-305.	• AEs, SAEs and TEAEs, changes in hematology and blood chemistry values, assessments of physical examinations, vital signs and ECGs.
• To characterize the PK properties of LOXO-305.	• Plasma concentration of LOXO-305 and PK parameters including, but not limited to, AUC_{0-24}, C_{max}, T_{max}, $T_{1/2}$
• To determine the association of clinical response categories	• Symptomatic response: improvement in cancer-related symptoms among patients with MCL associated with BOR • Functional response: improvement in physical function among patients with MCL associated with BOR
• To collect PRO data to explore disease-related symptoms and HRQoL	• Changes from baseline in disease-related symptoms and HRQoL measured by EORTC QLQ-C30
• To determine the relationship between PK and drug effects, including efficacy and safety	• Differences in efficacy and safety based on LOXO-305 PK parameters

Abbreviation: AE = adverse event; AUC_{0-24} = area under the concentration versus time curve from time 0 to 24 hours; BOR = best overall response; C_{max} = maximum drug concentration; CLL = chronic lymphocytic leukemia; DOR = duration of response; ECGs = electrocardiograms; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0; HRQoL = health-related quality of life; IRC = Independent Review Committee; MCL = mantle cell lymphoma; NHL = non-Hodgkin lymphoma; ORR = overall

response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PRO = patient reported outcomes; SAE = serious adverse event; SLL = small lymphocytic lymphoma; $T_{1/2}$ = terminal elimination half-life; TEAE = treatment emergent adverse event; T_{max} = time to maximum plasma concentration; WM = Waldenström macroglobulinemia.

STUDY DESIGN:

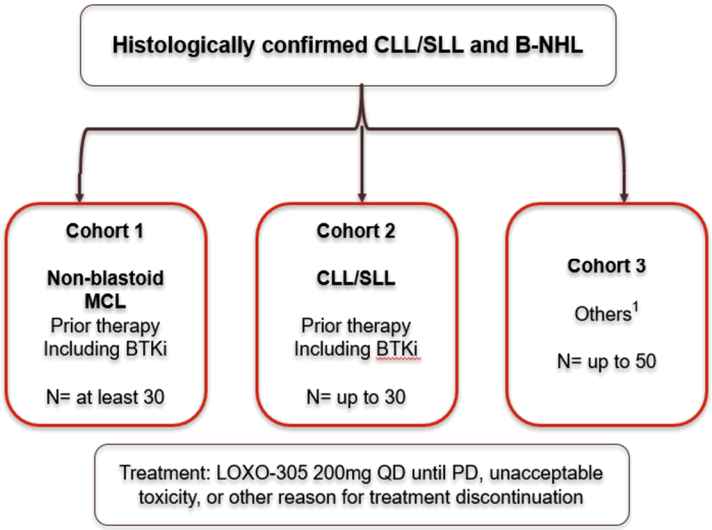
This is an open-label, multi-center phase 2 study to evaluate efficacy and safety of oral LOXO-305 as monotherapy in patients with MCL, CLL/SLL and other types of B-cell NHL who have failed or are intolerant (as per the definitions in Appendix D) to standard of care.

The recommended phase 2 dose is 200 mg once daily (QD). Patients will be enrolled to 1 of 3 cohorts depending on tumor histology and prior treatment history. Cycle length will be 28 days.

The Study Schema is provided in Synopsis Figure 1: Study Schema.

At least 30 patients for Cohort 1, up to 30 patients for Cohort 2, and up to 50 patients for Cohort 3 are planned, thus approximately ~ 120 patients will be enrolled across all cohorts. (refer to Synopsis Figure 1: Study Schema):

- Cohort 1: Non-blastoid MCL patients with no central nervous system (CNS) metastases and treated with prior chemoimmunotherapy (refer to Synopsis Table 1) and a BTK-inhibitor (refer to Appendix E) containing regimen
- Cohort 2: CLL/SLL patients treated with a prior BTK inhibitor containing regimen
- Cohort 3:
  - MCL or CLL/SLL patients not meeting the definitions of Cohort 1 or Cohort 2 and having failed or intolerant to standard of care, or unsuitable for standard of care in the opinion of investigator;
  - Other B cell NHL (include but not limited to DLBCL, MZL and WM) patients having failed or intolerant to standard of care, or unsuitable for standard of care in the opinion of investigator.



[1]"**Others" Cohort for:**

a. MCL or CLL/SLL patients not meeting the definitions of Cohort 1 or Cohort 2 and having failed or intolerant to standard of care, or unsuitable for standard of care in the opinion of investigator;

b. Other B cell NHL (include but not limited to DLBCL, MZL and WM) patients having failed or intolerant to standard of care, or unsuitable for standard of care in the opinion of investigator.

Abbreviations: BTK = Bruton's tyrosine kinase; BTKi = BTK inhibitor; CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B cell lymphoma; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; NHL = non-Hodgkin lymphoma; PD = progressive disease; QD = once daily; SLL = small lymphocytic lymphoma; WM = Waldenström macroglobulinemia.

Synopsis Figure 1: Study Schema

Synopsis Table 1: Chemoimmunotherapy for MCL

Cohort	Therapy (including but not limited to)
Cohort 1: Non-blastoid MCL patients with no CNS metastases and treated with prior chemoimmunotherapy and BTK-inhibitor containing regimen	1. high dose cytarabine based therapy: (e.g., R-CHOP/R-DHAP, R-hyperCVAD) 2. rituximab based therapy (e.g., R-CHOP, BR, VR-CAP)

Inclusion Criteria:

1. Patients with histologically confirmed B-cell malignancy including:
   - Cohort 1 MCL: Confirmed diagnosis of non-blastoid MCL with no CNS metastases and with documentation of overexpression of cyclin D1 and/or t(11;14) and treated with prior chemoimmunotherapy and a BTK inhibitor containing regimen;
   - Cohort 2 CLL/SLL: Confirmed diagnosis of CLL/SLL by IWCLL 2018 criteria treated with a prior BTK inhibitor containing regimen;
   - Cohort 3 Others: Confirmed diagnosis of CLL/SLL by IWCLL 2018 criteria, WM with documentation of MYD88 mutation, MCL and other types of B-cell NHL (including but not limited to DLBCL and MZL) by WHO 2016 criteria, not otherwise specified in Cohort 1 and 2, and having failed or intolerant to standard of care, or unsuitable for standard of care in the opinion of investigator.

   For patients in each Cohort:
   - All patients must have disease requiring treatment;
   - Documented evidence of patients having failed or intolerant on the most recent line of therapy or relapse prior to study enrollment is required;
   - Patients in Cohort 1 and 2, relapsed/refractory or intolerant (as per the definitions in Appendix D) to a prior BTK inhibitor (investigational or approved, and either alone or in combination with other agents) treatment is required;
   - Patients with MCL in Cohort 1 who will be evaluated by Lugano criteria must have at least 1 site of radiographically assessable disease (i.e., lymph node longest diameter (LDi) >1.5 cm, extra nodal site >1.0 cm in LDi, or unequivocal hepatomegaly or splenomegaly due to disease). Patients with non-measurable disease are eligible and will be assigned to Cohort 3;
   - For CLL/SLL patients, at least 1 indication for treatment consistent with IWCLL 2018 criteria (refer to Appendix F) is required.
2. Eastern Cooperative Oncology Group (ECOG) 0-2.
3. At least 18 years of age.
4. Confirmation of availability of tumor sample along with pathology report for central pathology review as described in Section 7.4 of the Protocol for patients enrolled in Cohort 1.
5. Adequate hematologic status, defined as the following on or within 7 days of C1D1 before treatment:
   a. Absolute neutrophil count (ANC) $\geq 0.75 \times 10^9$/L without granulocyte-colony stimulating factor (GCSF) supporting within 7 days of Screening assessment; the patient may enroll below this threshold if there is documented bone marrow involvement considered to impair hematopoiesis.
   b. Platelet count $\geq 50 \times 10^9$/L not requiring transfusion or growth factors supporting within 7 days of Screening assessment; the patient may enroll below this threshold if there is documented bone marrow involvement considered to impair hematopoiesis.
   c. Hb $\geq$ 8 g/dL not requiring transfusion or growth factors supporting within 7 days of Screening assessment; the patient may enroll below this threshold if there is documented bone marrow involvement considered to impair hematopoiesis.
   d. Patients must be responsive to blood or platelets transfusion support if given for bone marrow involvement induced cytopenias. Patients refractory to transfusion support are not eligible. See also exclusion criteria item 18.
6. Adequate coagulation, defined as activated partial thromboplastin time (aPTT) and prothrombin time (PT) or (international normalized ration [INR]) not greater than 1.5 × upper limit of normal (ULN).
7. Adequate hepatic function, defined as:
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\leq$2.5 × ULN or $\leq$5 × ULN with documented liver metastases;
   b. Total bilirubin $\leq$1.5 × ULN or $\leq$3 × ULN with documented liver metastases and/or Gilbert's Disease. If total

bilirubin is >1.5 × ULN then direct/indirect or conjugated/unconjugated bilirubin tests should be performed for patients with hemolysis and/or Gilbert's syndrome, they may be enrolled if unconjugated/indirect bilirubin is <5 × ULN with sponsor approval.

8. Adequate renal function defined as creatinine clearance of ≥30 mL/ minute using Cockcroft/Gault Formula:

$$\frac{(140 - \text{age}) \times \text{body weight (kg)} \times 0.85 \text{ (if female)}}{\text{serum creatinine (mg/dL)} \times 72}$$

9. Ability to swallow tablets and comply with outpatient treatment, laboratory monitoring, and required clinic visits for the duration of study participation.
10. Willingness of men and women of reproductive potential (defined as following menarche and not postmenopausal [and 2 years of non-therapy-induced amenorrhea] or surgically sterile) to observe conventional and highly effective birth control methods with failure rates of <1% for the duration of treatment and for 6 months following the last dose of study treatment; this must include barrier methods such as condom or diaphragm with spermicidal gel. See Section 4.1 of this protocol for detailed listing of acceptable methods of birth control. Sperm donation is prohibited during the duration of participation on this protocol and for 6 months after the last dose of study drug.

Exclusion Criteria:

11. Investigational agent or anticancer therapy (including some Chinese traditional medicine with anti-tumor indication in label) within 5 half-lives or 14 days, whichever is shorter, prior to planned start of LOXO-305 except therapeutic monoclonal antibody treatment must be discontinued a minimum of 4 weeks prior to the first dose of LOXO-305. In addition, no concurrent systemic anticancer therapy is permitted.
    a. Continuation of certain standard of care anticancer therapies, including hormonal therapy for breast and prostate cancer, is allowed, provided they are not on the list of prohibited concomitant medications. Refer to Section 6.3.2 for allowed and Section 6.3.3 for prohibited medications.
12. Major surgery (excluding placement of vascular access or biopsy) within 4 weeks prior to planned start of LOXO-305.
13. Radiotherapy with a limited field of radiation for palliation within 7 days of the first dose of study treatment, except for patients receiving radiation to pelvis, skull or sternum (bone marrow area) or receiving whole brain radiotherapy, which must be completed at least 4 weeks prior to the first dose of study treatment.
14. Patients requiring therapeutic anticoagulation with warfarin.
15. Any unresolved toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE [version 5.0]) Grade 2 at the time of starting study treatment except for alopecia or otherwise specified in this eligibility criteria.
16. History of allogeneic or autologous stem cell transplant (SCT) or chimeric antigen receptor-modified T-cell (CAR-T) therapy within the 60 days prior to planned start of LOXO-305 treatment or with any of the following:
    a. Active graft versus host disease (GVHD);
    b. Cytopenia requiring transfusion support reflecting incomplete blood count recovery post-transplant;
    c. Need for anti-cytokine therapy for toxicity from CAR-T therapy; residual symptoms of neurotoxicity >Grade 1 from CAR-T therapy;
    d. Ongoing immunosuppressive therapy.
17. Known central nervous system (CNS) involvement by systemic lymphoma. Patients with previous treatment for CNS involvement who are neurologically stable (neurological symptoms and CNS imaging are stable and steroid dose is stable for 14 days prior to the first dose and no CNS surgery or radiation has been performed for 28 days, 14 days if stereotactic radiosurgery [SRS]) and without evidence of disease may be eligible and enrolled to Cohort 3 if a compelling clinical rationale is provided by the investigator and with documented sponsor approval. Primary CNS lymphoma is excluded.
18. Active uncontrolled auto-immune cytopenia (e.g., autoimmune hemolytic anemia [AIHA], idiopathic thrombocytopenic purpura [ITP]) where new therapy introduced, or concomitant therapy escalated within the 4 weeks prior to study enrollment is required to maintain adequate blood counts.
19. Significant cardiovascular disease defined as:
    a. Unstable angina, or
    b. History of myocardial infarction within 6 months prior to planned start of LOXO-305, or
    c. Documented left ventricular ejection fraction (LVEF) by any method of ≤45% in the 12 months prior to planned start of LOXO-305, assessment of LVEF during screening should be performed in selected patients as medically indicated or
    d. Any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification (refer

to Appendix G), or
   e. Uncontrolled or symptomatic arrhythmias
20. 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): $QTcF=QT/(RR^{0.33})$.
   a. 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 (agents known to cause QTc prolongation refer to Appendix H).
21. Patients who experienced a major bleeding event or grade ≥3 arrhythmia on prior treatment with a BTK inhibitor. NOTE: Major bleeding is defined as bleeding having one or more of the following features: potentially life-threatening bleeding with signs or symptoms of hemodynamic compromise; bleeding associated with a decrease in the hemoglobin level of at least 2 g per deciliter; or bleeding in a critical area or organ (e.g., retroperitoneal, intraarticular, pericardial, epidural, or intracranial bleeding or intramuscular bleeding with compartment syndrome).
22. Active 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 the sponsor makes it undesirable for the patient to participate in the trial. Screening for chronic conditions is not required.
23. Patients who have tested positive for Human Immunodeficiency Virus (HIV) are excluded due to potential drug-drug interactions between anti-retroviral medications and LOXO-305 and risk of opportunistic infections with both HIV and irreversible BTK inhibitors. For patients with unknown HIV status, HIV testing will be performed at Screening and result should be negative for enrollment.
24. Have active Hepatitis B or C.
   a. Patients with detectable hepatitis B virus (HBV) DNA and controlled disease may be permitted on therapy with sponsor approval. Concurrent viral suppressive treatment will be required for patients with detectable HBV DNA. Refer to Section 6.3.2 for allowed and Section 6.3.3 for prohibited medications.
   b. Patients with history of hepatitis C virus (HCV) infection who have completed viral suppressive therapy and have a viral load below the limit of quantification are allowed.
25. Clinically significant active malabsorption syndrome or other conditions likely to affect gastrointestinal (GI) absorption of the study drug.
26. Current treatment with certain strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers (refer to Appendix I) and/or strong p-glycoprotein (P-gp) inhibitors within 7 days before starting LOXO-305 (refer to Appendix J).
27. Pregnancy or lactation.
28. Active second malignancy unless in remission and with life expectancy >2 years and with documented sponsor approval. Refer to Protocol Exclusion Criteria (Section 4.2) for examples of allowed second malignancies.
29. Prior treatment with LOXO-305.
30. Patients with known hypersensitivity to any component or excipient of LOXO-305.

PLANNED SAMPLE SIZE:

CCI [redacted]

INVESTIGATIONAL PRODUCT:

LOXO-305 will be provided as tablets. The tablets will be provided to the sites for distribution to the patient for outpatient administration at assigned dose level. Dose is intended to be fixed (i.e., not weight-based or body surface area [BSA]-based).

TREATMENT PROCEDURES:

Patients will begin LOXO-305 on Cycle 1 Day 1 (C1D1) with 200 mg QD, and cycle length will be 28 days. Patients will continue dosing until progressive disease (PD) as defined by disease specific response criteria and assessed by investigator, unacceptable toxicity, or other reasons for treatment discontinuation. Patients with documented PD may be allowed to continue LOXO-305 if the patient is tolerating study drug and, in the opinion of the investigator, the patient is deriving clinical benefit from continuing study treatment, and continuation of treatment is approved by the sponsor, until the patient gets the 2nd PD, unacceptable toxicity occurs or the investigator agrees that the patient will no longer benefit from treatment. Patients continuing LOXO-305 treatment with sponsor approval should still follow on-treatment regular visit and relevant assessment.

STUDY ASSESSMENTS:

Safety observations include physical and neurological examination, body weight, ECOG score, clinical adverse events

(AEs), laboratory variables (hematology, serum or plasma chemistries, and urinalysis), ECGs and vital signs.

MCL patients in Cohort 1 with history of or evidence of GI involvement on baseline assessment may require appropriate upper and/or lower endoscopy procedure (if it is clinically safe) during screening with biopsy to document involvement at baseline, and follow up upper and/or lower endoscopy for documentation of complete response will be required for these patients, as appropriate.

Efficacy assessments include tumor evaluation (radiologic and laboratory) every 8 weeks beginning with Cycle 3 Day 1 (± 7 days) through Cycle 12 Day 1, then ~ every 12 weeks thereafter (± 2 weeks) for 1 year, then ~ every 6 cycles (± 4 weeks) thereafter, consistent with disease-defined criteria. An initial response evaluation (optional based on clinical indicated) may be conducted on Cycle 2 Day 1 (±7 days) with a confirmatory response evaluation conducted 4 weeks (Cycle 3 Day 1± 7 days) after the first tumor evaluation, if consistent with local institution and regulatory authority requirements.

Scans, bone marrow and peripheral blood samples (where applicable) used to assess response will be collected to permit independent review.

An End of Treatment (EOT) visit within 7 days of the last dose of LOXO-305 or the decision to terminate treatment is required.

In addition, a Safety Follow-up (SFU) visit between 4 and 5 weeks after the last dose of study treatment (i.e., 28 days after the last dose of study drug [+7 days]) is required to determine the status of any unresolved AEs.

All patients will enter Long-term Follow-up (LTFU) with visits ~ every 3 months (±1 month) for up to 2 years and ~every 6 months (±2 month) thereafter, for confirming the resolution of any serious adverse events (SAEs), PD if not occurring on study, subsequent anticancer therapy, and survival. LTFU may be conducted by phone if a patient unable to travel to clinic.

Patients who discontinue study treatment for reasons other than PD, withdrawal of consent or initiation of a new anticancer therapy, may continue undergoing disease assessment as appropriate to histology (as specified above) until PD, withdrawal of consent, or initiation of a new anticancer therapy.

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PK Time points are specified in protocol Section 7.2.

Additional PK may also be assessed when considered necessary by the investigator or the sponsor to understand the relationship between LOXO-305 exposure and safety or efficacy.

At study entry, tumor samples (lymph node/tumor biopsy or bone marrow) will be obtained from patients enrolled in Cohort 1 for disease and histology confirmation at central lab. Guidance is provided in the Laboratory Manual and Appendix K of the Protocol

STATISTICAL METHODS:

Safety Analyses:

The safety population will consist of all enrolled patients who receive at least 1 dose of LOXO-305. A baseline measurement and at least 1 laboratory or other safety-related measurement obtained after the start of study drug may be required for inclusion in the analysis of a specific safety parameter.

Efficacy Analyses:

Patients enrolled who meet the criteria for the primary analysis set (PAS) will be included in the primary analysis for Cohorts 1 and 2, as defined separately in the statistical analysis plan.

Overall response rate (ORR) will be assessed using Lugano criteria (Appendix A) or IWCLL (Appendix B) including assessment of complete response with incomplete marrow recovery (CRi), nodular PR (nPR), and PR with lymphocytosis (PR-L), or IWWM (Appendix C), as appropriate to tumor type. The estimate of the ORR will be calculated as the proportion of patients with best overall response (BOR) of PR or better, based on IWCLL, PR or better based on Lugano, and minor response or better for WM based on IWWM criteria as determined by IRC and by the treating investigator. The estimates of the ORR will be accompanied by a 2-sided 95% confidence interval (CI).

Waterfall plots will be used to depict graphically the maximum decrease from baseline in the sum of product diameters (SPD) of target lesions. Duration of response (DOR), progression-free survival (PFS), and overall survival (OS) will be summarized descriptively for each cohort using the Kaplan-Meier method.

Pharmacokinetic Analyses:

Plasma concentrations of LOXO-305 will be determined with a validated bioanalytical assay. The following PK parameters will be calculated from plasma concentrations if appropriate: C_{max}, T_{max}, AUC_{0-t} (area under the concentration versus time curve from time 0 to t), apparent oral clearance (CL/F), apparent volume of distribution (Vz/F), and $T_{1/2}$.

Summary statistics will be generated by cohort and across cohorts as appropriate.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or Term	Definition
AE	adverse event
AIHA	autoimmune hemolytic anemia
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
AUC_{0-t}	area under the concentration versus time curve from time 0 to t
BBB	bundle branch block
BCR	B cell receptor
BID	twice daily
BLC2	B-cell lymphoma 2
BMX	BMX tyrosine kinase
BOR	best overall response
BUN	blood urea nitrogen
BSA	body surface area
BTK	Bruton's tyrosine kinase
BTKi	Bruton's tyrosine kinase inhibitor
C1D1	Cycle 1 Day 1
C481	cysteine residue at position 481
CAR-T	chimeric antigen receptor-modified T cells
CHO	Chinese Hamster Ovary cells
CI	confidence interval
CL/F	apparent oral clearance of drug
CLL	chronic lymphocytic leukemia
C_{max}	maximum drug concentration
C_{min}	minimum drug concentration
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CRF	case report form
CRi	complete response with incomplete marrow recovery
CRP	clinical research physician
CYP3A4	cytochrome P450 3A4
CSR	clinical study report
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DAG	diacyl glycerol
DLBCL	diffuse large B cell lymphoma
DLT	dose-limiting toxicity

Abbreviation or Term	Definition
DNA	deoxyribonucleic acid
DOR	duration of response
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EOT	End of Treatment
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of
EORTC IL-63	European Organization for Research and Treatment of Cancer Items Library
ERK	extracellular signal-regulated kinase
FDA	Food and Drug Administration
FL	follicular lymphoma
FLC	free light chain
FOB	functional observational battery
GCP	Good Clinical Practices
GI	gastrointestinal
GLP	Good Laboratory Practice
GnRH	gonadotropin-releasing hormone
GVHD	graft versus host disease
Hb	hemoglobin
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDV	hepatitis D virus
hERG	human ether-à-go-go related gene
HIV	human immunodeficiency virus
HPBL	human peripheral blood lymphocytes
IB	Investigator's Brochure
IC50	50% inhibitory concentration
IC90	90% inhibitory concentration
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
ITK	IL2-inducible T-cell kinase
ITP	idiopathic thrombocytopenic purpura

Abbreviation or Term	Definition
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	Intravenous
K_m	Michaelis constant
LDH	lactate dehydrogenase
LDi	longest diameter
LDT	lymphocyte doubling time
LHRH	luteinizing hormone-releasing hormone
LMA	locomotor activity
LOXO-305	investigational product
LTFU	Long-term Follow-up
LVEF	left ventricular ejection fraction
LYN	LYN tyrosine kinase
MAPK	mitogen-activated protein kinase
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram
MR	minor response
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
NCI CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse
NFAT	nuclear factor of activated T cells
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NHL	non-Hodgkin lymphoma
nPR	nodular PR
ORR	overall response rate
OS	overall survival
PAS	primary analysis set
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
P-gp	p-glycoprotein
PI3K	PI3-kinase
PIP3	phosphatidylinositol 3-phosphate
PK	pharmacokinetic
PKC	protein kinase C
PLCg2	phospholipase C gamma 2
PR	partial response
PR-L	PR with lymphocytosis
PRO	patient reported outcome

Abbreviation or Term	Definition
PT	prothrombin time
QD	once daily
QTcF	QT interval corrected for heart rate (Fridericia's formula)
RBC	red blood cell
RNA	ribonucleic acid
R/R	relapsed/refractory
RT	Richter's transformation
SAE	serious adverse event
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
SPEP	serum protein electrophoresis
SRS	stereotactic radiosurgery
SUSARs	suspected unexpected serious adverse reactions
SYK	spleen associated tyrosine kinase
$T_{1/2}$	terminal elimination half-life
TBL	Total bilirubin
TEAE	treatment-emergent adverse event
TEC	Tec kinase
TLS	tumor lysis syndrome
T_{max}	time to maximum plasma concentration
TXK	TXK tyrosine kinase
ULN	upper limit of normal
VGPR	very good partial response
Vz/F	apparent volume of distribution
WBC	white blood cell
WHO	World Health Organization
WM	Waldenström macroglobulinemia
Xid	X-linked immunodeficiency
XLA	X-linked agammaglobulinemia
Y551	tyrosine residue 551

1. INTRODUCTION

1.1 BTK-Dependent Malignancies and Current Treatment Options

Bruton's Tyrosine Kinase (BTK) is a member of the Tec kinase (TEC) family of non-receptor tyrosine kinases (which includes BTK, IL2-inducible T-cell kinase [ITK], TEC, TXK tyrosine kinase [TXK], and BMX tyrosine kinase [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 tyrosine kinase (LYN) and spleen associated tyrosine kinase (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), mantle cell lymphoma (MCL) and marginal zone lymphoma (MZL, each related to germinal center B cells) and Waldenström 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).

