Statistical Analysis Plan Version 1 J2N-MC-JZNJ

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)

NCT04849416

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1. Statistical Analysis Plan for Clinical Study J2N-MC-JZNJ:

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)

LY3527727 (LOXO-305)

This is an open label, multi-center phase 2 study in patients with previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) or non-Hodgkin lymphoma (e.g., mantle cell lymphoma [MCL])

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Protocol J2N-MC-JZNJ
Phase 2

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2. Table of Contents

Section **Page**

Table of Contents

Table **Page**

Table of Contents

Figure **Page**

3. Revision History

Statistical analysis plan (SAP) Version 1 was approved on 25 June 2021 prior to the first data base lock. Version 1 was based on the Protocol J2N-MC-JZNJ amendment (a) approved on 01 March 2021.

The main changes of SAP Version 2 are listed below.

1. Quality of life analyses are updated to incorporate the supplemental EORTC IL63.
2. Additional analyses for CLL/SLL patients using the PR-L or better criterion to define response are added.
3. Electrocardiograms related analyses are updated based on the ECGs data collected on the CRF.
4. The scope of the analyses sets are modified to fit the registration purpose of a new indication and to keep consistent with the data scope included in the global clinical study report.
5. CCI
6. Analysis of adverse events of potential clinical significance is added to meet the medical need.
7. Provide some clarifications of the sample size.
8. Remove the definition of "efficacy evaluable" (defined as patients who had at least one post-baseline evaluable disease assessment) from the SAP and include those patients who are not efficacy evaluable into the denominator for the calculation of overall response rate.
9. Add the factor simplified MIPI score into the demographic and subgroup analyses of MCL patients.
10. Add some analyses to evaluate the impact of COVID-19.

4. Introduction

4.1. 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, International Workshop Guidelines for CLL/SLL (IWCLL 2018) and WM (IWWM), or other criteria as appropriate to tumor type, as assessed by an IRC	ORR by IRC
Secondary	
To assess 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}, $T_{1/2}$

Objectives	Endpoints
• 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; 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.

4.2. 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 to standard of care.

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Cohorts 1 through 3:

- Cohort 1: Non-blastoid MCL patients with no CNS metastases and treated with prior chemoimmunotherapy and a BTK inhibitor 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 JZNJ.4.1.

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.

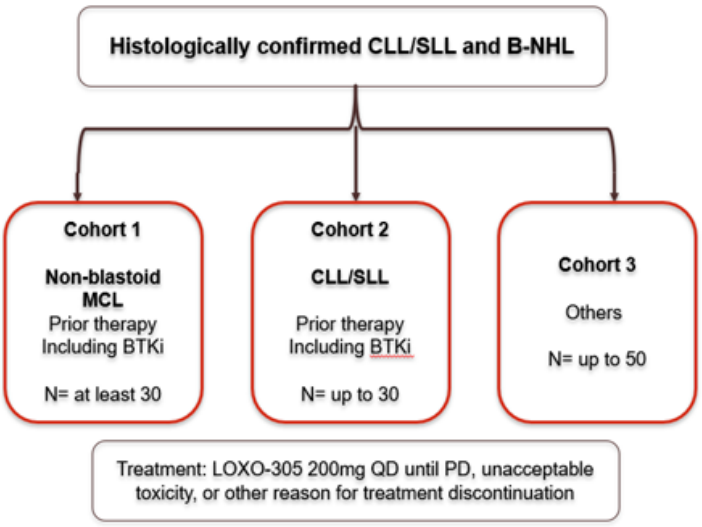

Figure JZNJ.4.1 Study Schema

Abbreviations: Ph[(K(P (– z(”– v zH(Ph[–(K(Ph[(– ≥–w– H(Q]](K(x≥ –x(’ „ ≥ x –x(’z ”z„ –vH(DLBCL = diffuse large B cell lymphoma; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; NHL = non-Hodgkin lymphoma; CNS = central nervous system; LTFU = long-term follow-up; PD = progressive disease; QD = once daily; SLL = small lymphocytic lymphoma; WM = Waldenström macroglobulinemia.