Covalent BTK inhibitors inhibit BTK by binding to the adenosine triphosphate (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). Three covalent BTK inhibitors have been approved globally for the treatment of patients with B cell malignancies, including ibrutinib, acalabrutinib, and zanubrutinib. These drugs have altered the treatment paradigms of many B-cell malignancies, including CLL/SLL, relapsed/refractory (R/R) MCL, Waldenström macroglobulinemia (WM), and marginal zone lymphoma (MZL). Ibrutinib is the only approved BTK inhibitor in China for patients with R/R MCL, CLL/SLL, or WM.

Importantly, however, long-term efficacy is ultimately limited by toxicity and acquired resistance. In R/R CLL, although initial response rates to ibrutinib are high, rates of treatment discontinuation are also high (~40%) with extended follow-up (Woyach et al. 2017, Mato et al. 2018). The most common reasons for treatment discontinuation in CLL are adverse events (AEs) in ~50% to 60%, progression in ~20% to 30%, and Richter's transformation (RT) in ~5% to 15% of patients. Toxicities of ibrutinib that lead to dose interruptions and treatment discontinuation include arthralgia, atrial fibrillation, rash, cytopenias, infection, pneumonitis, bleeding and diarrhea (Mato et al. 2018). These toxicities have been attributed to both on-target BTK inhibition and off-target inhibition of other kinases such as TEC (McMullen et al. 2014, Kamel et al. 2015). A retrospective analysis of the RESONATE trial indicated worse progression-free survival (PFS) in patients with R/R CLL with lower ibrutinib dose intensity and dose interruptions lasting for longer than 7 days, suggesting that treatment interruptions for toxicity can adversely impact long-term outcomes (Barr et al. 2017).

Recent analysis of primary CLL samples from patients with relapsed CLL who responded to, but then ultimately progressed on ibrutinib, has uncovered 2 primary mechanisms of acquired resistance: substitution at cysteine 481 (481), primarily with a serine residue (i.e., C481S) in the majority (67%) of patients, which prevent irreversible binding of covalent BTK inhibitors to BTK; activating mutations in PLCG2, a critical signaling effector downstream of BTK in 13%; and less commonly, both mutations occurring in the same patient (7%) (Woyach et al. 2017). These frequencies have been validated in more recent studies (Bonfiglio et al. 2018). Other studies have uncovered C481 substitution mutations in WM and MCL, indicating that C481 substitutions represent a common mechanism of "on target" resistance to irreversible BTK inhibitors in patients (Chiron et al. 2014, Xu et al. 2017).

There are no proven available therapies for patients with B-cell malignant lymphoma (especially MCL and CLL/SLL) who failed BTK inhibitors due to the development of resistance.

Management of MCL

MCL is a rare and aggressive subtype of non-Hodgkin lymphoma (NHL). Young and fit patients typically receive induction chemo-immunotherapy, followed by high-dose chemotherapy with autologous stem cell salvage, and finally rituximab maintenance. In transplant ineligible patients, induction chemo-immunotherapy followed by rituximab maintenance is an accepted alternate approach. Ultimately, none of these approaches are considered curative, and relapse is nearly universal.

Ibrutinib has been approved in China as salvage therapy for patients progressing following upfront chemo-immunotherapy, with or without transplant. A pooled analysis from 3 ibrutinib studies in previously treated MCL patients involving 370 relapsed MCL patients reported a mature median PFS of 12.5 months (Rule et al. 2019).

Outcomes in MCL patients following progression on BTK inhibitors are extremely poor, and there are no proven available therapies. No prospective trials have evaluated investigational agents in the post-BTK treatment setting but retrospective analyses have generated response rates to salvage therapies ranging from 30% to 55% across multiple studies, and characterized by a response duration that tends to be short, with PFS of approximately 3 months and overall survival (OS) of 8 to 9 months (Cheah et al. 2015, Martin et al. 2016, Epperla et al. 2017, Eyre et al. 2019). Chimeric antigen receptor-modified T cells (CAR-T) cell therapy for MCL patients who relapsed including after prior BTK inhibitor has recently gained approval in the United States based on single-arm phase 2 data (Wang et al. 2020). However, CAR-T therapy is still under development in China, and cell therapy products have significant barriers to access due to process, ethics, safety, and financial concerns, as well as the fact that the long-term remission of CAR-T therapies has yet to be verified. In summary, new effective and safe therapies are urgently needed for these patients.

Management of CLL/SLL

For newly diagnosed CLL/SLL, BTK inhibitors (ibrutinib or acalabrutinib), B-cell lymphoma 2 (BCL2) inhibitors (venetoclax), CD20 monoclonal antibodies and chemo-immunotherapy have been recommended as standard treatments internationally. Increasingly BTK inhibitors are becoming the preferred first-line therapy due to the desire to avoid the intensity of chemo-immunotherapy or inpatient monitoring for tumor lysis syndrome (TLS) (often required with initiation of venetoclax). In addition, patients find the favorable risk-benefit profile of BTK inhibitors combined with the convenience of oral dosing compelling. First-line BTK inhibitor use has meaningfully improved PFS and OS compared to chemo-immunotherapy (Shanafelt et al. 2019). Importantly, however, these therapies are not curative and patients eventually relapse. Following progression on BTK inhibitors, median OS in one recent study was only 22.7 months, demonstrating an ongoing unmet need for this population (Woyach et al. 2017).

Following treatment with a BTK inhibitor, available approved non-chemo-immunotherapy based treatment options include a BCL2 inhibitor (venetoclax) and PI3K inhibitors (idelalisib or duvelisib). Of note, studies used to support these regulatory approvals were conducted in patients who were almost exclusively BTK inhibitor naïve. For this reason, the true efficacy of these options after a BTK inhibitor remains investigational. Therefore, while some post-marketing studies in BTK inhibitor-treated patients have been conducted with these agents, to the sponsor's knowledge these data have not been reviewed by regulatory authorities and thus are not incorporated into existing prescribing information.

Venetoclax's indications are line-agnostic and thus technically include BTK-treated patients. However, the use of venetoclax is associated with several significant risks, most notably TLS. Nearly 70% of CLL patients initiating venetoclax meet medium or high-risk criteria (Davids et al. 2018, Jones et al. 2018). These patients require prolonged dose titration and intensive multiday monitoring as an outpatient (medium-risk patients) or inpatient (high- risk patients).

These safety precautions and monitoring scheme have likely limited patient access and can be challenging to implement, or even entirely impractical as in the case of oncologists without inpatient admitting privileges.

Another therapeutic option, PI3K inhibitors (idelalisib, duvelisib), also have important caveats which impact their clinical use. Specifically, both PI3K inhibitors carry black box safety concerns which factor into the risk-benefit determination of prescribing physicians, especially in the post-BTK setting. Important risks include infection, colitis, hepatitis, pneumonitis, skin toxicity and intestinal perforation. For these reasons, PI3K inhibitors are typically reserved for patients who have already exhausted alternative BTK- and BCL2- based therapies. Moreover, the efficacy of these agents was established in BTK naïve patients, raising questions regarding the applicability of these data in real world practice.

Indeed, post-marketing studies of these agents have reported poor outcomes in patients with prior exposure to BTK and/or BCL inhibitors. For example, one retrospective, multicenter study reported an overall response rate of only 28% (all partial responses) with idelalisib use following BTK inhibitor therapy (Mato et al. 2016), in contrast to the 84% overall response rate (ORR) reported in the package insert for idelalisib administered in combination with rituximab (Zydelig (idelalisib) USPI).

Despite the perception that novel drug therapies are more broadly available for all settings of disease, it is common that patients do not receive all classes of agents targeting the BCR pathway during the overall treatment course. Using data available from an oncology physician-based panel chart review study representing 485 practice settings across the United States, the Applicant queried CLL treatment sequence of BTKi, PI3Ki and BCL2 for utilization in 1st, 2nd, and 3rd line therapy during the 12-month time period ending 31 December 2019. For patients receiving ≥2 lines of therapy the data show that only <4% (497/14200) of patients receive treatment with all classes of agents targeting the BCR pathway. These data suggest that the standard sequential monotherapy approach to treatment is influenced by several factors including drug toxicity, patient preference, underlying disease attributes, and treatment setting and the evolution of recent data will result in the incorporation of targeted agents earlier in the treatment of CLL/SLL with fewer salvage options available earlier in the treatment sequence.

In China, ibrutinib and chemo-immunotherapy are the standard of care for newly diagnosed CLL/SLL patients. However, after disease progression while on ibrutinib, there is no available proven choice. A phase 2 study has been initiated to evaluate the efficacy of BCL2 inhibitor (Venetoclax) as monotherapy for previously treated del(17p) CLL/SLL patients and was included in the new drug application for R/R CLL early this year. Several PI3K inhibitors are still under development, and Venetoclax doesn't have much experience in the BTK failure population. Thus, recommendation for previously treated CLL/SLL patients is still to join clinical trials.

In summary, for patients with heavily-treated MCL and CLL/SLL who have received a prior BTK inhibitor, there is a significant unmet clinical need to identify new targeted therapies that potently and rapidly inhibit BTK in susceptible tumors, while sparing the inhibition of other off-target kinases and non-kinase that contribute to significant toxicity.

1.2 LOXO-305

A summary of the properties, and nonclinical and clinical findings of LOXO-305 is provided in Sections 1.2.1 to 1.2.3. Additional information on the nonclinical pharmacology, pharmacokinetics (PKs) and toxicity of LOXO-305 is provided in the LOXO-305 Investigator's Brochure (IB).

1.2.1 Chemistry and Description

LOXO-305 is a small molecule that binds to the ATP site of the BTK kinase, prevents ATP from binding, and inhibits BTK's kinase activity. There is no evidence of covalent or irreversible binding.

1.2.2 Nonclinical

The pharmacology, PK, and toxicology programs were designed to characterize the nonclinical efficacy, disposition, and safety of LOXO-305 and to enable selection of an appropriate starting dose for a phase 2 clinical study. These are described in detail in the LOXO-305 IB.

- Primary Pharmacodynamics

LOXO-305 causes potent dose-dependent inhibition of BTK kinase activity and tumor growth in multiple, biologically relevant BTK-dependent model systems in vitro and in vivo, including B-cell lymphoma cell lines and engineered cell lines. LOXO-305 inhibited the enzymatic activity of BTK and BTK C481S in the presence of ATP at the K_m concentration with 50% inhibitory concentration (IC_{50}) values CCI and was more than twice as potent on BTK C481S. LOXO-305 inhibited BTK and BTK C481S cellular activity including auto-phosphorylation, BTK-dependent proliferation, and activation of human B-cells with similar, low nanomolar potency. LOXO-305 significantly inhibited the growth of BTK-dependent tumors from 2 human lymphoma lines (OCI-Ly10 and TMD8) implanted into immunodeficient mice compared to vehicle-treated mice. LOXO-305 was well-tolerated by the mice in the tumor xenograft models.

- Secondary Pharmacodynamics

LOXO-305 at concentrations predicted to be achieved in humans is not expected to have a significant effect on a range of non-BTK targets and receptors. LOXO-305 was more than 300-fold selective for BTK versus 98% of 370 non-BTK kinases tested in an extensive in vitro kinase activity screen. This high degree of selectivity was maintained in additional enzyme and cell assays. LOXO-305 was at least 70-fold selective for BTK versus 98% of 180 non-BTK kinases screened in live human peripheral blood mononuclear cells (PBMCs) using chemoproteomics methods. In addition, LOXO-305 exhibited no significant target inhibition in an assay panel of 44 non-kinase receptors and enzymes.

- Pharmacokinetics

LOXO-305 has high permeability in vitro, but low aqueous solubility. To reduce the variability in oral absorption, a spray-dried dispersion (SDD) tablet formulation was developed that shows consistent oral bioavailability CCI The bioavailability of the SDD formulation was also not dependent on feeding state in dogs. The SDD tablet formulation has been used for human dosing.

CCI

LOXO-305 was metabolized slowly by human microsomal fractions and hepatocytes. The low rates of metabolism in both these human in vitro systems suggest that LOXO-305 will have low clearance in humans. In vitro data with cloned expressed cytochrome P450 enzymes and human liver microsomes indicate that LOXO-305 appears to be metabolized by cytochrome P450 (CYP450) 3A4 (CYP3A4).

There was very little metabolism of LOXO-305 in human hepatocytes and the only metabolite detected was a glucuronide of LOXO-305. The glucuronide formed by the human hepatocytes was also formed by rat and dog hepatocytes, supporting the use of rat and dog for nonclinical safety assessment.

Renal clearance of LOXO-305 in male and female rats was negligible. No renal clearance data are available in other species, but this pathway is often conserved across species and therefore, no renal clearance is expected in humans.

- Drug Interactions

LOXO-305 showed no detectable inhibition of CYP1A2, CYP2B6, CYP2C19 and CYP2D6, and weak inhibition of CYP2C8, CYP2C9, and CYP3A4 with K_i values ranging from 11.7 to 22.8 µM in human liver microsomes. After pre-incubation of microsomes with LOXO-305 and nicotinamide adenine dinucleotide phosphate (NADPH) for 30 minutes prior to addition of CYP450 probe substrate, the CYP3A4 inhibitory potency of LOXO-305 was increased, suggesting the potential for time-dependent inhibition of CYP3A4. Further kinetic evaluation confirmed that LOXO-305 is a time dependent inhibitor of CYP3A4 with a K_i value of 4.70±1.20 µM and a k_{inact} value of 2.44±0.15 h^{-1} resulting in Cl_{inact} values of 8.64 min^{-1} mM^{-1}.

In an in vitro hepatocyte assay, LOXO-305 induced mRNA for CYP3A4, CYP3A5, CYP2B6, and CYP2C19. For both CYP2B6 and CYP2C19 an increase in activity was seen. For CYP3A4, LOXO-305 did not cause an increase in activity, likely due to concurrent inhibition of CYP3A4 by LOXO-305. LOXO-305 caused a decrease in mRNA for CYP1A2 but did not lead to a reduction of CYP1A2 activity. In the study, CYP2D6, CYP2C8 and CYP2C9 mRNA were not induced.

In vitro LOXO-305 inhibited P-gp, BCRP, MATE1, and MATE2K. LOXO-305 did not inhibit OAT1 and weakly inhibited OATP1B1, OATP1B3, OCT1, OCT2, OAT3, and BSEP.

CCI

- Safety Pharmacology

Cardiac safety was evaluated in a Good Laboratory Practice (GLP) in vitro assay for human ether-à-go-go related gene (hERG) activity, in a GLP in vivo study in conscious telemetry-instrumented dogs, and in a GLP 28-day repeat-dose toxicology study (with electrocardiogram [ECG] monitoring and blood pressure measurements) in dogs. LOXO-305 had an hERG IC_{50} value of 32 µM, CCI There were no LOXO-305-related changes in any cardiovascular endpoints including QTc at doses up to 60 mg/kg in the GLP cardiovascular study in the conscious dogs. The C_{max} for this dose was 10000 ng/mL CCI Furthermore, there were no LOXO-305-related abnormalities in rhythm or waveform morphology based on comparison of pre-dose and postdose ECG recordings. Mean QTc interval was statistically significantly prolonged (+6%; +15 msec) in males administered 30/10 mg/kg/dose BID compared with controls. The prolongation in QTc was below the 10% increase or the threshold reported for canines exposed to therapeutic concentrations of drugs known to cause QT prolongation in humans (Toyoshima et al. 2005). Thus, the QTc changes that occurred in the males at 30/10 mg/kg/dose BID may be LOXO-305-related; however, these were physiologically unimportant and nonadverse.

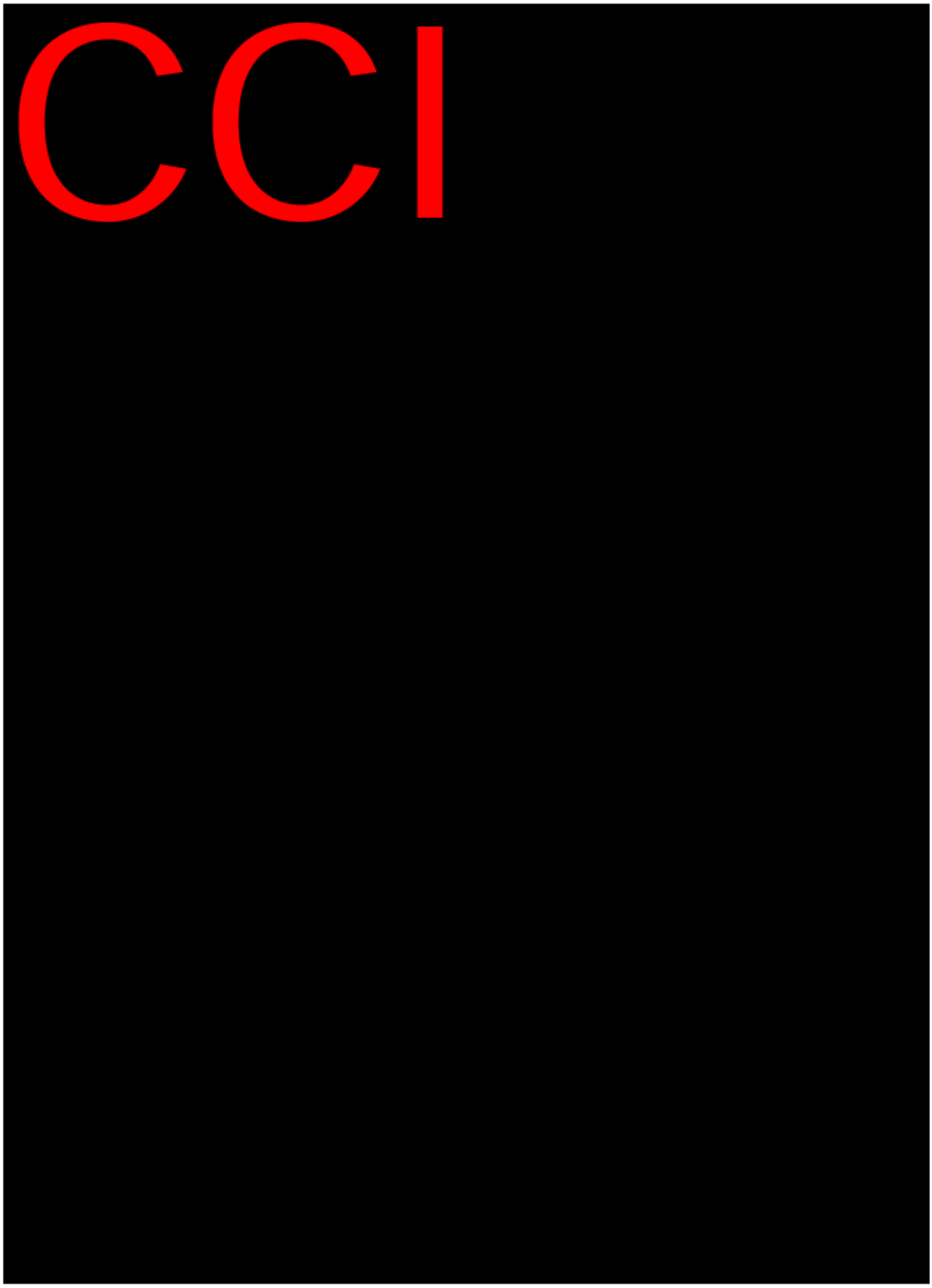
Potential effects of LOXO-305 on the central nervous system (CNS) were evaluated as part of the GLP 28-day repeat-dose study in rat functional observational battery (FOB) tests and locomotor activity (LMA) assessments. There were no LOXO-305-related findings in the FOB or LMA after 4 weeks of dosing or at recovery at doses of up to 500 mg/kg/dose BID in male rats and 175 mg/kg/dose BID in female rats.

LOXO-305 had no effect on respiration rate in the dog at doses up to 30/10 mg/kg/dose BID.

- Toxicology

Targets of toxicity were characterized in repeated dose studies conducted in two relevant toxicity species. Certain targets (the hematopoietic and lymphoid systems) were found in both the rat and the dog. Rat specific changes in the pancreas are species specific and seen with other BTK inhibitors (Bhaskaran et al, 2018). Dog specific changes in lung and large intestine were lesions contributing to moribundity in high dose animals in the 28-day study. Doses evaluated in the 28-day dog study demonstrated a steep dose response curve for toxicity and pronounced changes in hematologic parameters at high exposures. When comparing the two species at high doses and corresponding exposures, the dog was more susceptible to the toxic effects of LOXO-305 than the rat and was considered the more sensitive species.

1.2.3 Clinical Experience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1.2.4 Determination of Recommended Phase 2 Dose

On 5 March 2020,the Safety Review Committee Meeting for Study LOXO-BTK- 18001 recommended that 300 mg QD be the final and highest dose evaluated as part of the dose escalation. This decision was based on several factors. First, doses as low as 25 mg QD showed anti-tumor activity, including a number of PRs as early as 8 weeks at this dose. The relationship between dose and exposure is linear from 25 mg QD through 300 mg QD. Therefore, the dose regimen of 200 mg QD to 300 mg QD offers an CCI than appears needed for anti-tumor activity. Specifically, at a dose of 200 mg QD the mean CCI At a dose of 300 mg QD, unbound mean C_{min} and C_{max} of unbound LOXO-305 levels are approximately CCI, respectively. Finally, doses of 200 mg QD to 300 mg QD appear to be safe and well-tolerated.

Given the totality of efficacy, clinical PK, and safety data, the sponsor and Safety Review Committee decided that further dose escalation is not medically justified and therefore no maximum tolerated dose (MTD) will be established for LOXO-305.

Upon review of the safety, efficacy and PK data obtained from patients enrolled in Study LOXO-BTK-18001, the dose of 200 mg QD has been selected as the recommended dose of LOXO-305 for continued clinical evaluation.

This recommendation was based on the following:

- Safety data were supportive of the 200 mg QD dose
- MTD was not identified
- Safety data were also supportive of the 300 mg QD dose, with a linear dose/exposure relationship (C_{max} and AUC), providing an exposure margin in the event that intrinsic or extrinsic factors lead to higher exposures
- Complete and partial responses were observed across a range of doses from 25 mg QD to 300 mg QD
- At dose levels of 100 mg QD and higher, the trough unbound concentrations of LOXO-305 in plasma exceeded the IC_{90} for BTK inhibition throughout the dosing interval, which is considered a relevant biomarker based on the non-covalent interaction of LOXO-305 with BTK

1.3 Anticipated Risks

1.3.1 Anticipated Risks of LOXO-305 from Animal Studies

Based on the most common findings in the animal toxicology studies, the theoretical risks of human exposure to LOXO-305 include the following:

- Loss of appetite
- Decrease in body weight
- Decrease in white blood cell (WBC) including neutrophils (significant), lymphocytes, monocytes, eosinophils
- Decreases in red cell mass (red blood cell [RBC], hemoglobin [Hb], hematocrit) and reticulocytes
- Decrease in platelets
- Decrease in albumin, total protein and/or increase in globulin
- Increased body temperature

- Lethargy, decreased energy
- Lung and large intestine inflammation with correlative laboratory findings consistent with an inflammatory response
- Gastrointestinal (GI) symptoms/signs: nausea, vomiting, loose stools, diarrhea, abdominal discomfort, dehydration
- Effects on a developing fetus (refer to the LOXO-305 IB)

Theoretical risks based on less common or isolated findings in the animal toxicology studies include:

- Increase in cholesterol
- Prolonged clotting times
- Increases in liver function tests (e.g., Alanine aminotransferase [ALT])
- Infections
- Non-adverse QTc increase

1.3.2 Safety Experience Reported with Other BTK Inhibitors

Ibrutinib (I) is a marketed BTK inhibitor in China and acalabrutinib (A) and zanubrutinib (Z) are marketed in the United States with known safety profiles. Of note, the clinical AE profiles associated with these irreversible BTK inhibitors may be due to both on target (BTK) and off target (e.g., other TEC kinases, epidermal growth factor receptor [EGFR]) inhibition, and LOXO-305 is designed to avoid the off targets of currently available irreversible BTK inhibitors. Commonly occurring AEs observed in patients receiving treatment with these BTK inhibitors include:

- Hemorrhage (I, A, Z)
- Infections (I, A, Z)
- Cytopenias (I, A, Z), including Grade 3-4 neutropenia and thrombocytopenia
- Cardiac arrhythmias (I, A)
- Hypertension (I, Z)
- Second primary malignancies (I, A, Z)
- TLS (I)
- Embryo-fetal toxicity (I, Z)
- Rash (Z)
- Musculoskeletal pain (Z)
- Hypokalemia (Z)

1.4 Benefit/Risk

When viewed as a whole, the benefit/risk ratio for LOXO-305 in this study is favorable. Patients with BTK-dependent malignancies (i.e., CLL/SLL, MCL, WM, MZL and other NHLs) who have failed irreversible BTK inhibitors due to progression with or without acquired resistance or those patients with treatment intolerance to prior BTK represent populations with high unmet need. As discussed in Section 1.1, available therapies for these patients provide short-term palliation (i.e., idelalisib, chemotherapy, anti-CD20 monoclonal antibody therapy) or have the potential to be very toxic (i.e., BCL2 inhibitors, CAR-T). Therefore, there is an urgent need to identify new targeted therapies that potently inhibit BTK (without or with C481 substitution mutations in tumor cells), while sparing other kinase and non-kinase off-targets that contribute to significant toxicity. The early clinical experience for this study suggests that LOXO-305 is effective in patients with previous progression on ibrutinib and both with and without confirmed C481 mutation in BTK.

Because LOXO-305 is an experimental medicine, it is possible that unforeseen, unknown or unanticipated AEs and toxicities may occur. However, as detailed below, this clinical protocol is designed to mitigate risks to patients through a detailed plan for careful safety monitoring, systematic review of AEs, SAEs, and PK, and active pharmacovigilance review to assess for safety signals or trends. This phase 2 study of LOXO-305 is required to understand the anti-tumor activity, safety and PK of LOXO-305 in patients with B-cell malignancies.

2. STUDY OBJECTIVES AND ENDPOINTS

Table 2.1 shows the objectives and endpoints of the study.

Table 2.1 Objectives and Endpoints

Objectives	Endpoints
Primary • To assess the anti-tumor activity of LOXO-305 based on ORR according to Lugano Treatment Response Criteria for MCL and other NHL (Appendix A),International Workshop Guidelines for CLL/SLL (IWCLL 2018, Appendix B) and WM (IWWM, Appendix C), or other criteria as appropriate to tumor type, as assessed by an IRC.	• ORR by IRC
Secondary • To assess, for each cohort, the anti-tumor activity of LOXO-305.	• ORR (by investigator) • BOR (by investigator and IRC) • DOR (by investigator and IRC) • PFS (by investigator and IRC) • OS
• To determine the safety profile and tolerability of LOXO-305.	• AEs, SAEs and TEAEs changes in hematology and blood chemistry values, assessments of physical examinations, vital signs, and ECGs
• To characterize the PK properties of LOXO-305.	• Plasma concentration of LOXO-305 and PK parameters including, but not limited to, AUC_{0-24}, C_{max}, T_{max}, $T_{1/2}$
• To determine the association of clinical response categories	• Symptomatic response: improvement in cancer-related symptoms among patients with MCL associated with BOR • Functional response: improvement in physical function among patients with MCL associated with BOR
• To collect PRO data to explore disease-related symptoms and HRQoL	• Changes from baseline in disease-related symptoms and HRQoL measured by EORTC QLQ-C30
• To determine the relationship between PK and drug effects, including efficacy and safety	• Differences in efficacy and safety based on LOXO-305 PK parameters

Abbreviations: AE = adverse event; AUC_{0-24} = area under the concentration versus time curve from time 0 to 24 hours; BOR = best overall response; C_{max} = maximum drug concentration; CLL = chronic lymphocytic leukemia; DOR = duration of response; ECGs = electrocardiograms; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0; HRQoL = health-related quality of life; IRC = Independent Review Committee; MCL = mantle cell lymphoma; NHL = non-Hodgkin lymphoma; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PRO = patient reported outcomes; SAE = serious adverse event; SLL = small lymphocytic lymphoma; $T_{1/2}$ = terminal elimination half-life; TEAE = treatment emergent adverse event; T_{max} = time to maximum plasma concentration; WM = Waldenström macroglobulinemia.

3. INVESTIGATIONAL PLAN

3.1 Study Design

This is an open-label, multi-center phase 2 study to evaluate efficacy and safety of oral LOXO-305 as monotherapy in patients with MCL, CLL/SLL, and other types of B-cell NHL who have failed or are intolerant (as per the definitions in Appendix D) to standard of care.

LOXO-305 is administered in oral form at dose of 200 mg QD which will be fixed as total milligram (mg; as opposed to weight or body surface area [BSA]-based).

Approximately ~120 patients eligible for this trial will be enrolled to 1 of 3 cohorts (at least 30 patients for Cohort 1, up to 30 patients for Cohort 2, and up to 50 patients for Cohort 3) assigned by tumor histology and prior treatment history. Cycle length will be 28 days.

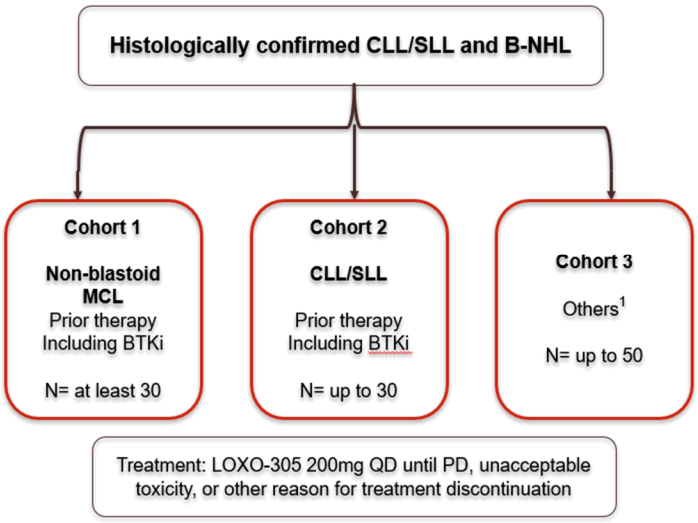
Cohorts 1 through 3:

- Cohort 1: Non-blastoid MCL patients with no CNS metastases and treated with prior chemoimmunotherapy (refer to Table 3.1) and a BTK inhibitor (refer to Appendix E) containing regimen
- Cohort 2: CLL/SLL patients treated with a prior BTK inhibitor containing regimen
- Cohort 3:
  - MCL or CLL/SLL patients not meeting the definitions of Cohort 1 or Cohort 2 and having failed or intolerant to standard of care, or unsuitable for standard of care in the opinion of investigator;
  - Other B cell NHL (include but not limited to DLBCL, MZL and WM) patients having failed or intolerant to standard of care, or unsuitable for standard of care in the opinion of investigator.

The Study Schema is provided in Figure 3.1.

This Phase 2 trial will consist of a Screening Period, a Treatment Period, an End of Treatment (EOT) visit, a Safety Follow-up (SFU) visit, and Long-term Follow-up (LTFU). Ongoing safety and disease assessments (for patients without PD), disease status, survival, and subsequent anticancer therapy(ies) will be assessed during LTFU.

A statistical justification for cohort size is discussed in Section 8.2.



[1] **"Others" Cohort for:**

a. MCL or CLL/SLL patients not meeting the definitions of Cohort 1 or Cohort 2 and having failed or intolerant to standard of care, or unsuitable for standard of care in the opinion of investigator;

b. Other B cell NHL (include but not limited to DLBCL, MZL and WM) patients having failed or intolerant to standard of care or unsuitable for standard of care in the opinion of investigator.

Abbreviations: BTK = Bruton's tyrosine kinase; BTKi = BTK inhibitor; CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B cell lymphoma; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; NHL = non-Hodgkin lymphoma; PD = progressive disease; QD = once daily; SLL = small lymphocytic lymphoma; WM = Waldenström macroglobulinemia

Figure 3.1 Study Schema

Table 3.1 Chemoimmunotherapy for MCL

Cohort	Therapy (including but not limited to)
Cohort 1: Non-blastoid MCL patients with no CNS metastases and treated with prior chemoimmunotherapy and BTK-inhibitor containing regimen	1. high dose cytarabine based therapy: (e.g., R-CHOP/R-DHAP, R-hyperCVAD) 2. rituximab based therapy (e.g., R-CHOP, BR, VR-CAP)

Abbreviations: BTK = Bruton's tyrosine kinase; CNS = central nervous system; MCL = mantle cell lymphoma.

3.2 General Treatment Procedures

Patients will receive 200 mg LOXO-305 QD on Cycle 1 Day 1 (C1D1) and cycle length is 28 days. Individual patients will continue LOXO-305 dosing until PD, unacceptable toxicity, or other reasons for treatment discontinuation, as outlined in Section 6.5. PD is defined by disease specific response criteria and assessed by the investigator. Patients with documented PD may be allowed to continue LOXO-305 if the patient is tolerating study drug and, in the opinion of the investigator, the patient is deriving clinical benefit from continuing LOXO-305, and continuation of treatment is approved by the sponsor until the patient gets the 2nd PD, unacceptable toxicity occurs, or the investigator agrees that the patient will no longer benefit from treatment. Patients continuing LOXO-305 treatment with sponsor approval should still follow on-treatment regular visit and relevant assessment.

All treated patients will undergo a SFU visit between 4 and 5 weeks after the last dose of study

treatment (i.e., 28 days after the last dose of study drug [+7 days]).

After treatment discontinuation, all patients will enter the LTFU period of the study. Patients who discontinue study treatment for reasons other than PD, withdrawal of consent, or initiation of a new anticancer therapy(ies), will also be assessed for progression of disease during LTFU until PD, withdrawal of consent, or initiation of a new anticancer therapy(ies). Once PD is confirmed (or 2nd PD is confirmed for patients continuing LOXO-305 treatment after 1st PD approval by sponsor), patients will be followed for survival status by telephone.

4. SELECTION OF STUDY POPULATION

Potential patients must sign an informed consent form (ICF) before any study-specific screening tests may be conducted, except other specified in protocol.

4.1 Inclusion Criteria

1. Patients with histologically confirmed B-cell malignancy including:
   - Cohort 1 MCL: Confirmed diagnosis of non-blastoid MCL with no CNS metastases and with documentation of overexpression of cyclin D1 and/or t(11;14) and treated with prior chemoimmunotherapy and a BTK inhibitor-containing regimen;
   - Cohort 2 CLL/SLL: Confirmed diagnosis of CLL/SLL by IWCLL 2018 criteria treated with a prior BTK inhibitor containing regimen;
   - Cohort 3 Others: Confirmed diagnosis of CLL/SLL by IWCLL 2018 criteria, WM with documentation of MYD88 mutation, MCL and other types of B-cell NHL (including but not limited to DLBCL and MZL) by World Health Organization (WHO) 2016 criteria, not otherwise specified in Cohorts 1 and 2, and having failed or intolerant to standard of care, or unsuitable for standard of care in the opinion of investigator.

   For patients in each Cohort:
   - All patients must have disease requiring treatment
   - Documented evidence of patients having failed or intolerant on the most recent line of therapy or relapse prior to study enrollment is required;
   - Patients in Cohort 1 and 2, relapsed/refractory or intolerant (as per the definitions in Appendix D) to a prior BTK inhibitor (investigational or approved, and either alone or in combination with other agents) treatment is required.
   - Patients with MCL in Cohort 1who will be evaluated by Lugano criteria must have at least 1 site of radiographically assessable disease (i.e., lymph node longest diameter (LDi) >1.5 cm, extra nodal site >1.0 cm in LDi, or unequivocal hepatomegaly or splenomegaly due to disease). Patients with non-measurable disease are eligible and will be assigned to Cohort 3.
   - For CLL/SLL patients, at least 1 indication for treatment consistent with IWCLL 2018 criteria (refer to Appendix F) is required.
2. Eastern Cooperative Oncology Group (ECOG) 0-2.
3. At least 18 years of age.
4. Confirmation of availability of tumor sample along with pathology report for central pathology review as described in Section 7.4 of the Protocol for patients enrolled in Cohort 1.
5. Adequate hematologic status, defined as the following on or within 7 days of C1D1 before treatment:
   a. Absolute neutrophil count (ANC) $\geq 0.75 \times 10^9$/L without granulocyte-colony stimulating factor (GCSF) supporting withing 7 days of Screening assessment; the patient may enroll below this threshold if there is documented bone marrow involvement considered to impair hematopoiesis.
   b. Platelet count $\geq 50 \times 10^9$/L not requiring transfusion or growth factors supporting within 7 days of Screening assessment; the patient may enroll below this threshold if there is

documented bone marrow involvement considered to impair hematopoiesis.

c. Hb ≥ 8 g/dL not requiring transfusion or growth factors supporting within 7 days of Screening assessment; the patient may enroll below this threshold if there is documented bone marrow involvement considered to impair hematopoiesis.

d. Patients must be responsive to blood or platelets transfusion support if given for bone marrow involvement induced cytopenias. Patients refractory to transfusion support are not eligible. See also exclusion criteria item 18.

6. Adequate coagulation, defined as activated partial thromboplastin time (aPTT) and prothrombin time (PT) or (international normalized ration [INR]) not greater than 1.5 × upper limit of normal (ULN).

7. Adequate hepatic function, defined as:

   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤2.5 × ULN or ≤5 × ULN with documented liver metastases

   b. Total bilirubin ≤1.5 × ULN or ≤3 × ULN with documented liver metastases and/or Gilbert's Disease. If total bilirubin is >1.5 × ULN then direct/indirect or conjugated/unconjugated bilirubin tests should be performed for patients with hemolysis and/or Gilbert's syndrome, they may be enrolled if unconjugated/indirect bilirubin is <5 × ULN with sponsor approval.

8. Adequate renal function defined as creatinine clearance ≥30 mL/ minute using Cockcroft/Gault Formula:

$$\frac{(140 - \text{age}) \times \text{body weight (kg)} \times 0.85 \text{ (if female)}}{\text{serum creatinine (mg/dL)} \times 72}$$

9. Ability to swallow tablets and comply with outpatient treatment, laboratory monitoring, and required clinic visits for the duration of study participation.

10. Willingness of men and women of reproductive potential (defined as following menarche and not postmenopausal [and 2 years of non-therapy-induced amenorrhea] or surgically sterile) to observe conventional and highly effective birth control methods with failure rates of <1% for the duration of treatment and for 6 months following the last dose of study treatment; this must include barrier methods such as condom or diaphragm with spermicidal gel. For male subjects 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:

    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 (CTFG 2014).

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.

4.2 Exclusion Criteria

11. Investigational agent or anticancer therapy (including some Chinese traditional medicine with anti-tumor indication in label) within 5 half-lives or 14 days, whichever is shorter, prior to planned start of LOXO-305 except therapeutic monoclonal antibody treatment must be discontinued a minimum of 4 weeks prior to the first dose of LOXO-305. In addition, no concurrent systemic anticancer therapy is permitted.
    a. Continuation of certain standard of care anticancer therapies, including hormonal therapy for localized breast and prostate cancer, is allowed, provided they are not on the list of prohibited concomitant medications. Refer to Section 6.3.2 for allowed and Section 6.3.3 for prohibited medications.
12. Major surgery (excluding placement of vascular access or biopsy) within 4 weeks prior to planned start of LOXO-305.
13. Radiotherapy with a limited field of radiation for palliation within 7 days of the first dose of study treatment, except for patients receiving radiation to pelvis, skull or sternum (bone marrow area)or receiving whole brain radiotherapy, which must be completed at least 4 weeks prior to the first dose of study treatment.
14. Patients requiring therapeutic anticoagulation with warfarin.
15. Any unresolved toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE [version 5.0]) Grade 2 at the time of starting study treatment except for alopecia or otherwise specified in this eligibility criteria.
16. History of allogeneic or autologous stem cell transplant (SCT) or chimeric antigen receptor-modified T-cell (CAR-T) therapy within the 60 days prior to planned start of LOXO-305 treatment or with any of the following:
    a. Active graft versus host disease (GVHD)
    b. Cytopenia requiring transfusion support reflecting incomplete blood count recovery post-transplant
    c. Need for anti-cytokine therapy for toxicity from CAR-T therapy; residual symptoms of neurotoxicity > Grade 1 from CAR-T therapy
    d. Ongoing immunosuppressive therapy
17. Known CNS involvement by systemic lymphoma. Patients with previous treatment for CNS

involvement who are neurologically stable (neurological symptoms and CNS imaging are stable and steroid dose is stable for 14 days prior to the first dose and no CNS surgery or radiation has been performed for 28 days, 14 days if stereotactic radiosurgery [SRS]) and without evidence of disease may be eligible and enrolled to Cohort 3 if a compelling clinical rationale is provided by the investigator and with documented sponsor approval. Primary CNS lymphoma is excluded.

18. Active uncontrolled auto-immune cytopenia (e.g., autoimmune hemolytic anemia [AIHA], idiopathic thrombocytopenic purpura [ITP]) where new therapy introduced, or concomitant therapy escalated within the 4 weeks prior to study enrollment is required to maintain adequate blood counts.
19. Significant cardiovascular disease defined as:
    a. Unstable angina, or
    b. History of myocardial infarction within 6 months prior to planned start of LOXO-305, or
    c. Documented left ventricular ejection fraction (LVEF) by any method of ≤45% in the 12 months prior to planned start of LOXO-305, assessment of LVEF during screening should be performed in selected patients as medically indicated, or
    d. Any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification (refer to Appendix G), or
    e. Uncontrolled or symptomatic arrhythmias
20. Prolongation of the QT interval corrected of heart rate (QTcF) >470 msec on at least 2/3 consecutive ECGs, and mean QTcF >470 msec on all 3 ECGs, during Screening. QTcF is calculated using Fridericia's Formula (QTcF): $QTcF = QT/(RR^{0.33})$.
    a. 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 (agents known to cause QTc prolongation refer to Appendix H).
21. Patients who experienced a major bleeding event or grade ≥3 arrhythmia on prior treatment with a BTK inhibitor.

    NOTE: Major bleeding is defined as bleeding having one or more of the following features: potentially life-threatening bleeding with signs or symptoms of hemodynamic compromise; bleeding associated with a decrease in the hemoglobin level of at least 2 g per deciliter; or bleeding in a critical area or organ (e.g., retroperitoneal, intraarticular, pericardial, epidural, or intracranial bleeding or intramuscular bleeding with compartment syndrome).
22. Active 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 the sponsor makes it undesirable for the patient to participate in the trial. Screening for chronic conditions is not required.
23. Patients who have tested positive for human immunodeficiency virus (HIV) are excluded due to potential drug-drug interactions between anti-retroviral medications and LOXO-305 and risk of opportunistic infections with both HIV and irreversible BTK inhibitors. For patients with unknown HIV status, HIV testing will be performed at Screening and result should be negative for enrollment.
24. Have active hepatitis B or C.
    a. Patients with detectable hepatitis B virus (HBV) DNA and controlled disease may be

permitted on therapy with sponsor approval. Concurrent viral suppressive treatment will be required for patients with detectable HBV DNA. Refer to Section 6.3.2 for allowed and Section 6.3.3 for prohibited medications.

b. Patients with history of hepatitis C virus (HCV) infection who have completed viral suppressive therapy and have a viral load below the limit of quantification are allowed.

25. Clinically significant active malabsorption syndrome or other conditions likely to affect GI absorption of the study drug.
26. Current treatment with certain strong CYP3A4 inhibitors or inducers (refer to Appendix I) and/or strong P-gp inhibitors within 7 days before starting LOXO-305 (refer to Appendix J)
27. Pregnancy or lactation.
28. Active second malignancy unless in remission with life expectancy >2 years and with documented sponsor approval. Examples include:
    a. Adequately treated nonmelanomatous skin cancer or lentigo maligna melanoma without current evidence of disease
    b. Adequately treated cervical carcinoma in situ without current evidence of disease
    c. Localized (e.g., lymph node negative) breast cancer treated with curative intent with no evidence of active disease present for more than 3 years and receiving adjuvant hormonal therapy
    d. Localized prostate cancer undergoing active surveillance
29. Prior treatment with LOXO-305.
30. Patients with known hypersensitivity to any component or excipient of LOXO-305.

5. ENROLLMENT PROCEDURES

For all patients, a copy of the redacted Molecular Pathology Report must be submitted to the sponsor or designee during screening for review prior to patient enrollment. The planned cohort of the study and a patient number will be assigned that will be used throughout both Screening and study participation.

Patients who cannot complete the procedures within the screening window may be rescreened, and certain screening procedures may not need to be repeated with documented sponsor approval. Certain procedures that were obtained as part of the patient's standard care prior to providing informed consent for this study (i.e., hematology, imaging), 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 Table 7.1.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened, only after discussion with and permission from the Lilly clinical research physician (CRP) or designee. Patients may be eligible for re-screening up to 2 times in any of the following circumstances:

- Patients who have become eligible to enroll in the study as the result of a protocol amendment.
- Patients whose status has changed such that the eligibility criterion that caused the patient to screen fail would no longer cause the patient to screen fail again.
- Patients who complete screening and meet all inclusion and exclusion requirements but are unable to be enrolled due to extenuating circumstances (such as severe weather, or child illness).

Each time rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number.

This is an open-label study and all patients who meet all criteria for enrollment will receive LOXO-305 treatment. Dispensing and tracking LOXO-305 treatment will be accomplished using an interactive Web/voice response system (IxRS).

6. TREATMENTS AND ADMINISTRATION

6.1 Investigational Product

LOXO-305 will be provided by the sponsor as tablets. To reduce variability in oral absorption, a spray-dried dispersion (SDD) tablet formulation was developed for use in humans (refer to Section 1.2.2-Pharmacokinetics). The tablet will be provided to the sites for distribution to the patient for outpatient administration at the assigned dose level.

The site pharmacist will dispense bottles to the patient in an amount necessary to allow for outpatient administration at the assigned dose level. Dosing is intended to be fixed (i.e., not weight-based or BSA-based).

Tablets are to be stored at room temperature according to investigational product label.

6.2 LOXO-305 Administration

6.2.1 General Dosing Instructions

All patients taking LOXO-305 should not consume grapefruit or grapefruit products, starfruit, Seville oranges or marmalade containing Seville oranges from the 3 days prior to start of study therapy until therapy is stopped. Prohibited concomitant medications and contraindications are discussed in Sections 6.3.3 and 6.3.4, respectively.

LOXO-305 will be administered to patients in oral tablet form at 200 mg QD, and cycle length will be 28 days. Dosing for an individual is recommended at a consistent time each day.

LOXO-305 may be taken with or without food and drink.

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

Patients will begin to receive LOXO-305 on C1D1 and continue study treatment dosing in a continuous 28-days cycle until PD, 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 (including but not limited to no rapid disease progression, stable performance status, and no serious complications due to disease progression) and continuation of treatment is approved by the sponsor until the patient gets the 2nd PD, unacceptable toxicity occurs or the investigator agrees that the patient will no longer benefit from treatment. Patients must provide written informed consent prior to receiving additional LOXO-305 treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options. Patients continuing LOXO-305 treatment with sponsor approval should still follow on-treatment regular visit and relevant assessment, and are recommended with close tumor assessment (i.e., 4-8 weeks after 1st PD) to evaluate patients'

benefit from the following treatment per investigator discretion.