A detailed description of the study design is contained in the protocol. The SAP is written with consideration of the recommendations outlined in key regulatory guidance documents, including the ≤ –yz’– z(z –’zy(Guidance for Industry: Statistical Principles for Clinical Trials .

5. Statistical Hypotheses

Treatment of patients with previously BTKi treated mantle cell lymphoma (MCL) with LOXO-305 will provide a clinically meaningful overall response rate (ORR).

6. Sample Size Determination

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

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7. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Entered	All participants who sign informed consent.
Enrolled	All eligible patients.
Primary analysis set (PAS)	will include all patients enrolled in Cohort 1 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.
Supplemental analysis set 1 (SAS1)	MCL patients (in Cohort 1 and Cohort 3) who were treated with prior BTK inhibitor-containing regimen but do not meet at least 1 of the PAS criteria, including both non-blastoid and blastoid patients.
Supplemental analysis set 2 (SAS2)	MCL patients who were not treated with prior BTK inhibitor-containing regimen, including both non-blastoid and blastoid patients.
Efficacy analysis set (EAS)	MCL (in Cohort 1 and Cohort 3) and CLL/SLL (in Cohort 2 and Cohort 3) patients who meet the following criteria: Treated with prior BTK inhibitor-containing regimen; Received at least 1 dose of study drug.
Per-protocol (PP)	All enrolled patients who are compliant with the study protocol without important protocol violations that significantly affect the primary endpoint.
Safety	All enrolled patients who received at least 1 dose of study drug.

* Lesion measurability is based on Investigator assessment, defined as lymph node longest diameter (LDi) > 1.5 cm, or extra nodal site > 1.0 cm in LDi by computed tomography (CT).

A patient listing of the population details will be provided. This listing will include investigator site, patient identifier, inclusion/exclusion flag for each population.

8. Statistical Analyses

8.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. All confidence intervals (CIs) will be given at a 2-sided 95% level, unless otherwise stated. Statistical analysis will be performed using SAS software (SAS, version 9.4 or higher).

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

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

Disease assessments for the key efficacy endpoint in this study are derived from the IRC. Additional analyses based on investigator assessment will be provided.

The primary endpoint is ORR based on IRC assessment. The primary analysis of ORR is based on the MCL patients in PAS.

Efficacy analyses for non-blastoid or blastoid MCL patients will be performed on SAS1 and SAS2 as defined in Section 7. Safety analyses will be performed by tumor types (MCL and CLL/SLL) pooled across cohorts on the safety population.

Additional efficacy analyses on EAS for the prior BTKi-treated MCL and CLL/SLL patients across cohorts will be included in the CSR. The analyses for the other analyses sets may also be included in the CSR if deemed necessary.

Furthermore, response assessment will be based on IWCLL 2018 for CLL/SLL, IWWM for WM, Lugano 2014 for MCL and for other NHL (MZL, DLBCL, etc.), or other criteria as appropriate to tumor type, as assessed by IRC or investigator.

8.1.1. Definitions

- Study day will be calculated based on the first dose date of LOXO-305 as follows:
    - Assessment date/event date -first dose date of LOXO-305+1, if assessment date or event date first dose date;
    - Assessment date/event date -first dose date of LOXO-305, if assessment date or event date < first dose date.
- Baseline Measurement: the last value recorded for a variable prior to the patient receiving the first dose of LOXO-305.
- Common Conventions

- 1 year = 365.25 days.
- 1 month = 30.4375 days.
- Percent change from baseline = 100 * (Test Value at Visit X Baseline Value) / Baseline Value.

8.1.2. Handling of Dropouts or Missing Data

For data summarized over time by visit, no imputations will be performed on missing data. All analyses will be based on observed data only. The effective sample sizes at each assessment visit will be based on the total number of patients with non-missing data for the parameter of interest at that visit.