Effects of LOXO-305 on coagulation are unknown. Thus, patients undergoing major surgical procedures should have LOXO-305 held at least 3 days prior and 3 days post procedure and for surgery on CNS or liver or other critical organs which may be most prone to bleed, LOXO-305 should be held at least 7 days prior and 7 days post procedure; the sponsor should be notified of the planned procedure and planned dose hold.

6.2.2 Dose Delays/Modifications

Cycles are 28 days in duration regardless of dose interruption unless the dose interruption includes Day 1 of the next cycle in which case the next cycle will start with resumption of study drug. In this situation, disease assessments should continue to follow the original schedule.

Dose hold or reduction will be implemented for any patient who experiences a clinically significant AE considered related to LOXO-305 as assessed by CTCAE v5.0. For CLL/SLL patients, hematologic toxicity will also be assessed by CTCAE v5.0.

Toxicities such as nausea, vomiting, or diarrhea, or dizziness or dehydration related to these symptoms, may be managed with increased supportive care, including hydration, electrolyte repletion, and the use of anti-emetics such as serotonin type 3 (5-HT3) antagonists and/or anti-diarrheal medications such as loperamide as appropriate.

For a patient who experiences a clinically significant AE considered related to LOXO-305 (e.g., ≥ Grade 3 AE, Grade 2 AE not resolved within 48 hours with appropriate supportive care [e.g., nausea not improved with antiemetics] as assessed by CTCAE v5.0 and considered intolerable by the patient or the investigator, or AE more than 1 grade change from baseline if baseline is Grade 2 or above), investigator should discuss with sponsor and ***may*** have LOXO-305 dosing held for up to 28 days to evaluate the AE and to allow for recovery (to Grade 1 or less or baseline if baseline is Grade 2 or above).

Upon recovery, investigator should discuss with sponsor and the patient may restart therapy as outlined in (Table 6.1) if it is considered in his/her best interest to continue therapy. Any continued dosing before a clinically significant AE recovers to Grade 1 or less, or baseline if baseline is Grade 2 or above, should be discussed and get documented sponsor approval. If the AE does not recover to Grade 1 or less, or baseline if baseline is Grade 2 within 28 days, the patient will have treatment permanently discontinued, unless there is a compelling clinical rationale for dose holding for more than 28 days or additional dose reduction(s) articulated by the investigator and approved by the sponsor. For each patient, a maximum of 2 dose reductions will be allowed, unless there is a compelling clinical rationale for additional dose reduction(s) articulated by the investigator and approved by the sponsor (Table 6.1).

Table 6.1 Suggested Dose Reduction Levels for LOXO-305 for Toxicity Management

Adverse Events*	Occurrences Requiring Dose Modification	LOXO-305 (Starting dose 200 mg QD)	LOXO-305 Modification
• ≥ Grade 3 AE • Grade 2 AE not resolved within 48 hours with appropriate supportive care and considered intolerable by the patient or the investigator • AE more than 1 grade change from baseline if baseline is Grade 2 or above	First occurrence	No change	Hold LOXO-305 until recovery to Grade 1 or baseline; may restart at original dose level (200 mg QD)
	Second occurrence	100 mg QD	Hold LOXO-305 until recovery to Grade 1 or baseline; may restart at one dose level lower (100 mg QD)
	Third occurrence	50 mg QD	Hold LOXO-305 until recovery to Grade 1 or baseline; may restart at one dose level lower (50 mg QD)
	Fourth occurrence	Discontinue	Discontinue

* For patients enrolled with AST or ALT >1.5 × ULN at baseline a dose interruption should be implemented if the AST or ALT >3 × baseline or AST or ALT ≥2 × baseline with concurrent total bilirubin ≥2 × ULN. An evaluation for potential alternative causes of liver dysfunction should be conducted. Dose interruptions and/or modifications may also be undertaken for Grade 2 AEs deemed to be intolerable in the setting of chronic study drug administrations. Patients found to have treatment-emergent laboratory toxicity of Grades 3 or 4 will be monitored at least weekly until resolution.

Patients who have been dose-reduced and who tolerate LOXO-305 without toxicity for at least 2 weeks may be re-escalated to the next higher dose level, not to exceed 200 mg QD, at the discretion of the investigator and approved by the sponsor. If the LOXO-305 dose is reduced for apparent treatment-related toxicity, the dose need not be re-escalated.

All dose interruptions and dose modifications and the reasons for those changes will be recorded in the Case Report Form (CRF).

6.3 Prior and Concomitant Medications

6.3.1 General

Concomitant medications will include ongoing medications and all medications that were administered within 14 days prior to the planned start of study drug or from Screening (whichever is shorter) through the SFU visit (at least 28 days [+7 days] after the last dose of study drug) and are to be recorded in the CRF. These are to include prescription and nonprescription medications, transfusions, vitamins, nutritional supplements, and other remedies. Excluded medications are indicated in the Exclusion Criteria (Section 4.2).

6.3.2 Allowed Concomitant Medications

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 guidelines; red blood cell (RBC) and platelet transfusions; anti-emetic, analgesic, and antidiarrheal medications; electrolyte repletion (e.g., calcium and magnesium) to correct low electrolyte levels; glucocorticoids (approximately 20 mg per day prednisone or equivalent for ~14 days, unless there is a compelling clinical rationale for a higher dose articulated by the

investigator and approved by the sponsor), including short courses to treat asthma, chronic obstructive pulmonary disease, etc.; thyroid replacement therapy for hypothyroidism; and bisphosphonates, denosumab. and other medications for the treatment of osteoporosis, prevention of skeletal-related events from bone metastases, and/or hypoparathyroidism. Continuation of standard of care medications, including hormonal therapy for patients with prostate cancer (e.g., gonadotropin-releasing hormone [GnRH] or luteinizing hormone-releasing hormone [LHRH] agonists) and breast cancer (e.g., GnRH/LHRH agonists, aromatase inhibitors, selective estrogen receptor modulators [SERMs] or degraders [SERDs]), that the patient has been on for the previous 28 days, are allowed, provided they are not on the list of prohibited concomitant medications (refer to Section 6.3.3).

Local treatment while receiving LOXO-305 (e.g., palliative radiation therapy or surgery for bone metastases) is permitted with documented sponsor approval. 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. However, the sponsor recommends holding LOXO-305 for ~3-5 half-lives before and after radiation therapy or surgery. Any concern for disease flare due to a prolonged LOXO-305 dose interruption should be discussed with the sponsor, who may permit holding LOXO-305 for a shorter period of time.

6.3.3 Prohibited Concomitant Medications

As LOXO-305 is a substrate of CYP3A4, patients should not take strong inhibitors or inducers of CYP3A4 as they could alter drug's PK. 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. Refer to Appendix I. Grapefruit, Seville oranges, starfruit or products with these fruits should be avoided for the duration of treatment.

Given that LOXO-305 is a substrate of P-gp, patients should not take strong inhibitors of P-gp as they could alter drug's PK. Mild inhibitors of P-gp should be taken with caution; refer to Appendix J.

If during the study, patients require initiation of treatment with strong inhibitors or inducers of CYP3A4 or P-gp inhibitors, for clinical reasons, then the sponsor should be consulted to determine whether LOXO-305 should be stopped, and therefore whether the patient should be removed from the study. Moderate inhibitors or inducers of CYP3A4 should be taken with caution. Any exceptions to the above must be approved by the sponsor.

In addition, except as indicated in Section 6.3.2, patients are not allowed to receive concomitant systemic anti-cancer agents (including some Chinese traditional medicine with anti-tumor indication in label), hematopoietic growth factors for prophylaxis in Cycle 1, therapeutic monoclonal antibodies, drugs with immunosuppressant properties, or any other investigational agents besides LOXO-305. No new or alternative systemic anticancer therapy is allowed prior to documentation of PD in accordance with protocol-specified disease response criteria.

6.3.4 Contraindications

LOXO-305 is contraindicated in patients with known hypersensitivity to any of its tablet components.

6.4 Duration of Treatment

It is anticipated that a patient on this study will receive treatment with open-label LOXO-305 until the patient is able to obtain commercially available LOXO-305 in China, the patient does not meet criteria requiring discontinuation of treatment (refer to Section 6.5), and the patient's participation in the study has not ended. Upon commercial availability in China 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. The sponsor also reserves the right to discontinue the study for clinical or administrative reasons at any time.

6.5 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 7.17). Over the course of the study, the investigator and/or the sponsor should remove a patient from treatment for any of the reasons listed below:

- PD

  Exception: Patients with documented PD who are tolerating study therapy and, in the opinion of the investigator, are deriving clinical benefit from continuing study treatment, may continue treatment with documented sponsor approval until the patient gets the 2nd PD, unacceptable toxicity occurs or the investigator agrees that the patient will no longer benefit from treatment. Patients continuing LOXO-305 treatment with written informed consent and sponsor approval should still follow on-treatment regular visit and relevant assessment, and are recommend with close tumor assessment (i.e., 4-8 weeks after 1st PD) to evaluate patients' benefit from the following treatment per investigator discretion.
- Unacceptable toxicity
- Intercurrent illness compromising ability to fulfill protocol requirements
- Pregnancy
- Requirement for alternative treatment in the opinion of the investigator, unless such treatment is temporary (e.g., local radiation or surgery for disease that does not meet the definition of PD)
- Dose delay >28 days, unless a clinical need for prolonged delay has been determined by the investigator with documented sponsor approval
- Significant noncompliance with protocol (Patients take <75% or ⩾125% of the planned does as prescribed per cycle)
- Withdrawal of consent by the patient
- Lost to follow-up
- Death

- Study terminated by sponsor

At the time a patient discontinues treatment, all safety data normally required at the EOT and SFU visit will be obtained if possible, as outlined in Section 7.15. Patients will enter LTFU where they may be required to undergo disease assessments (refer to Section 7.17).

6.5.1 Discontinuation of Inadvertently Enrolled Patients

If the sponsor or the investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly CRP and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without study drug. Patients who are discontinued from study drug will have follow-up procedures performed as shown in the Table 7.1.

6.6 Discontinuation from Study

Discontinuation from the study and reasons for end of study could be:

- Withdrawal of consent by the patient
- Lost to follow-up
- Death
- Study terminated by sponsor
- The clinical trial will be discontinued or terminated in case of an unacceptable risk, any relevant toxicity, or a negative change in the risk/benefit assessment. These might include the occurrence of adverse events which in character, severity or frequency are new in comparison to the existing risk profile. In addition, any data deriving from other clinical trials or toxicological studies which negatively influence the risk/benefit assessment might cause discontinuation or termination of the study.

For each disease-defined cohort, consideration of termination will use the same safety considerations. Individual cohorts may be terminated based on inadequate enrolment, low ORR, or shorter than anticipated duration of response (DOR). An individual cohort close but overall enrolment to the study may continue.

Sample size justification for each cohort is provided in Section 8.2.

Patients who are discontinued from the study will have follow-up procedures performed as shown in the Table 7.1.

6.7 Lost to Follow-Up

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

Study site personnel, or an independent third party, will attempt to collect the survival status for all enrolled patients who are lost to follow-up, including enrolled patients who do not receive study drug, within legal and ethical boundaries. Public sources may be searched for survival status information. If the patient's survival status is determined, the survival status will be documented, and the patient will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect survival status information.

7. STUDY PROCEDURES AND ASSESSMENTS

Descriptions of assessments are provided in Sections 7.1 through 7.17 below. Specific timing requirements for study procedures and assessments by diagnosis at enrollment are provided in Table 7.1.

For PK sampling days and time points, see Table 7.2.

Routine laboratories, for example serum chemistries, hematology, and urinalysis, will be performed locally. Unless otherwise noted, the routine laboratories and procedures will be performed prior to dosing as noted, and routine evaluations performed within 2 days prior of the visit day will not be considered protocol deviations.

Additional guidance for study assessments and procedures and collection of samples for central assessments is provided in Appendix K and the Laboratory Manual.

Table 7.1 Schedule of Assessments

Evaluation	Screening*	Cycle 1 (D1-D28)				Cycles 2 through 12	Cycles 13 and Higher	EOT**	SFU	LTFU
									801	802 - 8XX
Visit Window	**D0 (-28 Days)**	**D1 (-2 Days)**	**D8 (± 2 Days)**	**D15 (± 2 Days)**	**D22 (±2 Days)**	**D1 (± 3 Days)**	**D1 (±3 Days)**	**≤ 7 days after last dose or decision to terminate treatment**	**28 days (+7 days) after last dose of study drug**	**Every 3 months ± 1 month for up to 2 years after last dose of study drug**
Results of tests below are required for enrollment										
Informed consent	X									
Medical, surgical, malignancy history[a]	X									
Physical examination and ECOG[b]	X	X	X	X		Day 1 each cycle		X	X	
Vital signs[c]	X	X	X	X		Day 1 each cycle		X	X	
12-lead ECG[d]	X	X	X			Day 1 every other cycle, C2 through 12, then as clinically indicated		X	X	
Hematology[e]	X	X	X	X		Day 1 each cycle		X	X	
Blood chemistries[f]	X	X	X	X		Day 1 each cycle		X	X	
Coagulation panel[g]	X	As clinically indicated								
Urinalysis[h]	X	X				Day 1 each cycle through C12, then as clinically indicated		X		
Serum or urine pregnancy test (if applicable)[i]	X					Day 1 each cycle				
HIV[j]	X									

Evaluation	Screening*	Cycle 1 (D1-D28)				Cycles 2 through 12	Cycles 13 and Higher	EOT**	SFU	LTFU
									801	802 - 8XX
Visit Window	**D0 (-28 Days)**	**D1 (-2 Days)**	**D8 (± 2 Days)**	**D15 (± 2 Days)**	**D22 (±2 Days)**	**D1 (± 3 Days)**	**D1 (±3 Days)**	**≤ 7 days after last dose or decision to terminate treatment**	**28 days (+7 days) after last dose of study drug**	**Every 3 months ± 1 month for up to 2 years after last dose of study drug**
CMV, Hepatitis B and Hepatitis C testing[j]	X									
Documentation of histologic diagnosis and relevant biomarkers[k]	X									
Documentation or sampling required during screening but results not required prior to enrollment										
Tumor sample obtained for central pathology review[l]	X									
Bone marrow aspirate and/or biopsy[m]	X	For confirmation of CR and at PD (optional) (refer to Appendix K)								
Upper and lower endoscopy[w]	X	For confirmation of CR in MCL patients of Cohort 1 only (refer to Appendix K)								
For CLL/SLL Lymphocyte subsets[n]	X					Every 8 weeks beginning with C3D1 (±7 days)	Every 12 weeks (±2 weeks) beginning with C13D1 for 1 year, then every 6 cycles (±4 weeks) after	X		X[x]

Evaluation	Screening*	Cycle 1 (D1-D28)				Cycles 2 through 12	Cycles 13 and Higher	EOT**	SFU	LTFU
									801	802 - 8XX
Visit Window	**D0 (-28 Days)**	**D1 (-2 Days)**	**D8 (± 2 Days)**	**D15 (± 2 Days)**	**D22 (±2 Days)**	**D1 (± 3 Days)**	**D1 (±3 Days)**	**≤ 7 days after last dose or decision to terminate treatment**	**28 days (+7 days) after last dose of study drug**	**Every 3 months ± 1 month for up to 2 years after last dose of study drug**
For patients with known paraprotein: SPEP, serum immunofixation, serum FLC, quantitative Immunoglobulins, total protein[o]	X					Every 8 weeks beginning with C3D1 (±7 days)	Every 12 weeks (±2 weeks) beginning with C13D1 for 1 year, then every 6 cycles (±4 weeks) after	X		X[x]
Radiologic disease assessment[p]	X					Every 8 weeks beginning with C3D1 (±7 days)	Every 12 weeks (±2 weeks) beginning with C13D1 for 1 year, then every 6 cycles (±4 weeks) after	X		X[x]
Items starting with Cycle 1										
Blood samples for PK[q]	Refer to Table 7.2									
Telephone follow-up					X					X
Survival status[r]										X
LOXO-305 administration		X →						X		

Evaluation	Screening*	Cycle 1 (D1-D28)				Cycles 2 through 12	Cycles 13 and Higher	EOT**	SFU	LTFU
									801	802 - 8XX
Visit Window	D0 (-28 Days)	D1 (-2 Days)	D8 (± 2 Days)	D15 (± 2 Days)	D22 (±2 Days)	D1 (± 3 Days)	D1 (±3 Days)	≤ 7 days after last dose or decision to terminate treatment	28 days (+7 days) after last dose of study drug	Every 3 months ± 1 month for up to 2 years after last dose of study drug
Patient dosing diary[s]		X →						X		
Concomitant medication[t]	X →								X	
Adverse event[u]	X →								X	
EORTC QLQ-C30[v]		X				X	X	X		
EORTC IL63 (MCL patients only)[v]		X				X	X	X		

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; aPTT = activated partial thromboplastin time; BUN = blood urea nitrogen; C = cycle; CLL = chronic lymphocytic leukemia; CMV = cytomegalovirus; CR = complete response; CRF = case report form; CRi = complete response with incomplete hematologic recovery; D = day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EDC = Electronic Data Capture; EORTC IL-63 = European Organization for Research and Treatment of Cancer Items Library 63; EORTC QLD-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; EOT = End of Treatment; FLC = free light chain; GI = gastrointestinal; HbA1c = hemoglobin A1c; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg-hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; INR = international normalized ratio; LDH = lactate dehydrogenase; LTFU = Long-term Follow- up; MCL = mantle cell lymphoma; NHL = Non-Hodgkin Lymphoma; PCR = polymerase chain reaction; PD = progressive disease; PK = pharmacokinetics; PR = partial response; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; RNA = ribonucleic acid; SAE = serious adverse event; SFU = safety follow-up; SLL = small lymphocytic lymphoma; SPEP = serum protein electrophoresis; WBC = white blood cell; WM = Waldenström macroglobulinemia.

* Certain procedures that were obtained as part of the patient's standard care prior to providing informed consent for this study (i.e., hematology, imaging), may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria. In Table 7.1, if results are noted as required prior to starting LOXO-305, results of these studies may be required before patients may be officially enrolled.

** End of Treatment (EOT) assessments and procedures will be conducted within7 days of the last dose or the decision to terminate treatment. If lab testing is performed ≤7 days prior to EOT, to repeat testing does not need to occur on EOT. It is not an additional visit, which may happen in scheduled visit.

Note: Study conduct during exceptional circumstances please refer to Appendix O.

a. 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 on the appropriate CRF.
b. Physical examination includes neurological examination, review of relevant systems, height and weight at Screening and C1D1 (within 3 days). Symptom-directed physical examination including weight should be performed at appropriate regular time points of disease assessment.
c. Systolic and diastolic blood pressure, heart rate (pulse is acceptable if patients are not under cardiac arrythmias), respiratory rate, and body temperature.
   - For vital signs assessed at PK time points, vital signs including weight should be conducted prior to actual PK blood sampling pre-dose (initial dose) (up to 4 hours pre-dose, as close to dosing as possible is preferred), and on C1D1 and C1D8 vital signs should also be conducted post-dose at 2 hours (±15 minutes).
   - For vital signs assessed at non-PK time points: pre-dose (up to 4 hours pre-dose, as close to dosing as possible is preferred)
d. Triplicate ECGs performed at least 5 minutes apart and within 1 day should be performed during Screening and during C1D1 and C1D8 at the following time points: pre- dose (initial dose) (up to 4 hours pre-dose), 2 and at 4 hours post-dose (±15 minutes). In addition, single ECG should be obtained at 2 hours post-dose (±15 minutes) on D1 of every other cycle of C2 through C12. Additional ECGs may be performed if clinically indicated. If an unscheduled ECG is done at any time and a new, clinically significant abnormality is identified, 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, clinical details must be captured in EDC and/or submitted as requested and required by sponsor. QTcF will be calculated using Fridericia's Formula (refer to Section 4.2, Exclusion Criterion 20).
e. Hematology includes hemoglobin, hematocrit, RBC count, WBC count, platelet count, percent or absolute WBC count differential (neutrophils, lymphocytes, eosinophils, basophils, and monocytes). For WM and CLL/SLL patients, blood samples should also be provided for central assessment on C1D1, ±7 days of each radiologic disease assessment and at disease progression. Screening results performed within 7 days of C1D1 are acceptable as C1D1 results. Please enter the data correctly in the CRF.
f. Chemistry from plasma or serum includes sodium, potassium, chloride, glucose, BUN/urea, creatinine, calcium, magnesium, phosphorus, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, gamma-glutamyl transferase, creatine kinase, LDH, uric acid/urate. Lipase should be performed with D1 blood chemistries for each cycle, Cycle 1-12. Screening results performed within 7 days of C1D1 are acceptable as C1D1 results.
g. Coagulation panel includes aPTT and PT (INR).
h. Urinalysis should include color, appearance, specific gravity, pH, glucose, bilirubin, ketones, occult blood, protein, leukocytes, nitrites, and urobilinogen. Screening results performed within 7 days of C1D1 are acceptable as C1D1 results.
i. All women who are not postmenopausal (and 2 years of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at Screening within 7 days before Cycle 1 Day 1 (C1D1). In addition, for women of childbearing potential, a serum or urine pregnancy test must be performed prior to treatment on Day 1 of each subsequent cycle of study treatment.
j. Patients with a positive HIV test are excluded from study participation. If Hep B or C testing indicates acute or chronic infection or reactivation of infection, obtain viral load (e.g., quantitative HBV-DNA, HCV-RNA) and obtain consultation with a physician with expertise in management of active infection and only patients meet the eligibility criteria 24 can be enrolled. Either CMV PCR or antigen tests should be performed during screening to r/o active viral infection. Refer to Sections 6.3.2 and 6.3.3 for allowed and prohibited concomitant medications, respectively, which should be shared with the consultant physician.
k. Anonymized/redacted pathology report(s) confirming histologic diagnosis and the status of any known biomarkers (e.g., FISH, IGVH, p53, karyotype for CLL/SLL, MYD88, CXCR4 for WM, Ki67 staining for MCL) should be submitted. In patients with MCL, documentation of cyclin D1 overexpression and/or t(11;14) positive status must be provided either as a pathology report from anytime in the patient's past or from current tissue testing. Patients may not be enrolled without documentation of Cyclin D1 and/or t(11;14) status. In patients with WM, documentation of MYD88 mutation must be provided either as a pathology report from the patient's past history or from current tissue testing. Patients with WM may not be enrolled without documentation of MYD88 mutation.

l. At study entry, adequate tissue sample (lymph node/tumor biopsy is preferred)) at screening is required for patients enrolled in Cohort 1 for central pathology review, Guidance is provided in the Laboratory Manual and Appendix K of Protocol.
   - For MCL patient, tissue samples must include up to 10 unstained slides or representative sections of archived paraffin block for Central Pathology review.
   - If tumor sample cannot be obtained safely, the patient may be enrolled in Cohort 3 if other eligibility criteria has been checked.

   For Central Pathology review, the site should also submit a de-identified surgical pathology report of the patient's original diagnosis of lymphoma and ancillary studies which were used to establish the original diagnosis such as flow cytometry, immunohistochemistry, FISH, cytogenetics, or molecular studies.

m. For CLL/SLL, WM, indolent NHL, and selected cases of high−grade NHL, baseline bone marrow aspirate and/or biopsy is required unless was already done after the last treatment or while progressing on the most recent and within 90 days of Screening. Bone marrow biopsies performed while still receiving the most recent treatment are allowed if the patient was progressing at the time of the bone marrow biopsy. Adequate amount of samples, fresh or archived, must be available as defined in the Laboratory Manual for central baseline assessment. Refer to Section 7.4 Appendix K and the Laboratory Manual for guidance regarding requirements for sample submission based on histology. Patients with other response assessments consistent with CR may need to undergo bone marrow biopsy and/or aspiration in order to confirm CR (refer to Section 7.4 and Appendix K). All MCL patients whose other response assessment are consistent with CR and known bone marrow involvement at baseline must undergo a bone marrow biopsy in order to confirm CR.

n. For CLL/SLL patients, T-cell, B-cell and NK cell subsets and absolute B-cell count, to be assessed centrally; local assessment is optional.

o. For WM patients and other patients if M-protein known to be present at baseline, should be assessed locally and samples provided for central assessment. A separate testing of serum total protein should also be assessed centrally for helping establish the report.

p. Refer to Section 7.8 and Appendix A, Appendix B, and Appendix C for specific radiologic disease assessment guidelines. Investigators may conduct an initial tumor evaluation on C2D1 (±7 days) (optional based on clinical indicated) and a confirmatory tumor evaluation a minimum of 4 weeks (C3D1 ±7 days) after the first tumor evaluation if consistent with local regulatory authority requirements. At baseline imaging should include chest, abdomen, and pelvis, and other areas with disease involvement. Follow-up imaging includes chest, abdomen, pelvis and any areas known to have disease involvement at baseline. Other areas such as the neck, head and extremities may be imaged if disease involvement is suspected. For patients (e.g., CLL or WM) with documented disease involving blood/bone marrow but no documented baseline radiographic findings and where radiology is not required for routine response assessment, imaging is to be performed every 6 cycles (i.e., end of cycle 6, end of cycle 12) for the duration of study treatment. Clinical PD should be assessed with radiographic imaging unless most recent imaging was performed within 28 days of clinical PD.

q. Refer to Table 7.2.

r. Patients will be followed for survival status, date of progression, and subsequent anticancer therapy(ies) by telephone or other method.

s. Includes LOXO-305 dosing.

t. Concomitant medications, including ongoing medication(s) plus those administered within 14 days prior to the planned start of treatment.

u. AEs should be recorded from the time that written informed consent has been obtained through the SFU Visit. All SAEs should be recorded begins after the patient has signed the ICF and has received investigational product through 28 days after the last dose. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines if it is considered reasonably possibly related to study procedure. SAEs occurring after the SFU visit and judged by the investigator as related to study drug should be reported.

v. Refer to Appendix M.

w. Patients with MCL in Cohort 1 with history or evidence of GI involvement on baseline assessment may require appropriate upper and/or lower endoscopy procedure (if it is clinically safe) during screening with biopsy to document involvement at baseline. Patients with MCL in Cohort 1 with known or evidence of GI involvement (through clinical, imaging or endoscopy) at baseline, whose other disease assessments suggest CR must undergo Esophagogastroduodenoscopy and/or Colonoscopy with random segmental biopsies to confirm CR (if it is clinically safe).

x. If a patient discontinues study treatment for reasons other than PD, withdrawal of consent or initiation of a new anticancer therapy(ies), the patient is required to undergo tumor assessment in the time windows of LTFU until PD (even if PD occurs after 2 years), withdrawal of consent, or initiation of a new anticancer therapy(ies), utilizing the same modality(ies) used for the baseline imaging assessment.


CCI

7.1 Study Assessments

7.1.1 Informed Consent

Patients must be able to provide written informed consent and meet eligibility criteria prior to enrollment. The ICF must be signed before any protocol-specified procedures are performed except as noted in Section 7.1.2. Additional details are provided in Section 10.1.3.

7.1.2 Screening

The screening procedures must be conducted within 28 days prior to C1D1, unless otherwise noted. Patients who cannot complete the procedures within the screening window and who do not meet the criteria for participation in this study (screen failure) may be rescreened after discussion with and permission from the Lilly CRP or designee, and certain screening procedures may not need to be repeated with documented sponsor approval. Certain procedures (i.e., hematology, imaging) that were obtained as part of the patient's standard care prior to providing informed consent for this study, 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 Table 7.1. The results should be recorded in the Screening set of CRFs.

Screening tests other than radiology that are completed in the 7 days prior to start of study drug administration will be accepted as fulfilling the C1D1 assessments; repeat testing on C1D1 is not necessary for this scenario and results should be recorded in the Screening set of CRFs.

7.1.3 Enrollment

Enrollment procedures will be conducted in accordance with the Schedule of Assessments (Table 7.1). Patients who meet eligibility criteria outlined in Section 4 will be enrolled in this study. The investigator may repeat qualifying laboratory tests and vital signs/ECGs prior to enrollment and within screening window, if a non-qualifying finding is considered an error, and/or if an acute finding is likely to meet eligibility criteria on repeat testing.

7.1.4 Medical and Surgical History, and Demographics

All conditions ongoing and relevant past surgical and medical history should be collected. Medical, surgical, and malignancy history, including the disease under study as well as history of any other malignancy, diagnosis dates, types and prior treatments for the malignancy, etc. should be recorded on the appropriate CRF. Demographics including age, gender, race, and ethnicity will be recorded.

7.1.5 Physical Examination

Physical examinations will be conducted in accordance with the Schedule of Assessments (Table 7.1) and will include body weight, and height, neurological examination and review of relevant systems at Screening and C1D1. Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results. Symptom-directed physical examination may be performed at other time points after Screening in accordance with the Schedule of Assessments (Table 7.1).

7.1.6 Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be assessed in all patients in accordance with the Schedule of Assessments (Table 7.1). The ECOG performance scale is provided in Appendix L. The ECOG performance status will assist in assessing how a patient's disease is progressing or responding, assessing how the disease affects the daily living abilities of the patient, and determining the appropriate treatment and prognosis.

7.1.7 Vital Signs

Vital signs will be measured pre-dose in accordance with the Schedule of Assessments (Table **7.1**) and should include systolic and diastolic blood pressure, heart rate (pulse is acceptable if patients are not under cardiac arrythmias), respiratory rate, and body temperature.

At PK time points, vital signs particularly weight should be assessed as indicated in the Schedule of Assessments (Table 7.1), prior to actual PK blood sampling pre-dose (initial dose) (up to 4 hours pre-dose, as close to dosing as possible is preferred), and on C1D1 and C1D8 vital signs should also be conducted post-dose at 2 hours (±15 minutes). At non-PK time points, vital signs should be assessed at pre-dose (up to 4 hours pre-dose, as close to dosing as possible is preferred).

7.1.8 Electrocardiograms

Twelve-lead resting ECGs will be performed in accordance with the Schedule of Assessments (Table 7.1). Triplicate ECG should be performed at least 5 minutes apart and within one day during Screening, and during C1D1 and C1D8 at the following time points: pre-dose (initial dose) (up to 4 hours pre-dose), 2 and at 4 hours post-dose (±15 minutes). In addition, single ECG should be obtained at 2 hours post-dose (±15 minutes) on D1 of every other cycle of C2 through C12. To minimize variability, it is important that patients are in a resting position for at least 5 minutes prior to each 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 CRF.

We 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).
    - 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 bundle branch block (BBB), ECGs must be manually reviewed by a qualified physician and the QTc value must be corrected (utilizing locally approved correction factors) and this value should be entered into the CRF.
- If an unscheduled ECG is done at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG testing.
- If triplicate ECGs are obtained to confirm a Grade 3 AE (QTcF ≥501 msec or ≥ baseline 60 msec) as outlined in the NCI 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 CRF.

7.1.9 Laboratory Tests

Local laboratories will be utilized for routine laboratory tests, for example, blood chemistries from serum or plasma, hematology, and urinalysis. For ≥Grade 3 laboratory toxicity, laboratory testing should be repeated at least once a week until levels normalize or return to approximate baseline levels. Certain laboratory tests will also be assessed centrally depending on diagnosis at enrollment (e.g., complete blood count and lymphocyte subsets for CLL/SLL/WM patients, serum protein electrophoresis (SPEP) /immunofixation /serum free light chain (FLC)/quantitative Igs for WM patients). 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 Appendix K and the Laboratory Manual.

- Hematology

For all enrolled patients: Hematology should be assessed locally in accordance with the Schedule of Assessments (Table 7.1) and should include assessment of the following: hemoglobin, hematocrit, RBC count, WBC count, platelet count, percent or absolute WBC count differential (neutrophils, lymphocytes, eosinophils, basophils, and monocytes).

For WM and CLL/SLL patients: Blood samples for central assessment should also be collected on C1D1, ±7 days of each radiologic disease assessment and at disease progression.

- Blood Chemistries

Blood chemistries from serum or plasma should be assessed locally in accordance with the Schedule of Assessments (Table 7.1) and should include assessment of the following: sodium, potassium, chloride, glucose, blood urea nitrogen (BUN)/urea, creatinine, calcium, magnesium, phosphorus, total protein, albumin, total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase, gamma-glutamyl transferase, creatine kinase, uric acid/urate, and LDH. Lipase should be performed with D1 laboratory tests for each cycle, Cycles 1 through 12. Screening results performed within 7 days of C1D1 are acceptable as C1D1 results.

- Coagulation

The coagulation panel should include aPTT and PT (INR) and should be assessed locally during Screening and then only as clinically indicated. If PT measured in seconds is not available, then INR alone will suffice.

- Urinalysis

Urinalysis should be assessed locally in accordance with the Schedule of Assessments (Table **7.1**) and should include color, appearance, specific gravity, pH, glucose, bilirubin, ketones, occult blood, protein, leukocytes, nitrites, and urobilinogen.

- Pregnancy Testing

For appropriate patients: Pregnancy testing (serum or urine) must be conducted locally in accordance with the Schedule of Assessments (Table 7.1). Pregnancy reporting information is provided in Section 9.4. 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 prior treatment on Day 1 of each subsequent cycle of 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.

- Viral testing: HIV, CMV, Hepatitis B/C

Viral testing should be assessed at baseline locally in accordance with the Schedule of Assessments (Table 7.1) and should include testing for HIV, cytomegalovirus (CMV) (quantitative polymerase chain reaction [PCR] or antigenemia), 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. Patients with a positive HIV test 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. 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 detectable HBV DNA and controlled disease may be permitted on therapy with sponsor approval. Concurrent viral suppressive treatment will be required for patients with detectable HBV DNA (refer to Sections 6.3.2 and 6.3.3 for allowed and prohibited concomitant medications which should be shared with the consultant physician) and undergo regular monitoring of viral load during treatment and for at least 12 months after study treatment completion. Patients with history of HCV infection who have completed viral suppressive therapy and have a viral load below the limit of quantification are allowed. Either CMV PCR or antigen tests should be performed during screening to r/o active viral infection.

- Lymphocyte Subsets

For CLL/SLL patients: Lymphocyte subsets should be assessed centrally in accordance with the Schedule of Assessments (Table 7.1) and should include T-cell, B-cell and NK cell subsets and absolute B-cell count. Blood samples for local assessment can be done per investigator discretion.

- SPEP, Serum Immunofixation, Serum FLC, Quantitative Immunoglobulins, Total Protein For WM patients and any patients where a paraprotein is known: local and central assessment of SPEP, serum immunofixation, serum FLC, and quantitative immunoglobulins should be assessed in WM patients (and other patients if M-protein known to be present at baseline) in accordance with the Schedule of Assessments (Table 7.1). A separate testing of serum total protein should also be assessed centrally for helping establish the report.

7.2 Pharmacokinetics

PK samples should be collected in accordance with the Schedule of Assessments (Table 7.2). Additional PK assessments may be conducted in patients when considered necessary by the investigator to understand exposure in relationship to possible safety or efficacy findings or if there is a change to the formulation of LOXO-305 administered.

For C1D1, sampling should be timed to initial start of LOXO-305. For sampling after C1D1, sampling should be timed to the LOXO-305 dose taken for the day.

The plasma concentration of LOXO-305 will be determined with a validated bioanalytical assay and used to calculate PK parameters as described in Section 8.3.4. These parameters will be used to assess linearity of exposure and accumulation of drug exposure with time. Concentrations of LOXO-305 may also be used for population-PK analyses, to be reported in a separately report by the sponsor.

7.3 Telephone Follow-up

The site will contact the patient by telephone in accordance with the Schedule of Assessments (Table 7.1) to assess for LOXO-305 tolerability, continuation of study drug, and whether the patient needs to return to clinic earlier than planned. If not tolerating the drug well, the patient should be seen at least every 14 days to assess AEs, and the patient should be contacted regularly to assess AE status.

7.4 Central Tumor Sample Submission (Peripheral Blood, Bone Marrow, Tissue)

Adequate tissue samples at screening are required from patients enrolled in Cohort 1 for central pathology review to be performed retrospectively. Patients with inadequate tissue sample availability may still be enrolled in Cohort 3 if other eligibility criteria have been checked.

For patients enrolling with MCL, nodal tissue is preferred (vs marrow) and must include up to 10 unstained slides (or representative sections of archived paraffin block). De-identified surgical pathology reports of the patient's diagnosis of lymphoma and ancillary studies, such as flow cytometry, immunohistochemistry, FISH, cytogenetics, or molecular studies, which were used to establish the diagnosis are also requested.

For MCL: for Screening, bone marrow biopsy is required for baseline assessment, and patients in Cohort 1 with known or evidence of GI involvement appropriate upper and/or lower endoscopy may be performed if it is clinically safe for baseline assessment and if not performed within 42 days of enrollment. Adequate sample as Lab Manual is required to submit for central assessment.

For response assessment: Bone marrow biopsy should be done as appropriate for confirmation of CR if known disease involvement at baseline. Other assessments suggest CR, esophagogastroduodenoscopy and colonoscopy with random segmental biopsies is required, if clinically safe, for confirmation of CR in Cohort 1 MCL patients with known GI involvement at baseline. Adequate sample as Lab Manual is required to submit for central review. Bone marrow and endoscopy for local response assessment at the time points specified in Table 7.1 and Appendix K are also required.

For CLL/SLL: for Screening, peripheral blood and bone marrow biopsy with aspirate are required for baseline tumor assessment, and adequate sample as Lab Manual required also should submit for central assessment.

For response assessment: Peripheral blood is required. Bone marrow biopsy and aspiration is required for confirmation of CR and should be done in appropriate settings where all other assessments suggest CR and adequate sample as Lab Manual is required to submit for central review. Peripheral blood and bone marrow for local response assessment at the time points specified in Table 7.1 and Appendix K are also required.

For WM: for Screening, peripheral blood and bone marrow biopsy with aspirate are required for baseline assessment and adequate sample as Lab Manual is required to submit for central assessment.

For response assessment: Peripheral blood is required. Bone marrow biopsy and aspiration is required for confirmation of CR and should be done in appropriate settings where all other assessments suggest CR and adequate sample as Lab Manual is required to submit for central review. Peripheral blood and bone marrow for local response assessment at the time points specified in Table 7.1 and Appendix K are also required.

For indolent NHL (e.g., MZL, follicular lymphoma [FL]): for Screening: Bone marrow biopsy is required for marrow involvement assessment and adequate sample as Lab Manual required also should submit for central assessment.

For response assessment: Bone marrow biopsy is required for confirmation of CR and should be done in appropriate settings if known disease involvement at baseline and all other assessments suggest CR and adequate sample as Lab Manual required also should submit for central assessment.

For non-MCL high grade NHL (e.g., diffuse large B cell lymphoma [DLBCL]): For Screening: Bone marrow biopsy is required only if clinical suggestion of marrow involvement is noted, i.e., unexplained cytopenia, and adequate sample as Lab Manual required also should submit for central assessment.

For response assessment: Bone marrow biopsy should be done as appropriate for confirmation of response assessment only if known disease involvement at baseline; per Lugano staging criteria, positron emission tomography (PET) scan assessment of marrow response is acceptable.

7.5 Pathology and Molecular Reports

Anonymized/redacted pathology report(s) confirming histologic diagnosis and relevant biomarkers (e.g., FISH, IGVH, p53, karyotype for CLL/SLL, MYD88, CXCR4 status for WM, Ki67 staining for MCL) should be submitted. For patients with MCL, documentation of Cyclin D1 overexpression and/or t(11;14) positive status must be provided either from any time in the patient's history or from current biopsy studies in order for enrollment to proceed. For patients with WM, documentation of MYD88 mutation must be provided either from any time in the patient's history or from current biopsies studies in order for the patient to proceed.

7.6 Bone Marrow Aspirate and Biopsy

For patients enrolled with CLL/SLL, WM, low grade NHL, and selected high grade NHL (refer to Section 7.4): A bone marrow aspirate and/or biopsy should be collected during Screening, for confirmation of CR and (optional) at disease progression in accordance with the Schedule of Assessments (Table 7.1). All MCL patients, whose other response assessments are consistent with CR and known disease involvement at baseline, must undergo bone marrow biopsy to confirm CR. Samples for central assessment should also be collected in accordance with the Schedule of Assessments (Table 7.1) and outlined in Section 7.4 "Central Tumor Sample submission". If a bone marrow biopsy and/or aspiration was done after the last treatment or while progressing on the most recent treatment and within 90 days of Screening and samples are available of sufficient quality and quantity for central analysis, these do not need to be repeated during Screening. Guidance on sample collection and timing is provided in Appendix K and the Laboratory Manual.

7.7 Gastrointestinal Endoscopy

For MCL patients in Cohort 1 with known or evidence of GI involvement appropriate upper and/or lower endoscopy may be performed if it is clinically safe for baseline assessment, if not performed within 42 days of enrollment. For enrolled patients with MCL with known GI involvement (through clinical, imagine or endoscopy) at baseline in Cohort 1, who are in radiographic and bone marrow CR, esophagogastroduodenoscopy and colonoscopy with random segmental biopsies must be performed as appropriately, to evaluate for GI involvement with MCL and to confirm CR.

7.8 Radiologic Disease Assessment

Radiologic disease assessment will be conducted by the investigator in accordance with the Schedule of Assessments (Table 7.1) and the Imaging Manual. Investigators should use the

same method consistently for an individual patient throughout the study. For NHL, the preferred imaging is PET/CT, and appropriate method in accordance with Lugano guidance should be selected based on patients pathologic diagnosis, FDG avidity and lesion location etc.. For patients with NHL, baseline scans should assess the chest, abdomen, and pelvis. Other areas such as the neck, head and extremities should be scanned should there be known disease present. Follow up CT scans may be limited to chest, abdomen and pelvis as well as areas of known measurable and non-measurable disease. Assessments of both measurable and non-measurable disease will be made by the investigator using criteria as appropriate to cancer type; SLL response should be assessed by IWCLL criteria. The following Appendices should be referred to for specific radiologic disease assessment information:

- Appendix A Lugano Classification of Response in Non-Hodgkin Lymphoma
- Appendix B Chronic Lymphocytic Leukemia Response Assessment (IWCLL)
- Appendix C Waldenström Macroglobulinemia Response Assessment (IWWM)

For patients (e.g., CLL or WM) with documented disease involving blood/bone marrow but no documented baseline radiographic findings and where radiology is not required for routine response assessment, imaging is to be performed every 6 cycles (i.e., end of Cycle 6, end of Cycle 12) for the duration of receipt of study treatment. If tumor involvement is identified during routine assessments, then the radiographic assessment schedule will revert to the standard schedule.

In addition, investigators may conduct an initial tumor evaluation on C2D1 (±7 days) (optional based on clinical indicated) and a confirmatory tumor evaluation a minimum of 4 weeks (C3D1±7d) after the first tumor evaluation, if consistent with local regulatory authority requirements.

Clinical PD should be assessed with radiographic imaging unless most recent imaging was performed within 28 days of clinical PD.

If patient terminates treatment prior to scheduled disease assessments, the patient should have assessment done at the EOT visits (does not need to be repeated if performed within 2 weeks prior to the EOT visits, or if tumor progression was previously determined).

Patients who are unable to undergo CT scans with contrast due to allergy to contrast dye, may substitute magnetic resonance imaging (MRI) with gadolinium or appropriate method per investigator discretion and should discuss with sponsor.

7.9 Survival Status

Patients will be followed for survival status, date of progression, and subsequent anticancer therapy(ies) by telephone or other method.

7.10 Study Drug and Dosing Diary

Study drugs taken orally should be administered in accordance with the Schedule of Assessments (Table 7.1) and Section 6. Completion of the outpatient dosing diary will include

recording of LOXO-305 dosing.

7.11 Concomitant Medication

Concomitant medications should be recorded in accordance with the Schedule of Assessments (Table 7.1).

All medications that were used from 14 days prior to the planned start of study drug or from Screening (whichever is shorter) through SFU (at least 28 days [+7 days] after the last dose of study drug) will be recorded in the CRF. These are to include prescription and nonprescription medications, transfusions, vitamins and nutritional supplements, and other remedies. Excluded prior medications are excluded via the eligibility criteria (Section 4.2). Additional guidance regarding concomitant medications is provided in Section 6.3.

7.12 Adverse Events/Serious Adverse Events

Adverse events should be recorded in accordance with the Schedule of Assessments (Table 7.1) and Section 9.

7.13 Patient-reported Outcomes (PRO) Assessments

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), the supplementary 'cancer-related symptom' assessments for MCL (European Organization for Research and Treatment of Cancer Items Library 63 [EORTC IL63]) (refer to Appendix M) will be administered in accordance with the Schedule of Assessments (Table 7.1). Each assessment should be performed as early as possible during the clinic visit, before the patient interacts extensively with staff and before the patient learns the results of their restaging. Physicians and staff should refrain from viewing results prior to completion of the clinic visit. PRO assessments will be administered according to Schedules of Assessments in Table 7.1 in countries where the questionnaires have been translated into the native language(s) of the region. Only patients fluent in an available translated language should complete the questionnaires.

Although individual patients may vary in their response time, 2 recent publications have evaluated survey completion times. One study among patients with advanced cancer suggests that a 20-item assessment (approximately half of the 38-39 total items to be completed in this study) can be completed in an average of less than 4 minutes when administered via paper (Bennett et al. 2016). In a second study, 67 items (28-29 more than in this study) were completed in an average of 15 minutes; 100% of patients reported the completion time as "about right", 79% were willing to answer more questions (Girgis et al. 2017).

7.14 Central Collection of Radiographic Studies and Samples

Baseline screening radiographic studies and all subsequent radiographic studies will be collected for independent radiological review.

Baseline and subsequent samples (peripheral blood, bone marrow aspiration, biopsy and/or tissue samples) required for response assessment according to disease-defined criteria will be collected.

7.15 End of Treatment

Within 7 days after last dose of study drug or at the time of the decision to terminate treatment, the EOT assessments and procedures will be conducted in accordance with the Schedule of Assessments (Table 7.1). If lab testing is performed ≤7 days prior to EOT, repeat testing does not need to occur on EOT.

7.16 Safety Follow-up

The safety follow-up assessments will be conducted in accordance with the Schedule of Assessments (Table 7.1). Safety follow-up procedures may be performed as part of the EOT visit if the latter was performed at least 28 days after final dose of the last cycle.

7.17 Long-Term Follow-up

The LTFU assessments and procedures will be conducted in accordance with the Schedule of Assessments (Table 7.1). After treatment discontinuation, LTFU will occur approximately every 3 months (±1 month) for up to 2 years and every 6 months (±2 month) thereafter, until the patient experiences PD, withdraws consent for further participation, is lost to follow-up, has died, or close of the study.

Assessments may include: subsequent anticancer therapy(ies) and survival status. LTFU may be conducted by phone. 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.

If a patient discontinues study treatment for reasons other than PD, withdrawal of consent or initiation of a new anticancer therapy(ies), the patient is required to undergo disease assessment as specified in Appendix A, Appendix B, and Appendix C until PD (even if PD occurs after 2 years), withdrawal of consent, or initiation of a new anticancer therapy(ies), utilizing the same modality(ies) used for the baseline imaging assessment.

8. STATISTICAL CONSIDERATIONS

A full Statistical Analysis Plan (SAP) will provide specific details on the analytical methods and data displays.

8.1 Analysis Populations

8.1.1 Safety Population

The safety population will be used primarily for the analysis of safety data and will consist of all enrolled patients who receive 1 or more doses of LOXO-305.

8.1.2 Primary Analysis Set

The Primary Analysis Set (PAS) will be used for the analysis of tumor response and other efficacy-related data of Cohort 1 and Cohort 2.

The PAS for Cohort 1 will include all patients enrolled in this cohort who meet the following criteria:

- Central histologically confirmed non-blastoid MCL with no CNS metastases and treated with prior chemoimmunotherapy and BTK inhibitor-containing regimen.
- Measurable disease at baseline as assessed using Lugano criteria
- Received at least 1 dose of study drug

The PAS for Cohort 2 will include all patients enrolled in this cohort who meet the following criteria:

- CLL/SLL previously treated with a BTK inhibitor
- Measurable disease at baseline as assessed using IWCLL
- Received at least 1 dose of study drug

Details of analysis sets will be provided in SAP.