8.1.3. Unscheduled Visits

In general, for by-visit summaries, data will be presented based on the visit number. Visit windowing will not be used for handling unscheduled visits. Instead, all unscheduled visits will wz(v –≤ zy(v(––(v,, z(•(i x≥zy ’zy 9(g x≥(–– (–’’(wz(– x’ yzd in data listings and will contribute to the derivation of best- or worst-case values where required. The visit number for unscheduled visits will be assigned by adding 0.01 to the visit number of the previously scheduled visit to facilitate chronological sorting.

8.2. Participant Disposition

The number and percentage of patients in each analyses set will be summarized by study center.

The disposition of patients will be summarized by tabulating the number and percentage of patients within each of the following study epochs as of the data cutoff date:

- Treatment disposition
  - Continuing to receive LOXO-305 with documented Progressive Disease
  - Continuing to receive LOXO-305 without documented Progressive Disease
  - Permanently discontinued LOXO-305 and the primary reason
- Study disposition: patients who discontinued from study and the primary reason

If the reason for discontinuation of treatment or study is adverse event (AE) or death, the associated AE or cause of death will be reported.

- Time on Study

Time on study (TOS) will be summarized descriptively. For patients who did not exit the study as of the data cutoff date, TOS will be calculated as follows:

TOS (months) = (Data Cutoff Date First Dose Date + 1) / 30.4375

The data cutoff date will be used for patients continuing in the treatment phase or the follow-up periods. For patients who exited the study on or before the data cutoff date, TOS will be calculated as:

TOS (months) = (Study Exit Date – First Dose Date + 1) / 30.4375.

8.2.1. Protocol Deviations

Important protocol deviations (IPD) that potentially compromise the data integrity and patients' safety will be summarized for the enrolled population. CCI

[redacted]

8.3. Primary Endpoint Analyses

8.3.1. Overall Response Rate by IRC (MCL)

The primary endpoint is ORR based on IRC assessment and Lugano 2014. The analysis of ORR will be conducted on the PAS patients.

BOR is defined as the best response designation for each patient that is recorded between the date of the first dose of LOXO-305 and the date of documented PD per Lugano criteria or the date of subsequent anti-cancer therapy, whichever is earlier.

The BOR (complete response (CR), partial response (PR), stable disease (SD), PD, and not evaluable (NE)) will be summarized descriptively to show the number and percentage of patients in each response category. All MCL patients, whose other response assessments are consistent with CR, must undergo bone marrow biopsy to confirm CR if had bone marrow involvement at baseline.

ORR and the corresponding 95% two-sided CI will be calculated. ORR will be estimated based on the proportion of patients with BOR of CR or PR. Two-sided 95% CI will be calculated using the exact binomial distribution.

The tumor-burden change will be calculated for each patient in the PAS as the percentage change from baseline in the sum of the product of the diameters (SPD) of target tumor lesions (up to six) at each assessment time point. Waterfall plots will be used to depict graphically the best change for each patient.

Swimmer plots will be used to show the occurrence of clinical outcomes of interest over time (e.g., CR/PR, PD, treatment discontinuation, death).

Supplementary analyses of ORR will also be performed on the SAS1, SAS2, EAS and the PP population of the PAS defined in Section 7.

8.3.2. Overall Response Rate by IRC (CLL/SLL)

The endpoint is IRC-assessed ORR per iwCLL 2018 response criteria. The analysis of ORR will be conducted on the EAS-CLL/SLL patients.

BOR is defined as the best response for each patient that is recorded between the date of the first dose of LOXO-305 and the date of documented PD, or the date of subsequent anti-cancer therapy, whichever is earlier. Best overall assessment categories include (in descending order of extent of response): CR, complete response with incomplete bone marrow recovery (CRi), nodular partial response (nPR), PR, partial response with lymphocytosis (PR-L), SD, PD, and NE. For patients enrolled with CLL/SLL, bone marrow aspirate and biopsy should be collected for confirmation of CR.