8.2 Determination of Sample Size

CCI [redacted] The decision to further investigate certain cohorts will be based on comprehensive evaluation of the risk-benefit profile.

Table 8.1 provides guidance for interpretation of the treatment effect for each cohort based on the observed ORR.

[redacted]

8.3 Statistical Analyses

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

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. All CIs will be given at a 2-sided 95% level, unless otherwise stated.

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.

Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP and clinical study report (CSR).

The assumptions for each statistical method may be evaluated. If there is violation of assumptions, alternative statistical methods may be used.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

8.3.1 Demographics and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics for all enrolled patients will be tabulated. Patients will be tabulated by cohort and overall.

8.3.2 Safety Analyses

Safety will be assessed by clinical review of all relevant parameters including AEs, SAEs, TEAEs, laboratory values, vital signs, ECG results, and concomitant medications. Unless specified otherwise, the safety analyses will be conducted for the safety population defined in Section 8.1. A baseline measurement and at least 1 laboratory or other safety-related measurement obtained after the start of study drug may be required for inclusion in the analysis of a specific safety parameter. Tabulations will be provided by cohort and overall.

Investigator will report a verbatim AE term. The reported AE term will be assigned a standardized preferred term using MedDRA. The investigator will grade the severity of each AE

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

Safety analyses will include summaries of the following:

- adverse events, including severity and possible relationship to study treatment
- serious adverse events, including possible relationship to study treatment
- adverse events leading to dose adjustments, treatment discontinuation, or death
- discontinuations from study treatment or death

8.3.3 Efficacy Analyses

The primary analysis of efficacy will be based on the PAS. These analyses will be summarized by the specific B-cell malignancy (MCL and CLL/SLL).

ORR will be assessed using Lugano criteria (Appendix A) or IWCLL (Appendix B) including assessment of complete response with incomplete marrow recovery (CRi), nodular PR (nPR), and PR with lymphocytosis (PR-L), or IWWM (Appendix C), as appropriate to tumor type. The estimate of the ORR will be calculated as the proportion of patients with best overall response (BOR) of PR or better, based on IWCLL, PR or better based on Lugano, and minor response or better for WM based on IWWM criteria as determined by IRC and by the treating investigator. The estimates of the ORR will be accompanied by a 2-sided 95% CI. Waterfall plots will be used to depict graphically the maximum decrease from baseline in the sum of product diameters (SPD) of target lesions.

DOR will be calculated for patients who achieve a response of PR or better (minor response or better for WM). For such patients, DOR is defined as the number of months from the start date of the first documented response to the earlier of the documentation of definitive disease progression or death from any cause. Patients who are alive and without documented PD as of data analysis cutoff date will be censored. Details of the censoring rules will be provided in SAP.

PFS will be derived for each patient as the number of months from the date of the first dose of study drug to the earlier of documented PD or death due to any cause. Patients who are alive and without documented PD as of data analysis cutoff date will be censored. Details of the censoring rules will be provided in SAP.

OS will be derived for each patient as the number of months from the date of the first dose of study drug to the date of death, irrespective of cause. Patients who are alive or lost to follow-up as of a data analysis cutoff date will be censored. The censoring date will be determined from the last date the patient was known to be alive or data analysis cutoff date, whichever occurs first. Details of the censoring rules will be provided in SAP.

DOR, PFS, and OS will be summarized descriptively using the Kaplan-Meier method.

Patients enrolled in Cohort 3 will be evaluated for efficacy in an exploratory manner separately from the primary efficacy analysis for Cohorts 1 and 2, but they will be included in the overall safety analysis.

The association of clinical response categories (BOR) with changes in cancer-related symptoms (using EORTC symptom assessments) and physical function (using the EORTC-QLQ-C30 Physical Functioning Subscale) for patients with MCL, CLL/SLL and other NHL tumors will be assessed.

8.3.4 Pharmacokinetic Analyses

Plasma concentrations of LOXO-305 will be determined with a validated bioanalytical assay. The following PK parameters will be calculated from plasma concentrations determined on the patients as illustrated in Section 7.2. If appropriate: C_{max}, T_{max}, area under the concentration versus time curve from time 0 to t (AUC_{0-t}), apparent oral clearance (CL/F), apparent volume of distribution (Vz/F), and $T_{1/2}$.

Summary statistics will be generated by cohort and across cohorts as appropriate.

8.3.5 Primary Analysis

The main data cutting-off and primary analysis will be performed after all enrolled patients have been followed up for sufficient amount of time (6 months). However, the primary analysis may be provided or updated upon request from regulatory authorities at any time during the study.

9. ADVERSE EVENTS

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

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator. Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

The investigator will record all relevant AE and SAE information in the case report form (CRF). After the ICF is signed, study site personnel will record via CRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure, investigational product, via CRF. The investigator should provide AE verbatim terms and then the terms will be mapped by Lilly or its designee to corresponding terminology within the MedDRA Lower level term dictionary. The investigator will use NCI CTCAE v5.0 to assign AE severity grades.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, or a study procedure, taking into account the disease, concomitant treatment or pathologies. A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, and/or study procedure and the AE. The investigator answers yes/no when making this assessment. 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) unless the disease progression is assessed as related to study treatment. 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.

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via CRF, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

Because of the well documented lymphocytosis that occurs early with approved BTK inhibitors and is not associated with PD, progressive lymphocytosis on LOXO-305 in the absence of other signs of PD (e.g., splenomegaly, enlarging lymph nodes, disease-related constitutional symptoms) will not be considered PD.

9.1 Serious Adverse Event Reporting

An SAE is any AE from this study that results in one of the following outcomes:

- Death
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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 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 before signing of the informed consent. However, 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 sponsor. The CRF must be updated to reflect this information. In the event that the overdose is associated with an SAE, the 2 events should be linked. In the event of an AE associated with an overdose, an SAE report form must be completed detailing the AE and the overdose details.

All AEs occurring after signing the ICF are recorded in the CRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the patient has signed the ICF and has received investigational product through 28 days after the last dose. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines if it is considered reasonably possibly related to study procedure. SAEs occurring after the SFU visit and judged by the investigator as related to study drug should be reported. Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the patient disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-

hour notification requirement refers to the initial SAE information and all follow-up SAE information. Patients with a serious hepatic adverse event should have additional data collected using the CRF (see Section 9.2).

Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. Lilly has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance documents.

Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study patients, to monitor quality, and to facilitate process and product improvements.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.2 Hepatic Safety Monitoring

Close hepatic monitoring and evaluation.

If one or more of these following conditions occur:

If a patient with baseline results of	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥5x ULN or ALT or AST ≥3x ULN concurrent with TBL ≥2x ULN
ALT or AST ≥1.5x ULN	ALT or AST ≥3x baseline or ALT or AST ≥2x baseline concurrent with TBL ≥2x ULN

liver testing should be repeated within 2 to 4 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if a potential condition is improving or worsening. If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible cause of abnormal liver tests (refer to Appendix N) should be initiated by the investigator in consultation with the study Lilly CRP. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), history of concomitant medications (including over-the-counter, herbal and dietary supplements, history of alcohol drinking and other substance abuse). Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels. Dose modification should follow that outlined in Section 6.2.2.

In addition, the evaluation should include a blood test for prothrombin time (PT-INR); serological tests for viral hepatitis A, B, C, E, autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan). Based on the patient's history and initial evaluation results, further testing should be considered in consultation with the Lilly designated medical monitor, including tests for hepatitis D virus (HDV), CMV, Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's

disease, blood alcohol levels, urinary ethyl glucuronide, and serum phosphatidylethanol. Based on the circumstances and the investigator's assessment of the patient's clinical condition, the investigator should consider referring the patient for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, and/or a liver biopsy.

Hepatic Safety Data Collection

Additional safety data (also refer to Appendix N) should be collected via the CRF if one or more of the following conditions occur:

In patients enrolled with baseline ALT or AST <1.5 x ULN

- Elevation of serum ALT or AST to ≥5x ULN on 2 consecutive tests
- The combination of elevated ALT or AST ≥3 x ULN and elevated TBL ≥2 x ULN

In patients enrolled with baseline ALT or AST ≥1.5 x ULN

- Elevated ALT or AST ≥3 x baseline on 2 consecutive tests
- The combination of elevated ALT or AST ≥2 x baseline and elevated TBL ≥2 x ULN

In all study patients

- Discontinuation from study treatment due to a hepatic event or abnormality of liver tests
- Occurrence of a hepatic event considered to be a SAE

9.3 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.

9.4 Pregnancy Reporting

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

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 sponsor. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy.

10. STUDY ADMINISTRATION

10.1 Regulatory and Ethical Considerations

10.1.1 Regulatory Authority Approval

This study will be conducted in accordance with the standard of International Council for Harmonisation-Good Clinical Practice (ICH GCP), an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with these standards provides assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles in the Declaration of Helsinki, and that the clinical study data are credible.

10.1.2 Ethics Approval

It is the responsibility of the investigator to ensure that the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) has reviewed and approved this protocol prior to initiating the study. The investigator must provide the sponsor or sponsor's representative with current and revised IRB/IEC membership rosters that include the members' occupations and qualifications.

The IRB/IEC must also review and approve the clinical site's ICF, other written information provided to the patient, and all advertisements that may be used for patient recruitment. The investigator will provide the study monitor with copies of these documents and of dated IRB/IEC approval(s) prior to the start of the study.

If the protocol or the ICF is amended during the study, the investigator is responsible for ensuring that the IRB/IEC has reviewed and approved these amended documents. Approval of the amended documents must be obtained from the IRB/IEC before implementation and before new patients are consented to participate in the study using the amended version of the ICF. The investigator must provide the sponsor with the dated IRB/IEC approval of the amended documents as soon as available.

10.1.3 Patient Informed Consent

Prior to study entry, the investigator or designee will explain the nature, purpose, benefits, and risks of participation in the study to each patient, patient's legally acceptable representative, or impartial witness. Written informed consent must be obtained prior to the patient entering the study (before initiation of any study-related screening procedure). Sufficient time will be allowed to discuss any questions raised by the patient. The ICF must be signed by all patients. The process of obtaining consent will be in compliance with all applicable regulations and ICH requirements.

If the ICF is amended during the study, the investigator must follow all applicable regulatory requirements pertaining to IRB/IEC approval of the amended form. The clinical site must use the amended ICF for all new patients and must re-consent any ongoing patients with the amended ICF, if instructed to do so by the IRB/IEC.

The sample ICF prepared by the sponsor is provided in the Study Manual. The consent and re-consenting process should be properly documented in the source documentation.

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

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.

10.1.5 Sponsor Safety Reporting to Regulatory Authorities

The sponsor or its representative is required to report certain study events in an expedited manner to the Regulatory Authorities 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.

10.2 Data Management

Source documents will be maintained by sites and used to enter data and complete the CRFs in the clinical database (electronic data capture [EDC]). The sponsor's monitors will routinely review the source documentation and verify the corresponding data entered on CRFs in the clinical database. All entered, changed, and final data shall be available with a validated audit trail report or data extract report. The CRFs shall be considered complete when all expected data has been entered and all discrepancies have been resolved or documented.

The investigator must sign all CRFs according to the EDC requirements.

10.3 Study Monitoring

Prior to the start of the study, the sponsor's monitor will contact the clinical site to discuss the protocol and data collection procedures and conduct applicable training of site personnel. The sponsor and its designees will also periodically contact the clinical site during the conduct of the study (which will include on-site visits) in accordance with applicable regulations and GCP. During these contacts, the monitoring activities will include:

- Checking and assessing the progress of the study
- Reviewing study data collected to date for completeness and accuracy
- Conducting source document verifications by reviewing each patient's CRF against source documents
- Identifying any issues and addressing resolutions
- Recording and reporting protocol deviations not previously reported to the sponsor
- Confirming that SAEs have been properly reported to the sponsor and submitted to the IRB/IEC, if appropriate.

These activities will be done in order to verify that the data are authentic, accurate, and complete; that the safety and rights of the patient are being protected; and that the study is conducted in accordance with the currently approved protocol, ICH GCP, and all applicable regulatory requirements. Additionally, to ensure compliance with ICH GCP and all applicable regulatory requirements, the sponsor or designee may conduct a quality assurance audit.

10.4 Termination

Upon completion of the study, the following activities, when applicable, must be conducted by the site monitor and the investigator:

- Submission of all study data to the sponsor
- Completion of all data clarifications and/or resolutions
- Reconciliation and final disposition of investigational product
- Review of site study files for completeness

In addition, the sponsor reserves the right to temporarily suspend or prematurely terminate this study for any reason.

If the study is suspended or terminated for safety reasons, the sponsor will promptly inform the investigator and will also inform the IRB/IEC with the reasons for the action. In the event of prematurely termination, all study data must be submitted to the sponsor. In addition, the clinical site must document final disposition of all unused investigational product in accordance with the sponsor's procedures.

10.5 Records Retention

Patient records, source documents, monitoring visit logs, investigational product inventory, regulatory documents, and other correspondence pertaining to the study must be maintained in the appropriate site study files according to ICH GCP and applicable regulatory requirement(s). These records will be retained for the period required by the institution or site policy. Prior to transfer or destruction of these records, the sponsor must be notified in writing.

10.6 Confidentiality of Information

Patient names will remain confidential and will not be supplied to the sponsor or its designee. The investigator will maintain a personal patient identification list (patient and treatment numbers with the corresponding patient names) to enable records to be identified.

11. APPENDICES

Appendix A Lugano Classification of Response in Non-Hodgkin Lymphoma

Table 11.1 Lugano Classification of Response

Response and Site	PET-CT–Based Response	CT-Based Response
Complete [a]	**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**
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
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured 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	Regrowth of previously resolved lesions 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.

a. For MCL in Cohort 1, bone marrow biopsy and aspiration, esophagogastroduodenoscopy (EDG) and colonoscopy with random segmental biopsies (for patients with known or evidence of GI involvement at baseline) must be performed to confirm radiographic CR.

* 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.

For complete Lugano Classification, please refer to: Cheson et al. 2014.

Appendix B Chronic Lymphocytic Leukemia Response Assessment (IWCLL)

Table 11.2 Response Definition after Treatment of CLL/SLL Patients

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

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

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

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

For complete IWCLL guideline, please refer to Hallek et al. 2018.

In addition to the CR, PR, PD and SD response definition as listed in the table above, the protocol requires response assessments of complete response with an incomplete marrow recovery (CRi), nodular Partial Response (nPR), and PR with lymphocytosis (PR-L), as explained below:

- In assessing response, PR-L, which is defined as only 1 abnormal Group A criteria met in the setting of lymphocytosis not meeting PR criteria, may also be summarized for patients with CLL/SLL so as to not underestimate overall response in the setting of BTK inhibitor therapy (Cheson et al. 2012).

- For CRi response, patients must fulfill all criteria for a CR with persistent anemia, neutropenia and thrombocytopenia and investigator must attribute these cytopenias as related to investigational drug and not due to the underlying disease.
- For nPR, patients must fulfill all criteria for a CR, but the bone marrow biopsy/aspirate shows B-lymphoid nodules which are evidence for residual disease.

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

Appendix C Waldenström Macroglobulinemia Response Assessment (IWWM)

Table 11.3 Waldenström Macroglobulinemia Response Assessment Criteria

Response Category	Description
CR	Absence of serum monoclonal IgM protein by immunofixation Normal serum IgM level Complete resolution of extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline Morphologically normal bone marrow aspirate and trephine biopsy
VGPR	Monoclonal IgM protein is detectable ≥ 90% reduction in serum IgM level from baseline[a] Complete resolution of extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
PR	Monoclonal IgM protein is detectable ≥ 50% but < 90% reduction in serum IgM level from baseline[a] Reduction in extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
MR	Monoclonal IgM protein is detectable ≥ 25% but < 50% reduction in serum IgM level from baseline[a] No new signs or symptoms of active disease
SD	Monoclonal IgM protein is detectable < 25% reduction and < 25% increase in serum IgM level from baseline[a] No progression in extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
PD	≥ 25% increase in serum IgM level[a,b] from lowest nadir (requires confirmation) and/or progression in clinical features attributable to the disease

Abbreviations: CR = complete remission; MR = minor response; PD = progressive disease; PR = partial remission; SD = stable disease; VGPR = very good partial response.

[a] Sequential changes in IgM levels may be determined by either M-protein quantitation by densitometry or total serum IgM quantitation by nephelometry.

[b] An absolute increase of >5 G/L (0.5 g/dL) is required when the increase of IgM component is the only applicable criterion.

For complete IWWM guideline, please refer to: Anderson, J Natl Compr Canc Netw. 2012; 10(10):1211-1219.

Appendix D Treatment Failure and Intolerance

Treatment Failure:

Relapse: evidence of disease progression according to disease-defined criteria in a patient who has previously achieved a complete response (CR) or partial response (PR) for ≥6 months (WM patients with an IWWM defined minor response for ≥6 months would also be considered as relapsed at time of disease progression).

Refractory disease: treatment failure as defined by less than CR or PR (i.e., stable disease [SD], nonresponse, progressive disease [PD]) or progression within 6 months from the last dose of therapy.

Treatment Intolerance:

- ≥1 Grade 3 or ≥2 Grade 2 non-hematologic toxicities or
- ≥1 Grade 3 neutropenia with infection or fever or
- ≥1 Grade 4 hematologic toxicity
- The above leads to treatment discontinuation for ≥14 days without disease progression (patient could have progressed after 14 days)
- Toxicities should resolve to ≤ Grade 1 off therapy

References:

(Hallek et al. 2018, Mato 2018)

Appendix E Prior BTK Inhibitors

This list represents the names of known BTK inhibitors. If a patient has been on a BTK inhibitor that is not represented on this list, the sponsor should be contacted for a discussion regarding the prior BTK inhibitor to ensure appropriate cohort assignment at patient enrollment.

Prior BTK inhibitors used in the treatment of CLL/SLL or NHL include, but are not limited to:

- Acalabrutinib
- DTRMWXHS-12
- GDC-0853
- Ibrutinib
- Orelabrutinib (ICP-022)
- SHR1459
- TG-1701
- Zanubrutinib (BGB-3111)
- Evobrutinib (M7583)

Appendix F Indication for Treatment of CLL/SLL

For treatment initiation, at least 1 of the following criteria should be met:

1. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia. Cutoff levels of Hb <10 g/dL or platelet counts <100 $\times$ 10^9/L are generally regarded as indication for treatment. However, in some patients, platelet counts <100 $\times$ 10^9/L may remain stable over a long period; this situation does not automatically require therapeutic intervention.
2. Massive (i.e., ≥6 cm below the left costal margin) or progressive or symptomatic splenomegaly.
3. Massive nodes (i.e., ≥10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
4. Progressive lymphocytosis with an increase of ≥50% over a 2-month period, or lymphocyte doubling time (LDT) <6 months. LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months; patients with initial blood lymphocyte counts <30 $\times$ 10^9/L may require a longer observation period to determine the LDT. Factors contributing to lymphocytosis other than CLL (e.g., infections, steroid administration) should be excluded.
5. Autoimmune complications including anemia or thrombocytopenia poorly responsive to corticosteroids.
6. Symptomatic or functional extranodal involvement (e.g., skin, kidney, lung, spine).
7. Disease-related symptoms as defined by any of the following:
    a. Unintentional weight loss ≥10% within the previous 6 months.
    b. Significant fatigue (i.e., ECOG performance scale 2 or worse; cannot work or unable to perform usual activities).
    c. Fevers ≥38.0°C for 2 or more weeks without evidence of infection.
    d. Night sweats for ≥1 month without evidence of infection.

Appendix G New York Heart Association (NYHA) Functional Classification

Table 11.4 Classes of Heart Failure

Class	Patient Symptoms	Class	Objective Assessment
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).	A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).	B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.	C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.	D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

Appendix H Examples of Agents Known to Cause QTc Prolongation

Table 11.5 Examples of Agents Known to Cause QTc Prolongation

Examples of Agents Known to Cause QTc Prolongation	
amiodarone	ibogaine
anagrelide	ibutilide
azithromycin	levofloxacin
chloroquine	levomepromazine (methotrimeprazine)
chlorpromazine	levosulpiride
cilostazol	methadone
ciprofloxacin	moxifloxacin
citalopram	ondansetron
clarithromycin	papaverine HCl (intracoronary)
cocaine	pentamidine
disopyramide	pimozide
dofetilide	procainamide
domperidone	propofol
donepezil	quinidine
dronedarone	roxithromycin
droperidol	sevoflurane
erythromycin	sotalol
escitalopram	sulpiride
flecainide	sultopride
fluconazole	terlipressin
halofantrine	terodiline
haloperidol	thioridazine
hydroquinidine, dihydroquinidine	

Note: The above list is not exhaustive. Please refer to www.crediblemedicines.com for a current list of agents known to cause QTc prolongation, as well as agents with a possible or conditional risk.

Appendix I Inhibitors and Inducers of CYP3A4

Table 11.6 Inhibitors of CYP3A4

Strong inhibitors [a]	Moderate inhibitors [b]
boceprevir	amprenavir
clarithromycin	aprepitant
cobicistat	atazanavir (see atazanavir and ritonavir)
conivaptan	atazanavir and ritonavir
danoprevir and ritonavir	cimetidine
diltiazem	ciprofloxacin
elvitegravir and ritonavir	clotrimazole
grapefruit juice	crizotinib
idelalisib	cyclosporine
indinavir and ritonavir	darunavir
itraconazole	dronedarone
ketoconazole	duvelisib
lopinavir and ritonavir	erythromycin
nefazodone	fedratinib
nelfinavir	fluconazole
posaconazole	fluvoxamine
ribociclib	fosnetupitant and palonosetron (see also netupitant)
ritonavir	imatinib
saquinavir and ritonavir	indinavir (see indinavir and ritonavir)
telithromycin	isavuconazole
tipranavir and ritonavir	ledipasvir/sofosbuvir
Viekira Pak (paritaprevir and ritonavir and ombitasvir and/or dasabuvir)	lefamulin
voriconazole	letermovir
	magnolia vine (Schisandra sphenanthera)
	netupitant
	nilotinib
	tofisopam
	verapamil
	voxelotor

Abbreviations: AUC = area under the concentration versus time curve; CYP3A4 = cytochrome P450 3A4.

[a] Increases the AUC of the substrate by ≥5-fold.

[b] Increases the AUC of the substrate by 2- to 5-fold.

Table 11.7 Inducers of CYP3A4

Strong inducers [a]	Moderate inducers [b]
aminoglutethimide	almorexant
apalutamide	bosentan
avasimibe	cenobamate
carbamazepine	dabrafenib
enzalutamide	daclatasvir and asunaprevir and beclabu
fosphenytoin	danshen (Salvia miltiorrhiza)
ivosidenib	efavirenz
lumacaftor	encorafenib
mitotane	etravirine
phenobarbital	faldaprevir and efavirenz
phenytoin	genistein
rifabutin	lersivirine
rifampicin (rifampin)	lesinurad
rifapentine	lopinavir (alone)
St John's wort	lorlatinib
	modafinil
	nafcillin (intravenous)
	pentobarbital
	primidone
	telotristat ethyl
	thioridizine
	tipranavir and ritonavir
	tocilizumab (atlizumab)

Abbreviations: AUC = area under the concentration versus time curve; CYP3A4 = cytochrome P450 3A4.

[a] Decreases the AUC of the substrate by ≥80%.

[b] Decreases the AUC of the substrate by 50% to 80%.

Note: The above lists are not exhaustive. Also refer to: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions.

Appendix J P-gp inhibitors

Given that LOXO-305 is a substrate of P-gp, inhibitors of P-gp could adversely affect the metabolism of LOXO-305. Therefore, the use of strong P-gp inhibitors is contraindicated while taking LOXO-305.

Table 11.8 Examples of Strong P-gp Inhibitors

Amiodarone
Clarithromycin
Cyclosporine
Diltiazem
Donedarone
Erythromycin
Felodipine
Fluconazole
Itraconazole
Ketoconazole
Lapatinib
Lopinavir
Propafenone
Ranolazine
Ritonavir
Telaprevir
Saquinavir
Quinidine
Verapamil

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

Appendix K Guidelines for Patient Sample Collection for Central Analysis

Selected patient samples from peripheral blood, bone marrow and/or nodal/extra-nodal sites will be collected during the conduct of this study for central assessment (except for PK). The following table is meant to be a guide; refer to the Laboratory Manual for additional details.