BOR will be summarized descriptively to show the number and percentage of patients in each response category.

ORR is defined as the proportion of patients who achieve a BOR of CR, CRi, nPR, or PR (i.e., PR or better). The corresponding 95% two-sided CI will be calculated using the exact binomial distribution. The proportion of patients who achieve a BOR of PR-L or better will also be calculated.

Tumor burden will be assessed at baseline and at each subsequent disease assessment time point after the first dose. The longest diameter (LDi) and shortest diameter (SDi) of each target lesion identified on computed tomography (CT) (or magnetic resonance imaging [MRI]) will be measured and recorded. The product of perpendicular diameters (PPD) of the target lesions will be summed to obtain the sum of the product of the diameters (SPD). The tumor-burden change will be calculated for each patient as the percentage change from baseline in SPD of target lesions at each assessment time point at or before the initiation of subsequent anticancer therapy. Waterfall plots will be used to depict graphically the best change for each patient.

Swimmer plots will be used to show the occurrence of clinical outcomes of interest over time (e.g., responses, PD, treatment discontinuation, death).

Sensitivity analysis of ORR counting PR-L as response may also be performed upon request.

8.4. Secondary Endpoint Analyses (Efficacy)

8.4.1. Overall Response Rate by Investigator

The same analysis methods for IRC-assessed ORR will be applied to Investigator-assessed ORR. The discordance between responses assessed by the Investigator and IRC using the Lugano or iwCLL classification will be summarized.

8.4.2. Duration of Response

DOR will be calculated for patients who achieved BOR of PR or better (For CLL/SLL, if deemed necessary, DOR of patients who achieve a BOR of PR-L or better will also be calculated in addition to the DOR for PR or better). DOR is defined as the number of months from the date of the first documented response to the date of PD or death, whichever occurs earlier. Patients who

are alive and without documented PD as of the data analysis cutoff date will be censored. Details of the censoring rules are provided in Table JZNJ.8.1.

Table JZNJ.8.1. Censoring Rules for Duration of Response

Situation	Outcome	Date	Event Description/Censoring Reason
Progression documented on or before subsequent anticancer therapy or data cutoff, whichever occurred first	Event	Earliest date of disease assessment documenting progression	PD
Death without documented progression and not receiving subsequent anticancer therapy on or before data cutoff	Event	Date of death	Death
Documented progression or death after subsequent anticancer therapy and the subsequent anticancer started before data cutoff date	Censored	Date of last adequate disease assessment prior to subsequent anticancer therapy	Subsequent anticancer therapy
Documented progression or death after subsequent anticancer therapy and the subsequent anticancer started after data cutoff date	Censored	Date of last adequate disease assessment on or before data cutoff	Data cutoff
No documented progression or death at the time of data cutoff and subsequent anticancer therapy started before the data cutoff	Censored	Date of last adequate disease assessment prior to subsequent anticancer therapy	Subsequent anticancer therapy
No documented progression or death at the time of data cutoff and subject not received subsequent anticancer therapy or received it after the data cutoff	Censored	Date of last adequate disease assessment on or before data cutoff	Data cutoff
Documented progression or death immediately following 2 or more consecutively missed scheduled disease assessment visits	Censored	Date of last adequate disease assessment prior to the first of consecutively missed visits	Extended missing visits
Withdrew consent before documented progression or death	Censored	Date of last adequate disease assessment	Withdrew consent

Lost to follow-up before documented progression or death	Censored	Date of last adequate disease assessment	Lost to follow-up

DOR will be calculated as follows:

DOR (months) = (Event/Censoring Date Response Start Date + 1) / 30.4375

DOR will be summarized descriptively using the Kaplan-Meier method. The Kaplan-Meier estimate with 95% CI calculated using Brookmeyer and Crowley method will be provided for DOR time quartiles. The DOR survival v z(–≥(FB0 (QW – ≤(U zz y (• „ ’v(–’’(wz(provided for selected timepoints (e.g., 2, 4, 6, and 9 months.) The reason for censoring will be summarized.

8.4.3. Time to Response

TTR is defined as the number of months elapsed between the date of the first dose of LOXO-305 and the first documentation of response. IRC assessments, if performed, will serve as the principal data source. Additional analyses based on Investigator assessment will be provided.

TTR will be calculated as follows for patients who have a BOR of PR or better (for CLL/SLL, PR or better; if deemed necessary, PR-L or better will also be calculated for CLL/SLL):

TTR (months) = (Response Start Date First Dose Date + 1) / 30.4375

TTR will be summarized descriptively by calculating the median, interquartile range, and minimum and maximum values. The number and percentage of patients with TTR by the following time points, measured relative to the date of the first dose of LOXO-305, will be tabulated:

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8.4.4. Time to Best Response

TTBR is defined as the number of months elapsed between the date of the first dose of LOXO-305 and the first documentation of response, given that the response happens to be the BOR for this subject. IRC assessments, if performed, will serve as the principal data source. Additional analyses based on Investigator assessment will be provided.

TTBR will be calculated as follows for patients who have a BOR of PR or better (for CLL/SLL, PR or better; if deemed necessary, PR-L or better will also be calculated for CLL/SLL):

TTBR (months) = (Best Response Start Date First Dose Date + 1) / 30.4375

TTBR will be summarized descriptively in the same manner as TTR.

8.4.5. Progression Free Survival

PFS is defined as the number of months from the date of the first dose of LOXO-305 to the date of PD or death, whichever occurs earlier. Patients who are alive and without documented PD as of the data analysis cutoff date will be censored. Details of the censoring rules for analysis of PFS will be provided in Table JZNJ.8.2.

Table JZNJ.8.2. Censoring Rules for Progression Free Survival

Situation	Outcome	Date	Event Description/Censoring Reason
Progression documented on or before subsequent anticancer therapy or data cutoff, whichever occurred first	Event	Earliest date of disease assessment documenting progression	PD
Death without documented progression and not receiving subsequent anticancer therapy on or before data cutoff	Event	Date of death	Death
Documented progression or death after subsequent anticancer therapy and the subsequent anticancer started before data cutoff date	Censored	Date of last adequate disease assessment prior to subsequent anticancer therapy	Subsequent anticancer therapy
Documented progression or death after subsequent anticancer therapy and the subsequent anticancer started after data cutoff date	Censored	Date of last adequate disease assessment on or before data cutoff	Data cutoff
No documented progression or death at the time of data cutoff and subsequent anticancer therapy started before the data cutoff	Censored	Date of last adequate disease assessment prior to subsequent anticancer therapy	Subsequent anticancer therapy
No documented progression or death at the time of data cutoff and subject not received subsequent anticancer therapy or received it after the data cutoff	Censored	Date of last adequate disease assessment on or before data cutoff	Data cutoff
Documented progression or death immediately following 2 or more consecutively missed scheduled	Censored	Date of last adequate disease assessment prior to the first of consecutively	Extended missing visits

disease assessment visits		missed visits	
Withdrew consent before documented progression or death	Censored	Date of last adequate disease assessment	Withdrew consent
Lost to follow-up before documented progression or death	Censored	Date of last adequate disease assessment	Lost to follow-up
No adequate disease assessment	Censored	Date of first dose	No adequate disease assessment

PFS will be calculated as follows:

PFS (months) = (Event or Censoring Date First Dose Date + 1) / 30.4375

Unless specified otherwise, the analysis methods described in Section 8.4.2 for DOR will be used for PFS.

8.4.6. Overall Survival

OS is defined as the number of months from the date of the first dose of LOXO-305 to the date of death from any cause. Patients who are alive or lost to follow-up as of the data cutoff date will be censored to the date the patient is last known to be alive.