Table 11.9 Guidelines for Patient Sample Collection for Central Analysis

Tumor Type	Time Point	Peripheral Blood[a]	Bone Marrow[a]	Lymph Node/Tumor Tissue
MCL	**Baseline**		Required unless available after last treatment or while progressing on the most recent treatment and performed within 90 days	Required for patients enrolled in Cohort 1 for central pathology review
	Response time points		Required to confirm CR if known disease involvement at baseline	
	Progression		Optional	
CLL/SLL	**Baseline**	Required for response assessment[b]	Required unless available after last treatment or while progressing on the most recent treatment and performed within 90 days	
	Response time points	Required for response assessment[b]	Required at CR	
	Progression	Required for response assessment[b]	Optional	
WM	**Baseline**	Required for response assessment[b]	Required unless available after last treatment or while progressing on the most recent treatment and performed within 90 days	
	Response time points	Required for response assessment[b]	Required at CR	
	Progression	Required for response assessment[b]	Optional	

Tumor Type	Time Point	Peripheral Blood[a]	Bone Marrow[a]	Lymph Node/Tumor Tissue
Indolent NHL (e.g., MZL, FL)[c]	**Baseline**		Required unless available after last treatment or while progressing on the most recent treatment and performed within 90 days	
	Response time points		Required to confirm CR if known disease involvement at baseline	
	Progression		Optional	
Non-MCL High grade NHL (e.g., DLBCL)[c]	**Baseline**		May be required if unexplained cytopenia present at screening suggestive of bone marrow involvement unless available after last treatment or while progressing on the most recent treatment and performed within 90 days.	
	Response time points		Required at CR only if known disease involvement at baseline, per Lugano staging criteria, positron emission tomography (PET) scan assessment of marrow response is acceptable [a]	
	Progression		Optional	

Abbreviations: CLL = chronic lymphocytic leukemia; CR = complete remission; DLBCL = diffuse large b cell lymphoma; FL = Follicular lymphoma; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; NHL = non-Hodgkin lymphomas; SLL = small lymphocytic lymphoma; WM = Waldenström macroglobulinemia.

a Sample collection for local tumor assessment is also needed.

b Laboratory studies for response assessment includes blood count with differential for CLL patients and SPEP/immunofixation/serum free light chains/quantitative immunoglobulins for WM patients.

c According to Lugano staging criteria, PET scan can be used to assess bone marrow involvement and response in DLBCL.

Appendix L Eastern Cooperative Oncology Group Performance Scale Table

Table 11.10 Eastern Cooperative Oncology Group Performance Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix M Patient Reported Outcome (PRO) Assessments

EORTC QLQ-C30

Health-related quality of life will be assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0 (EORTC QLQ-C30; Aaronson, et al. 1993). It is a copyrighted instrument, which has been translated and validated in over 100 languages and is used in more than 3,000 studies worldwide. This study utilizes version 3.0, and the Study Manual should be consulted for instructions on implementing and scoring.

The EORTC QLQ-C30 consists of 30 total items within 3 dimensions:

- Global health status/quality of life (2 items)
- Functional scales (15 total items assessing 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).

Six of the 13 symptom items assessed by the EORTC QLQ-C30 are hypothesized to be associated with CLL/SLL: Dyspnea, Fatigue (3 items), General Pain, and Sleep Problems. Seven of the 13 are hypothesized to be associated with B-Cell NHL: Nausea, Dyspnea, Fatigue (3 items), General Pain, and Sleep Problems. These are supplemented by additional items from the EORTC Item Library: EORTC IL63 (for MCL).

Upon further exploration, a select number of these symptom items (in addition to those assessed by EORTC IL63) will be used to assess symptomatic response.

References:

EORTC website: http://groups.eortc.be/qol/eortc-qlq-c30 (Aaronson et al. 1993).

EORTC Symptom Assessments: EORTC IL63

In addition to the EORTC QLQ-C30, patients with MCL will complete a supplemental set of symptom items that are hypothesized to be associated with their respective malignancy:

- Patients with MCL will complete the EORTC IL63, which consists of 6 additional symptom items: Night sweats, Fever/Chills, Fatigue (3 items), and Bloating of the abdomen.

Upon further exploration, a select number of these symptom items (in addition to those assessed by the EORTC QLQ-C30) will be used to assess symptomatic response.

Appendix N Liver Safety: Suggested Actions and Follow-Up Assessments

Table 11.11 Liver Evaluation Testing

Hepatic Evaluation Testing – Refer to protocol Hepatic Safety Monitoring Section 9.2 for guidance on appropriate test selection.

- Results will be reported if a validated test or calculation is available.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - Red Blood Cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - White Blood Cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen Protein Adducts
Platelets	Alkaline Phosphatase Isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
Coagulation	Copper Ethyl Alcohol (EtOH)
Prothrombin Time, international normalized ratio (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (Quantitative)
Hepatitis A Virus (HAV) Testing:	Immunoglobulin IgG (Quantitative)
HAV Total Antibody	Immunoglobulin IgM (Quantitative)
HAV IgM Antibody	Phosphatidylethanol (PEth)
Hepatis B Virus (HBV) Testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug Screen
Hepatitis B surface antibody (Anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (Anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) [a]
HBV DNA [c]	Anti-actin antibody [b]
Hepatis C Virus (HCV) Testing:	Epstein-Barr Virus (EBV) Testing:
HCV antibody	EBV antibody

HCV RNA [c]	EBV DNA [c]
Hepatitis D Virus (HDV) Testing:	Cytomegalovirus (CMV) Testing:
HDV antibody	CMV antibody
Hepatitis E Virus (HEV) Testing:	CMV DNA [c]
HEV IgG antibody	Herpes Simplex Virus (HSV) Testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [c]	HSV (Type 1 and 2) DNA [c]
Microbiology	Liver Kidney Microsomal Type 1 (LKM-1) Antibody
Culture:	
Blood	
Urine	

[a] Not required if anti-actin antibody is tested.

[b] Not required if anti-smooth muscle antibody (ASMA) is tested.

[c] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

Appendix O Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

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

Exceptional circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

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

After approval by local Ethical Review Boards, regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required (for example, upon implementation and suspension of changes). All approvals and notifications must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with Good Clinical Practice, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed consent

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

- participation in remote visits, as defined in Section "Remote Visits,"
- a change in the method of study intervention administration,
- dispensation of additional study intervention during an extended treatment period,
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in study conduct during exceptional circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local

regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

Remote visits

Types of remote visits

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include but are not limited to concomitant medications.

Data capture

In source documents and the CRF, the study site should capture the visit method, with a specific explanation for any data missing because of missed in-person site visits.

Safety reporting

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of adverse events (AEs), serious adverse events (SAEs), and product complaints remain unchanged.

Return to on-site visits

Every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. The local laboratory must be qualified in accordance with applicable local regulations.

Study intervention and ancillary supplies (including participant diaries)

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include:

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit,
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf,
- arranging delivery of study supplies.

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.

- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at screening visit are valid for a maximum of 7 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

- If screening is paused for less than 7 days from screening visits to randomization visit: the participant will proceed to the next study visit per the usual Schedule of Activities, provided that randomization visit must be conducted within 7 days from first screening visit.
  - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay.
  - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If screening is paused for more than 7 days from screening visits to randomization visit: The participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. This rescreen is in addition to the one allowed by the main protocol. The screening procedures per the usual Schedule of Activities should be followed, starting at screening visit to ensure participant eligibility by randomization visit.

Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual Schedule of Activities. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

This table describes the allowed adjustments to visit windows.

Visit Number	Tolerance
Visit 1 through Visit 13 or higher treatment cycles	Visit performed within 7 days before the intended date, or up to 7 days after the intended date whenever possible and safe to do so.

As drug administration should be continuously, this visit window adjustment won't apply for drug dispense, which will follow original schedule if no signal for dose interruption per investigator discretion. For participants whose visits have extended windows, additional study

intervention may need to be provided to avoid interruption and maintain overall integrity of the study.

Documentation

Changes to study conduct will be documented

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

Source documents at alternate locations

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

Appendix P Protocol JZNJ Amendment (b) Summary: A Phase 2 Study of Oral LOXO-305 in Patients with Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) or Non-Hodgkin Lymphoma (NHL)

Overview

Protocol J2N-MC-JZNJ (a), A Phase 2 Study of Oral LOXO-305 in Patients with Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) or Non-Hodgkin Lymphoma (NHL), has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are described in the following table:

Amendment Summary for Protocol J2N-MC-JZNJ Amendment (a)

Section # and Name	Description of Change	Brief Rationale
Synopsis and Section 4.1 Inclusion Criteria 1	"Documented evidence of radiographically and/or histologically confirmed disease progression" was clarified as "Documented evidence of patients having failed or intolerant". Modified wording in Inclusion Criteria 1 of Section 4.1 to keep consistent with Synopsis.	Clarification and to keep consistent with synopsis
Synopsis and Section 4.1 Inclusion Criteria 5	Added a time limitation to clarify the definition of "adequate hematologic status".	Clarification
Synopsis STUDY ASSESSMENTS	Added "optional based on clinical indicated" to clarify the initial response evaluation and shorten response evaluation time window for the following evaluation. Added visit interval for ≥2 years LTFU for clarification.	Clarification
Synopsis STATISTICAL METHODS Efficacy Analyses and Section 8.3.3 Efficacy Analyses	PR-L was removed from ORR calculation.	Follow with China clinical trial practice
Section 4 SELECTION OF STUDY POPULATION	Added "except other specified in protocol" for clarification.	Clarification
Section 4.1 Inclusion Criteria 4	Added "of the Protocol" to keep consistent with synopsis.	To keep consistent with synopsis
Section 5 ENROLLMENT PROCEDURES	Modified wording for clarification.	Clarification
Section 6.2.2 Dose Delays/Modifications	Added wording to clarify the operation.	Clarification
Section 6.3.1 General	Added "whichever is shorter" to clarify the definition of concomitant medications.	Clarification
Section 6.3.2 Allowed Concomitant Medications	Added wording to clarify the operation of local treatment for target lesion.	Clarification
Section 7 Table 7.1 Schedule of Assessments (SOA)	Shorten visit window for cycles 13 and higher; Modified "bone marrow aspirate and biopsy" to be "bone marrow aspirate and/or biopsy" for clarification; Added the word "optional" to clarify bone marrow aspirate and/or biopsy is optional at PD.	Clarification
Footnote "*" of Table 7.1	Modified the note to keep consistent with section 5.	To keep consistent with previous wording
Note of Table 7.1	Added a sentence "Study conduct during exceptional circumstances please refer to Appendix O."	Clarification
Footnote "c" of Table 7.1	Added "pulse is acceptable if patients are not under cardiac arrythmias" to clarify the definition of heart rate.	Clarification
Footnote "e" of Table 7.1	Removed "bands" from WBC count differential.	To keep consistent with China clinical practice
Footnote "k" of Table 7.1	Minor modification for "t(11;14) status" to direct operation.	Clarification

Section # and Name	Description of Change	Brief Rationale
Footnote "m" of Table 7.1	Minor modification for clarification and consistency.	Clarification
Footnote "p" of Table 7.1	Minor modification for clarification and consistency.	Clarification
Footnote "w" of Table 7.1	Added "through clinical, imaging or endoscopy" to clarify how to estimate GI involvement at baseline.	Clarification
CCI	[redacted]	Important timepoint with no time window
Footnote "a" of Table 7.2	Modified the wording to keep consistent with the table.	To keep consistent with the content of Table 7.2
Section 7.1.2 Screening	Modified wording to keep consistent with section 5 and Table 7.1.	To keep consistent with previous wording
Section 7.1.3 Enrollment	Added "within screening window" to clarify time limitation for enrollment.	Clarification
Section 7.1.7 Vital Signs	Modified wording to keep consistent with SOA.	To keep consistent with SOA
Section 7.1.9 Laboratory Tests	Removed "bands" from WBC count differential and added a "," after "C1D1".	To keep consistent with SOA
Section 7.2 Pharmacokinetics	Modified the wording to keep consistent with the Table 7.2.	To keep consistent with the content of Table 7.2
Section 7.4 Central Tumor Sample Submission (Peripheral Blood, Bone Marrow, Tissue)	Separated the paragraph of MCL tumor sample collection and response assessment from Indolent NHL and modified wording for clarification.	Clarification
Section 7.5 Pathology and Molecular Reports	Modified wording to keep consistent with SOA.	To keep consistent with SOA
Section 7.6 Bone Marrow Aspirate and Biopsy		
Section 7.7 Gastrointestinal Endoscopy		
Section 7.8 Radiologic Disease Assessment		
Section 7.11 Concomitant Medication	Modified wording to keep consistent with Section 6.3.1.	To keep consistent with previous wording
Section 7.14 Central Collection of Radiographic Studies and Samples	Removed "and their associated reports" for clarification.	Clarification
Section 7.17 Long-Term Follow-up	Modified wording for clarification and to keep consistent with Synopsis.	To keep consistent with previous wording
Appendix A Table 11.1 Lugano Classification of Response and its footnote	Modified some errors and added wording based on Lugano Classification for clarification.	Clarification
Appendix B footnote of Table 11.2	Replaced "Source" with "For complete IWCLL guideline, please refer to" for clarification.	Clarification
Appendix C footnote of Table 11.3	Replaced "Source" with "For complete IWWM guideline, please refer to" for clarification.	Clarification
Appendix E Prior BTK Inhibitors	Added generic name for ICP-022.	Clarification

Section # and Name	Description of Change	Brief Rationale
Appendix K Table 11.9 Guidelines for Patient Sample Collection for Central Analysis	Separated MCL tumor sample collection and response assessment from Indolent NHL and modified wording to keep consistent with previous content.	Clarification
Appendix O Provisions for Changes in Study Conduct During Exceptional Circumstances	Added this appendix to direct the clinical trial operation during exceptional circumstances.	To direct operation in specific circumstance

Revised Protocol Sections

Note: Deletions have been identified by ~~strikethroughs~~.
Additions have been identified by the use of underscore.

SYNOPSIS

Inclusion Criteria:

1. Patients with histologically confirmed B-cell malignancy including:

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For patients in each Cohort:

- All patients must have disease requiring treatment;

- Documented evidence of ~~radiographically and/or histologically confirmed disease progression~~ patients having failed or intolerant on the most recent line of therapy or relapse prior to study enrollment is required;

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5. Adequate hematologic status, defined as the following on or within 7 days of C1D1 before treatment:

a. Absolute neutrophil count (ANC) $\geq 0.75 \times 10^9$/L without granulocyte-colony stimulating factor (GCSF) supporting within 7 days of Screening assessment; the patient may enroll below this threshold if there is documented bone marrow involvement considered to impair hematopoiesis.

b. Platelet count $\geq 50 \times 10^9$/L not requiring transfusion ~~support~~ or growth factors supporting within 7 days of Screening assessment; the patient may enroll below this threshold if there is documented bone marrow involvement considered to impair hematopoiesis.

c. Hb ≥ 8 g/dL not requiring transfusion ~~support~~ or growth factors supporting within 7 days of Screening assessment; the patient may enroll below this threshold if there is documented bone marrow involvement considered to impair hematopoiesis.

d. Patients must be responsive to blood or platelets transfusion support if given for bone marrow involvement induced cytopenias. Patients refractory to transfusion support are not eligible. See also exclusion criteria item 18.

STUDY ASSESSMENTS:

Efficacy assessments include tumor evaluation (radiologic and laboratory) every 8 weeks beginning with Cycle 3 Day 1 (± 7 days) through Cycle 12 Day 1, then ~ every 12 weeks thereafter (± 2 weeks) for 1 year, then ~ every 6 cycles (± 4 weeks) thereafter, consistent with disease-defined criteria. An initial response evaluation (optional based on clinical indicated) may be conducted on Cycle 2 Day 1 (±7 days) with a confirmatory response evaluation conducted 4 weeks (Cycle 3 Day 1± 7 days) after the first tumor evaluation ~~that shows a partial response (PR) or better~~, if consistent with local institution and regulatory authority requirements.

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All patients will enter Long-term Follow-up (LTFU) with visits ~ every 3 months (±1 month) for up to 2 years and ~every 6 months (±2 month) thereafter, for confirming the resolution of any serious adverse events (SAEs), PD if not occurring on study, subsequent anticancer therapy, and survival. LTFU may be conducted by phone if a patient unable to travel to clinic.

STATISTICAL METHODS:

Efficacy Analyses:

Patients enrolled who meet the criteria for the primary analysis set (PAS) will be included in the primary analysis for Cohorts 1 and 2, as defined separately in the statistical analysis plan.

Overall response rate (ORR) will be assessed using Lugano criteria (Appendix A) or IWCLL (Appendix B) including assessment of complete response with incomplete marrow recovery (CRi), nodular PR (nPR), and PR with lymphocytosis (PR-L), or IWWM (Appendix C), as appropriate to tumor type. ~~The inclusion of PR-L response is added to avoid underestimation of true clinical benefit (Cheson et al. 2012).~~ The estimate of the ORR will be calculated as the proportion of patients with best overall response (BOR) of PR~~-L~~ or better, based on IWCLL, PR or better based on Lugano, and minor response or better for WM based on IWWM criteria as determined by IRC and by the treating investigator. The estimates of the ORR will be accompanied by a 2-sided 95% confidence interval (CI).

4. SELECTION OF STUDY POPULATION

Potential patients must sign an informed consent form (ICF) before any study-specific screening tests may be conducted, except other specified in protocol.

4.1 Inclusion Criteria

1. Patients with histologically confirmed B-cell malignancy including:

……

For patients in each Cohort:

- All patients must have disease requiring treatment;
- Documented evidence of ~~radiographically and/or histologically confirmed disease progression~~ patients having failed or intolerant on the most recent line of therapy or relapse prior to study enrollment is required;

Patients in Cohort 1 and 2, relapsed/refractory or intolerant (as per the definitions in Appendix D) to a prior BTK inhibitor ~~treatment~~ (investigational or approved, and either alone or in combination with other agents) treatment is required.

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4 Confirmation of availability of tumor sample along with pathology report for central pathology review as described in Section 7.4 of the Protocol for patients enrolled in Cohort 1.

5. Adequate hematologic status, defined as the following on or within 7 days of C1D1

before treatment:

a. Absolute neutrophil count (ANC) ≥0.75×10^9/L without granulocyte-colony stimulating factor (GCSF) supporting within 7 days of Screening assessment; the patient may enroll below this threshold if there is documented bone marrow involvement considered to impair hematopoiesis.

b. Platelet count ≥50×10^9/L not requiring transfusion ~~support~~ or growth factors supporting within 7 days of Screening assessment; the patient may enroll below this threshold if there is documented bone marrow involvement considered to impair hematopoiesis.

c. Hb ≥ 8 g/dL not requiring transfusion ~~support~~ or growth factors supporting within 7 days of Screening assessment; the patient may enroll below this threshold if there is documented bone marrow involvement considered to impair hematopoiesis.

d. Patients must be responsive to blood or platelets transfusion support if given for bone marrow involvement induced cytopenias. Patients refractory to transfusion support are not eligible. See also exclusion criteria item 18.

……

5. ENROLLMENT PROCEDURES

Patients who cannot complete the procedures within the screening window may be rescreened, and certain screening procedures may not need to be repeated~~,~~ with documented sponsor approval. ~~including c~~Certain procedures that were obtained as part of the patient's standard care prior to providing informed consent for this study ~~with documented sponsor approval.~~(i.e., hematology, imaging), 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 Table 7.1.

6. TREATMENT AND ADMINISTRATION

6.2.2 Dose Delays/Modifications

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Upon recovery, investigator should discuss with sponsor and the patient may restart therapy as outlined in (Table 6.1) if it is considered in his/her best interest to continue therapy ~~and with documented sponsor approval~~. Any continued dosing before a clinically significant AE recovers to Grade 1 or less, or baseline if baseline is Grade 2 or above, should be discussed and get documented sponsor approval. If the AE does not recover to Grade 1 or less, or baseline if baseline is Grade 2 within 28 days, the patient will have treatment permanently discontinued, unless there is a compelling clinical rationale for dose holding for more than 28 days or additional dose reduction(s) articulated by the investigator and approved by the sponsor. For each patient, a maximum of 2 dose reductions will be allowed, unless there is a compelling clinical rationale for additional dose reduction(s) articulated by the investigator and approved by the sponsor (Table 6.1).

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Patients who have been dose-reduced and who tolerate LOXO-305 without toxicity for at least 2 weeks may be re-escalated to the next higher dose level, not to exceed 200 mg QD, ~~with continued re-escalation with the agreement~~ at the discretion of the investigator and approved by the sponsor. If the LOXO-305 dose is reduced for apparent treatment-related toxicity, the dose need not be re-escalated.

All dose interruptions and dose modifications and the reasons for those changes will be recorded in the Case Report Form (CRF).

6.3.1 General

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.,~~or from Screening (whichever is shorter) through the SFU visit (at least 28 days [+7 days] after the last dose of study drug) and are to be recorded in the CRF. These are to include prescription and nonprescription medications, transfusions, vitamins, nutritional supplements, and other remedies. Excluded medications are indicated in the Exclusion Criteria (Section 4.2).

6.3.2 Allowed Concomitant Medications

Local treatment while receiving LOXO-305 (e.g., palliative radiation therapy or surgery for bone metastases) is permitted with documented sponsor approval. 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.~~;~~ H~~h~~owever, the sponsor recommends holding LOXO-305 for ~3-5 half-lives before and after radiation therapy or surgery. Any concern for disease flare due to a prolonged LOXO-305 dose interruption should be discussed with the sponsor, who may permit holding LOXO-305 for a shorter period of time.