Based on these considerations, OS will be calculated as follows:

OS (months) = (Death or Censoring Date First Dose Date + 1) / 30.4375

The analysis methods described in Section 8.4.2 for DOR will be used for OS.

8.4.7. Subgroup Analysis (MCL)

In order to assess the consistency of ORR across selected subgroups and special populations, supportive analyses will be performed. These analyses will be conducted using the PAS, SAS1, SAS2 and EAS. The estimates of the ORR and DOR based on IRC and investigator assessments will be calculated for the subgroups defined by the following:

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(s-MIPI (low risk [0 to 3] versus intermediate risk [4 to 5] versus high risk [6 to 11] and low or intermediate risk versus high risk)

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(d – (z,, (xz''(v 'v (3mz :b 4(

(d – (QR=; (v y(Q≥z,, (3mz :b 4(

(f zv (• (y– x – v – (• ,, (≥z(,, (zxz (– (BTKi (PD, Toxicity, or other)

(f zv (• (y– x – ation from any prior BTKi (PD, Toxicity, other)

Forest plot for ORR based on IRC may be produced for selected subgroups and special population as defined above.

Tumor bulk is defined as the largest diameter of target lesions.

The s-MIPI score will be derived based on baseline values of 4 prognostic factors: age, ECOG, lactate dehydrogenase (LDH), and white blood cell (WBC). Points will be assigned to each of these factors as presented below, and the score will be derived by adding the points for all 4 factors. A score of 0 to 3 indicates low risk, 4 to 5 indicates intermediate risk, and 6 to 11 indicates high risk.

Points	Age(y)	ECOG	LDN ULN	WBC, 10^9/L
0	<50	0-1	<0.67	<6.7
1	50-59	-	0.67-0.99	6.7-9.9
2	60-69	2-4	1.0-1.49	10.0-14.9
3	(70	-	(1.5	(15.0

ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; WBC = white blood cell(s); ULN = upper limit of normal.

The listings for systemic therapies categories will be provided by medical teams for this subgroup analysis.

8.4.8. Subgroup Analysis (CLL/SLL)

A different set of subgroup factors is selected for CLL/SLL:

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- 17p deletion mutation presence (yes, no)
- 11q deletion mutation presence (yes, no)

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- 17p deletion and/or TP53 mutation (yes, no)
- 17p deletion and TP53 mutation (yes, no)

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(f zv (• (y– x – ation from any prior BTKi (PD, Toxicity, other)

8.5. Secondary Endpoint Analyses (Safety)

This section describes the statistical methods to be used for analyses intended to demonstrate the safety and tolerability of LOXO-305 in patients with CLL/SLL, MCL, and other NHL.

Safety data will be presented for patients with MCL, patients with CLL, and all patients in the safety population.

8.5.1. Treatment Emergent Adverse Events

The treatment-emergent period is defined as the period of time from the date of the first dose of LOXO-305 through the safety follow-up visit (28 days + 7 days window after the date of the last dose of LOXO-305) or the first date starting new anticancer therapy, whichever is earlier. AEs reported during the treatment-emergent period that either newly occurs or worsens after treatment baseline are considered treatment-emergent AEs (TEAEs). Summary tables will be provided for all reported TEAEs and treatment-emergent SAEs.

The reported AE term will be coded using the Medical Dictionary for Regulatory Activities (MedDRA 25.0). The severity of each AE will be graded by the Investigator based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE Version 5). If a severity grading scale does not exist for an AE, the Investigator will classify the

severity as mild, moderate, severe, life-threatening/debilitating, or fatal. The causal relationship wz zz (≥z(xx z xz(•(v (OS(v y(y (y ≤(–’’(wz(“ y≤zy(w (≥z(W z –≤v (v (z’v zy (((z’v zy 9(

TEAEs will be summarized based on the number and percentage of patients experiencing events by MedDRA system organ class and preferred term. If a patient experiences repeat episodes of the same AE (as defined by the MedDRA system organ class and preferred term), then the event with the highest reported severity grade and the strongest causal relationship to study drug will be used for purposes of the incidence tabulations.