7. STUDY PROCEDURES AND ASSESSMENT

Table 7.1 Schedule of Assessments

Evaluation	Screening*	Cycle 1 (D1-D28)				Cycles 2 through 12	Cycles 13 and Higher	EOT**	SFU	LTFU
									801	802 - 8XX
Visit Window	**D0 (-28 Days)**	**D1 (-2 Days)**	**D8 (±2 Days)**	**D15 (±2 Days)**	**D22 (±2 Days)**	**D1 (± 3 Days)**	**D1 (±~~3~~7 Days)**	**≤ 7 days after last dose or decision to terminate treatment**	**28 days (+7 days) after last dose of study drug**	**Every 3 months ± 1 month for up to 2 years after last dose of study drug**
Results of tests below are required for enrollment										
Informed consent	X									
Medical, surgical, malignancy history[a]	X									
Physical examination and ECOG[b]	X	X	X	X		Day 1 each cycle		X	X	
Vital signs[c]	X	X	X	X		Day 1 each cycle		X	X	
12-lead ECG[d]	X	X	X			Day 1 every other cycle, C2 through 12, then as clinically indicated		X	X	
Hematology[e]	X	X	X	X		Day 1 each cycle		X	X	
Blood chemistries[f]	X	X	X	X		Day 1 each cycle		X	X	
Coagulation panel[g]	X	As clinically indicated								
Urinalysis[h]	X	X				Day 1 each cycle through C12, then as clinically indicated		X		
Serum or urine pregnancy test (if applicable)[i]	X					Day 1 each cycle				
HIV[j]	X									

Evaluation	Screening*	Cycle 1 (D1-D28)				Cycles 2 through 12	Cycles 13 and Higher	EOT**	SFU	LTFU
									801	802 - 8XX
Visit Window	**D0 (-28 Days)**	**D1 (-2 Days)**	**D8 (±2 Days)**	**D15 (±2 Days)**	**D22 (±2 Days)**	**D1 (± 3 Days)**	**D1 (±37 Days)**	**≤ 7 days after last dose or decision to terminate treatment**	**28 days (+7 days) after last dose of study drug**	**Every 3 months ± 1 month for up to 2 years after last dose of study drug**
CMV, Hepatitis B and Hepatitis C testing[j]	X									
Documentation of histologic diagnosis and relevant biomarkers[k]	X									
Documentation or sampling required during screening but results not required prior to enrollment										
Tumor sample obtained for central pathology review[l]	X									
Bone marrow aspirate and/or biopsy[m]	X	For confirmation of CR and at PD (optional) (refer to Appendix K)								
Upper and lower endoscopy[w]	X	For confirmation of CR in MCL patients of Cohort 1 only (refer to Appendix K)								
For CLL/SLL Lymphocyte subsets[n]	X					Every 8 weeks beginning with C3D1 (±7 days)	Every 12 weeks (±2 weeks) beginning with C13D1 for 1 year, then every 6 cycles (±4 weeks) after	X		X[x]

Evaluation	Screening*	Cycle 1 (D1-D28)				Cycles 2 through 12	Cycles 13 and Higher	EOT**	SFU	LTFU
									801	802 - 8XX
Visit Window	**D0 (-28 Days)**	**D1 (-2 Days)**	**D8 (±2 Days)**	**D15 (±2 Days)**	**D22 (±2 Days)**	**D1 (± 3 Days)**	**D1 (±37 Days)**	**≤ 7 days after last dose or decision to terminate treatment**	**28 days (+7 days) after last dose of study drug**	**Every 3 months ± 1 month for up to 2 years after last dose of study drug**
For patients with known paraprotein: SPEP, serum immunofixation, serum FLC, quantitative Immunoglobulins, total protein[o]	X					Every 8 weeks beginning with C3D1 (±7 days)	Every 12 weeks (±2 weeks) beginning with C13D1 for 1 year, then every 6 cycles (±4 weeks) after	X		X[x]
Radiologic disease assessment[p]	X					Every 8 weeks beginning with C3D1 (±7 days)	Every 12 weeks (±2 weeks) beginning with C13D1 for 1 year, then every 6 cycles (±4 weeks) after	X		X[x]
Items starting with Cycle 1										
Blood samples for PK[q]	Refer to Table 7.2									
Telephone follow-up					X					X
Survival status[r]										X

Evaluation	Screening*	Cycle 1 (D1-D28)				Cycles 2 through 12	Cycles 13 and Higher	EOT**	SFU	LTFU
									801	802 - 8XX
Visit Window	D0 (-28 Days)	D1 (-2 Days)	D8 (±2 Days)	D15 (±2 Days)	D22 (±2 Days)	D1 (± 3 Days)	D1 (±~~3~~7 Days)	≤ 7 days after last dose or decision to terminate treatment	28 days (+7 days) after last dose of study drug	Every 3 months ± 1 month for up to 2 years after last dose of study drug
LOXO-305 administration		X						X		
Patient dosing diary[s]		X						X		
Concomitant medication[t]	X								X	
Adverse event[u]	X								X	
EORTC QLQ-C30[v]		X				X	X	X		
EORTC IL63 (MCL patients only)[v]		X				X	X	X		

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* Certain procedures that were obtained as part of the patient's standard care prior to providing informed consent for this study (i.e., hematology, imaging), may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria.~~Screening studies may be done on C1D1 prior to dosing of LOXO-305 with sponsor approval.~~ In Table 7.1, if results are noted as required prior to starting LOXO-305, results of these studies may be required before patients may be officially enrolled.

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Note: Study conduct during exceptional circumstances please refer to Appendix O.

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c. Systolic and diastolic blood pressure, heart rate (pulse is acceptable if patients are not under cardiac arrythmias), respiratory rate, and body temperature.

- For vital signs assessed at PK time points, vital signs including weight should be conducted prior to actual PK blood sampling pre-dose (initial dose) (up to 4 hours pre-dose, as close to dosing as possible is preferred), and on C1D1 and C1D8 vital signs should also be conducted post-dose at 2 hours (±15 minutes).
- For vital signs assessed at non-PK time points: pre-dose (up to 4 hours pre-dose, as close to dosing as possible is preferred)

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e. Hematology includes hemoglobin, hematocrit, RBC count, WBC count, platelet count, percent or absolute WBC count differential (neutrophils, ~~bands,~~ lymphocytes, eosinophils, basophils, and monocytes). For WM and CLL/SLL patients, blood samples should also be provided for central assessment on C1D1, ±7 days of each radiologic disease assessment and at disease progression. Screening results performed within 7 days of C1D1 are acceptable as C1D1 results. Please enter the data correctly in the CRF.

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k. Anonymized/redacted pathology report(s) confirming histologic diagnosis and the status of any known biomarkers (e.g., FISH, IGVH, p53, karyotype for CLL/SLL, MYD88, CXCR4 for WM, Ki67 staining for MCL) should be submitted. In patients with MCL, documentation of cyclin D1 overexpression and/or t(11;14) positive status must be provided either as a pathology report from anytime in the patient's past or from current tissue testing. Patients may not be enrolled without documentation of Cyclin D1 and/or t(11;14) status. In patients with WM, documentation of MYD88 mutation must be provided either as a pathology report from the patient's past history or from current tissue testing. Patients with WM may not be enrolled without documentation of MYD88 mutation.

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m. For CLL/SLL, WM, indolent NHL, and selected cases of high−grade NHL, baseline bone marrow aspirate and/or biopsy is required unless was already done after the last treatment or while progressing on the most recent and within 90 days of Screening. Bone marrow biopsies performed while still receiving the most recent treatment are allowed if the patient was progressing at the time of the bone marrow biopsy. Adequate amount of samples, fresh or archived, must be available as defined in the Laboratory Manual for central baseline assessment. Refer to Section 7.4, Appendix K and the Laboratory Manual for guidance regarding requirements for sample submission based on histology. Patients with other response assessments consistent with CR may need to undergo bone marrow biopsy and/or aspiration in order to confirm CR (refer to Section 7.4 and Appendix K). All MCL patients whose other response assessment are consistent with CR and known bone marrow involvement at baseline must undergo a bone marrow biopsy ~~and aspiration~~ in order to confirm CR.

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p. Refer to Section 7.8 and Appendix A, Appendix B, and Appendix C for specific radiologic disease assessment guidelines. Investigators may conduct an initial tumor evaluation on C2D1 (±7 days) (optional based on clinical indicated) and a confirmatory tumor evaluation a minimum of 4 weeks (C3D1 ±7 days) after the first tumor evaluation ~~that shows a CR or PR by disease specific criteria~~, if consistent with local regulatory authority requirements. At baseline imaging should include chest, abdomen, and pelvis, and other areas with disease involvement. Follow-up imaging includes chest, abdomen, pelvis and any areas known to have disease involvement at baseline. Other areas such as the neck, head and extremities may be imaged if disease involvement is suspected. For patients (e.g., CLL or WM) with documented disease involving blood/bone marrow but no documented baseline radiographic findings and where radiology is not required for routine response assessment, imaging is to be performed every 6 cycles (i.e., end of cycle 6, end of cycle 12) for the duration of study treatment. Clinical PD should be assessed with radiographic imaging unless most recent imaging was performed within 28 days of clinical PD.

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w. Patients with MCL in Cohort 1 with history or evidence of GI involvement on baseline assessment may require appropriate upper and/or lower endoscopy procedure (if it is clinically safe) during screening with biopsy to document involvement at baseline. Patients with MCL in Cohort 1 with known or evidence of GI involvement (through clinical, imaging or endoscopy) at baseline, whose other disease assessments suggest CR must undergo Esophagogastroduodenoscopy and/or Colonoscopy with random segmental biopsies to confirm CR (if it is clinically safe).


CCI

7.1 Study Assessments

7.1.2 Screening

The screening procedures must be conducted within 28 days prior to C1D1, unless otherwise noted. Patients who cannot complete the procedures within the screening window and who do not meet the criteria for participation in this study (screen failure) may be rescreened after discussion with and permission from the Lilly CRP or designee, and certain screening procedures may not need to be repeated~~,~~ with documented sponsor approval. ~~including c~~Certain procedures (i.e., hematology, imaging) that were obtained as part of the patient's standard care prior to providing informed consent for this study, 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 Table 7.1 ~~with documented sponsor approval~~. The results should be recorded in the Screening set of CRFs.

7.1.3 Enrollment

Enrollment procedures will be conducted in accordance with the Schedule of Assessments (Table 7.1). Patients who meet eligibility criteria outlined in Section 4 will be enrolled in this study. The investigator may repeat qualifying laboratory tests and vital signs/ECGs prior to enrollment and within Screening window, if a non-qualifying finding is considered an error, and/or if an acute finding is likely to meet eligibility criteria on repeat testing.

7.1.7 Vital Signs

Vital signs will be measured pre-dose in accordance with the Schedule of Assessments (Table 7.1) and should include systolic and diastolic blood pressure, heart rate (pulse is acceptable if patients are not under cardiac arrythmias), respiratory rate, and body temperature.

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7.1.9 Laboratory Tests

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- Hematology

For all enrolled patients: Hematology should be assessed locally in accordance with the Schedule of Assessments (Table 7.1) and should include assessment of the following: hemoglobin, hematocrit, RBC count, WBC count, platelet count, percent or absolute WBC count differential (neutrophils, ~~bands,~~ lymphocytes, eosinophils, basophils, and monocytes).

For WM and CLL/SLL patients: Blood samples for central assessment should also be collected on C1D1, ±7 days of each radiologic disease assessment and at disease progression.

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7.2 Pharmacokinetics

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7.4 Central Tumor Sample Submission (Peripheral Blood, Bone Marrow, Tissue)

Adequate tissue samples at screening are required from patients enrolled in Cohort 1 for central pathology review to be performed retrospectively. Patients with inadequate tissue sample availability may still be enrolled in Cohort 3 if other eligibility criteria have been checked.

For patients enrolling with MCL, nodal tissue is preferred (vs marrow) and must include up to 10 unstained slides (or representative sections of archived paraffin block). De-identified surgical pathology reports of the patient's diagnosis of lymphoma and ancillary studies, such as flow cytometry, immunohistochemistry, FISH, cytogenetics, or molecular studies, which were used to establish the diagnosis are also requested.

For MCL: for Screening, bone marrow biopsy is required for baseline assessment, and patients in Cohort 1 with known or evidence of GI involvement appropriate upper and/or lower endoscopy may be performed if it is clinically safe for baseline assessment and if not performed within 42 days of enrollment. Adequate sample as Lab Manual is required to submit for central assessment.

For response assessment: Bone marrow biopsy should be done as appropriate for confirmation of CR if known disease involvement at baseline. Other assessments suggest CR, esophagogastroduodenoscopy and colonoscopy with random segmental biopsies is required, if clinically safe, for confirmation of CR in Cohort 1 MCL patients with known GI involvement at baseline. Adequate sample as Lab Manual is required to submit for central review. Bone marrow and endoscopy for local response assessment at the time points specified in Table 7.1 and Appendix K are also required.

For CLL/SLL: for Screening, peripheral blood and bone marrow biopsy with aspirate are required for baseline tumor assessment, and adequate sample as ~~Appendix K and~~ Lab Manual required also should submit~~ted~~ for central assessment.

For response assessment: Peripheral blood is required. Bone marrow biopsy and aspiration is required for confirmation of CR and should be done in appropriate settings where all other assessments suggest CR and adequate sample as ~~Appendix K~~ Lab Manual is required to submit for central review. Peripheral blood and bone marrow for local response assessment at the time points specified in Table 7.1 and Appendix K are also required.

For WM: for Screening, peripheral blood and bone marrow biopsy with aspirate are required for baseline assessment and adequate sample as ~~Appendix K and~~ Lab Manual is required to

submit for central assessment.

For response assessment: Peripheral blood is required. Bone marrow biopsy and aspiration is required for confirmation of CR and should be done in appropriate settings where all other assessments suggest CR and adequate sample as ~~Appendix K and~~ Lab Manual is required to submit for central review. Peripheral blood and bone marrow for local response assessment at the time points specified in Table 7.1 and Appendix K are also required.

For ~~I~~indolent NHL (e.g., MZL, follicular lymphoma [FL]): for Screening: Bone marrow biopsy is required for marrow involvement assessment and adequate sample as ~~Appendix K and~~ Lab Manual required also should submit for central assessment.

For response assessment: Bone marrow biopsy ~~and aspiration~~ is required for confirmation of CR and should be done in appropriate settings ~~where~~ if known disease involvement at baseline and all other assessments suggest CR and adequate sample as ~~Appendix K and~~ Lab Manual required also should submit for central assessment.

For non-MCL ~~H~~high grade NHL (e.g., ~~MCL,~~ diffuse large B cell lymphoma [DLBCL]): For Screening: Bone marrow biopsy is required only if clinical suggestion of marrow involvement is noted, i.e., unexplained cytopenia, and adequate sample as ~~Appendix K and~~ Lab Manual required also should submit for central assessment.

~~For MCL patients in Cohort 1 with known or evidence of GI involvement appropriate upper and/or lower endoscopy may be performed if it is clinically safe for baseline assessment, if not performed within 42 days of enrollment.~~

For response assessment ~~(non-MCL)~~: Bone marrow biopsy ~~and aspiration~~ should be done as appropriate for confirmation of response assessment only if known disease involvement at baseline; per Lugano staging criteria, positron emission tomography (PET) scan assessment of marrow response is acceptable.

~~For MCL response assessment: Bone marrow biopsy and aspiration must be done for confirmation of CR and adequate sample is required to submit for central review. Esophagogastroduodenoscopy and colonoscopy with random segmental biopsies is required, if clinically safe, for confirmation of CR in MCL patients with known GI involvement at baseline.~~

7.5 Pathology and Molecular Reports

Anonymized/redacted pathology report(s) confirming histologic diagnosis and relevant biomarkers (e.g., FISH, IGVH, p53, karyotype for CLL/SLL, MYD88, CXCR4 status for WM, Ki67 staining for MCL) should be submitted. For patients with MCL, documentation of Cyclin D1 overexpression and/or t(11;14) positive status must be provided either from any time in the patient's history or from current biopsy studies in order for enrollment to proceed. For patients with WM, documentation of MYD88 mutation must be provided either from any time in the patient's history or from current biopsies studies in order for the patient to proceed.

7.6 Bone Marrow Aspirate and Biopsy

For patients enrolled with CLL/SLL, WM, low grade NHL, and selected high grade NHL (refer to Section 7.4) ~~with unexplained cytopenia or suspected bone marrow involvement~~: A bone

marrow aspirate and/or biopsy should be collected during Screening, for confirmation of CR and (optional) at disease progression in accordance with the Schedule of Assessments (Table 7.1). All MCL patients, whose other response assessments are consistent with CR and known disease involvement at baseline, must undergo bone marrow biopsy ~~and aspiration~~ to confirm CR. Samples for central assessment should also be collected in accordance with the Schedule of Assessments (Table 7.1) and outlined in Section 7.4 "Central Tumor Sample submission". If a bone marrow biopsy and/or aspiration was done after the last treatment or while progressing on the most recent treatment and within 90 days of Screening and samples are available of sufficient quality and quantity for ~~molecular~~central analysis, these do not need to be repeated during Screening. Guidance on sample collection and timing is provided in Appendix K and the Laboratory Manual.

7.7 Gastrointestinal Endoscopy

For MCL patients in Cohort 1 with known or evidence of GI involvement appropriate upper and/or lower endoscopy may be performed if it is clinically safe for baseline assessment, if not performed within 42 days of enrollment. For enrolled patients with MCL with known GI involvement (through clinical, imagine or endoscopy) at baseline in Cohort 1, who are in radiographic and bone marrow CR, esophagogastroduodenoscopy and colonoscopy with random segmental biopsies must be performed as appropriately, to evaluate for GI involvement with MCL and to confirm CR.

7.8 Radiologic Disease Assessment

Radiologic disease assessment will be conducted by the investigator in accordance with the Schedule of Assessments (Table 7.1) and the Imaging Manual. Investigators should use the same method consistently for an individual patient throughout the study. For NHL, the preferred imaging is PET/CT, and appropriate method in accordance with Lugano guidance should be selected based on patients pathologic diagnosis, FDG avidity and lesion location etc.. For patients with NHL, baseline scans should assess the chest, abdomen, and pelvis. Other areas such as the neck, head and extremities should be scanned should there be known disease present. Follow up CT scans may be limited to chest, abdomen and pelvis as well as areas of known measurable and non-measurable disease. Assessments of both measurable and non-measurable disease will be made by the investigator using criteria as appropriate to cancer type; SLL response should be assessed by IWCLL criteria. The following Appendices should be referred to for specific radiologic disease assessment information:

- Appendix A Lugano Classification of Response in Non-Hodgkin Lymphoma
- Appendix B Chronic Lymphocytic Leukemia Response Assessment (IWCLL)
- Appendix C Waldenström Macroglobulinemia Response Assessment (IWWM)

For patients (e.g., CLL or WM) with documented disease involving blood/bone marrow but no documented baseline radiographic findings and where radiology is not required for routine response assessment, imaging is to be performed every 6 cycles (i.e., end of Cycle 6, end of Cycle 12) for the duration of receipt of study treatment. If tumor involvement is identified during routine assessments, then the radiographic assessment schedule will revert to the standard

schedule.

In addition, investigators may conduct an initial tumor evaluation on C2D1 (±7 days) (optional based on clinical indicated) and a confirmatory tumor evaluation a minimum of 4 weeks (C3D1±7d) after the first tumor evaluation ~~that shows a CR or PR by disease-specific criteria~~, if consistent with local regulatory authority requirements.

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Patients who are unable to undergo CT scans with contrast due to allergy to contrast dye, may substitute magnetic resonance imaging (MRI) with gadolinium or appropriate method per investigator discretion and should discuss with sponsor.

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7.11 Concomitant Medication

Concomitant medications should be recorded in accordance with the Schedule of Assessments (Table 7.1).

All medications that were used from 14 days prior to the planned start of study drug or from Screening (whichever is shorter) ~~enrollment~~ through SFU (at least 28 days [+7 days] after the last dose of study drug) will be recorded in the CRF. These are to include prescription and nonprescription medications, transfusions, vitamins and nutritional supplements, and other remedies. Excluded prior medications are excluded via the eligibility criteria (Section 4.2). Additional guidance regarding concomitant medications is provided in Section 6.3.

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7.14 Central Collection of Radiographic Studies and Samples

Baseline screening radiographic studies and all subsequent radiographic studies ~~and their associated reports~~ will be collected for independent radiological review.

Baseline and subsequent samples (peripheral blood, bone marrow aspiration, ~~and~~ biopsy and/or tissue samples) required for response assessment according to disease-defined criteria will be collected.

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7.17 Long-Term Follow-up

The LTFU assessments and procedures will be conducted in accordance with the Schedule of Assessments (Table 7.1). After treatment discontinuation, LTFU will occur approximately every 3 months (±1 month) for up to 2 years and every 6 months (±2 month) thereafter, until the patient experiences PD, withdraws consent for further participation, is lost to follow-up, has died, or close of the study.

Assessments may include: subsequent anticancer therapy(ies) and survival status. LTFU may be conducted by phone. 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.

If a patient discontinues study treatment for reasons other than PD, withdrawal of consent or initiation of a new anticancer therapy(ies), the patient is required to undergo disease assessment ~~by imaging~~ as specified in Appendix A, Appendix B, and Appendix C until PD (even if PD occurs after 2 years), withdrawal of consent, or initiation of a new anticancer therapy(ies), utilizing the same modality(ies) used for the baseline imaging assessment.

8.3.3 Efficacy Analyses

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ORR will be assessed using Lugano criteria (Appendix A) or IWCLL (Appendix B) including assessment of complete response with incomplete marrow recovery (CRi), nodular PR (nPR), and PR with lymphocytosis (PR-L), or IWWM (Appendix C), as appropriate to tumor type. ~~The inclusion of PR-L response is added to avoid underestimation of true clinical benefit (Cheson et al. 2012).~~ The estimate of the ORR will be calculated as the proportion of patients with best overall response (BOR) of PR~~-L~~ or better, based on IWCLL, PR or better based on Lugano, and minor response or better for WM based on IWWM criteria as determined by IRC and by the treating investigator. The estimates of the ORR will be accompanied by a 2-sided 95% CI. Waterfall plots will be used to depict graphically the maximum decrease from baseline in the sum of product diameters (SPD) of target lesions.

DOR will be calculated for patients who achieve a response of PR or better (~~PR-L or better for CLL/SLL,~~ minor response or better for WM)……

11. APPENDICES

Appendix A Lugano Classification of Response in Non-Hodgkin Lymphoma

Table 11.1 Lugano Classification of Response

Response and Site	PET-CT–Based Response	CT-Based Response
Complete [a]	**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 ~~No evidence of FDG-avid disease in marrow~~ ~~Normal by morphology; if indeterminate, IHC negative~~
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 ~~Absent/normal, regressed, but no increase~~ ~~Spleen must have regressed by >50% in length beyond normal~~
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**
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	New or clear progression of preexisting nonmeasured 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	Regrowth of previously resolved lesions 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

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~~Source:~~ For complete Lugano Classification, please refer to ~~(~~Cheson et al. 2014~~)~~.

Appendix B Chronic Lymphocytic Leukemia Response Assessment (IWCLL)

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~~Source:~~ For complete IWCLL guideline, please refer to ~~(~~Hallek et al. 2018~~)~~.

Appendix C Waldenström Macroglobulinemia Response Assessment (IWWM)

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~~Source:~~ For complete IWWM guideline, please refer to Anderson, J Natl Compr Canc Netw. 2012; 10(10):1211-1219.

Appendix E Prior BTK Inhibitors

Prior BTK inhibitors used in the treatment of CLL/SLL or NHL include, but are not limited to:

- Acalabrutinib
- DTRMWXHS-12
- GDC-0853
- Ibrutinib
- Orelabrutinib (ICP-022)
- SHR1459
- TG-1701
- Zanubrutinib (BGB-3111)
- Evobrutinib (M7583)

Appendix K Guidelines for Patient Sample Collection for Central Analysis

Table 11.9 Guidelines for Patient Sample Collection for Central Analysis

Tumor Type	Time Point	Peripheral Blood[a]	Bone Marrow[a]	Lymph Node/Tumor Tissue
MCL	**Baseline**		Required unless available after last treatment or while progressing on the most recent treatment and performed within 90 days	Required for patients enrolled in Cohort 1 for central pathology review
	Response time points		Required to confirm CR if known disease involvement at baseline	
	Progression		Optional	
CLL/SLL	**Baseline**	Required for response assessment[a,b]	Required unless available after last treatment or while progressing on the most recent treatment and performed within 90 days	
	Response time points	Required for response assessment[a,b-e]	Required at CR[a]	
	Progression	Required for response assessment[a,b]	Optional	
WM	**Baseline**	Required for response assessment[a,b]	Required unless available after last treatment or while progressing on the most recent treatment and performed within 90 days	
	Response time points	Required for response assessment[a,b]	Required at CR[a]	
	Progression	Required for response assessment[a,b]	Optional	
Indolent NHL (e.g., MZL, FL)[c]	**Baseline**		Required unless available after last treatment or while progressing on the most recent treatment and performed within 90 days	

Tumor Type	Time Point	Peripheral Blood[a]	Bone Marrow[a]	Lymph Node/Tumor Tissue
	Response time points		Required to confirm CR if known disease involvement at baseline	
	Progression		Optional	
Non-MCL High grade NHL (e.g., ~~MCL,~~ DLBCL)[c]	**Baseline**		May be required if unexplained cytopenia present at screening suggestive of bone marrow involvement unless available after last treatment or while progressing on the most recent treatment and performed within 90 days.	~~Required for patients enrolled in Cohort 1 for central pathology review~~
	Response time points		~~MCL: patients, required to confirm CR; Non-MCL: patients, r~~Required at CR only if known disease involvement at baseline, per Lugano staging criteria, positron emission tomography (PET) scan assessment of marrow response is acceptable [a]	
	Progression		Optional	

Abbreviations: CLL = chronic lymphocytic leukemia; CR = complete remission; DLBCL = diffuse large b cell lymphoma; FL = Follicular lymphoma; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; NHL = non-Hodgkin lymphomas; SLL = small lymphocytic lymphoma; WM = Waldenström macroglobulinemia.

a ~~Indicates local collection and assessment as well.~~ Sample collection for local tumor assessment is also needed.

b Laboratory studies for response assessment includes blood count with differential for CLL patients and SPEP/immunofixation/serum free light chains/quantitative immunoglobulins for WM patients.

c According to Lugano staging criteria, PET scan can be used to assess bone marrow involvement and response in ~~high grade NHL~~DLBCL.

Appendix O Provisions for Changes in Study Conduct During Exceptional Circumstances

Added this appendix to direct clinical trial operation during exceptional circumstances. Detail information please refer to Appendix O.

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