Tabular summaries will be provided by maximum severity grade (all grades and grade ≥3) or SOC and PT or PT for:

(TEAE

(TEAE related to study drug

(OS (leading to study drug interruption or dose reduction

(OS (leading to treatment discontinuation

(gOS (including death).

8.5.2. Adverse Events of Special Interest

The following AEs were deemed AEs of special interest (AESI): cytopenias (specifically, anemia, thrombocytopenia and neutropenia), infections, bleeding, and atrial fibrillation/ atrial flutter. AESI categories were determined by medical review. Treatment-emergent AESI will be summarized for each category.

Cytopenias

Throughout the course of the global LOXO-305 clinical program, cytopenic effects were continually reviewed given the known BTK inhibitor therapy drug class risk of, most predominantly, neutropenia followed by thrombocytopenia and anemia. The incidence of these events, including those that led to study drug dose interruption, reduction, or discontinuation were monitored throughout and will be quantified.

Infections

R z((≥z(yz≤ zz(•(v –v – (•(z•z zy(z „ (≥v (z – (–≥– (≥z(xv z≤ (•(– •zx – 7(the overall incidence of infectious events will be assessed by analyzing the incidence of all terms within the system organ class of infections and infestations collectively. Patients will be considered by the event reported that had the greatest severity and strongest causality. The incidence of these events that led to study drug dose interruption, reduction, or discontinuation were monitored throughout and will be quantified.

Bleeding

Increased risk of bleeding is a known drug class risk of BTK inhibitor therapy. These events have commonly been further categorized as either bruising or hemorrhage or petechiae and purpura events. To inform the understanding of LOXO-305 within the context of this drug class, a similar approach has been used. Due to the degree of variation that exists within the category of hemorrhage, the overall incidence of hemorrhagic events will be assessed by analyzing the incidence of all terms within the standardized MedDRA query (SMQ) of hemorrhage terms, excluding lab terms. Patients will be included in the overall incidence based on the event reported with the maximum severity and strongest causality. The incidence of these events that led to study drug dose interruption, reduction, or discontinuation were monitored throughout and will be quantified.

Atrial Fibrillation and Atrial Flutter

Atrial fibrillation and atrial flutter are known drug class risks and the incidence of these events was monitored throughout the duration of the study. The incidence of these events that led to study drug dose interruption, reduction, or discontinuation were monitored throughout and will be quantified.

Additional AESI may be added based on review of the safety data before the final data extraction.

8.5.3. Adverse Events of Potential Clinical Significance

Adverse events of potential clinical significance (AEPCS) do not necessarily represent known on-target safety risks of the BTK inhibitor drug class but are potentially clinically significant based on general risks associated with anticancer treatment in this patient population, or on-target effects of the BTK inhibitor drug class that are potential, but not identified, risks. CCI [redacted] Treatment-emergent AEPCS will be summarized for each term.

8.5.4. Deaths

Death information is reported in the study case report form. Incidences of deaths are to be reported, along with the primary cause of death in a summary table. All deaths including on-study death (deaths that occurred within 28 days of study drug discontinuation) will be presented in a patient listing, which will supplement the narratives and will include the primary cause of death and the number of days between the date of the last dose of study drug and death.

8.5.5. Clinical Laboratory Evaluations

Gradable laboratory values will be assigned toxicity grades based on the NCI CTCAE V5. CCI [redacted]

The "worst" change (minimum and/or maximum) in each laboratory value occurring during treatment will be assessed by means of shift tables showing the number and proportion of

patients with directional shifts in CTCAE toxicity grades relative to the baseline grade. For laboratory variables without CTCAE toxicity grades, similar tables will be constructed showing shifts to outside (above or below) the local laboratory normal range relative to baseline.

Gradable parameters that have criteria available for both low and high values (e.g., hypercalcemia for a high value of calcium and hypocalcemia for a low value of calcium) based on the CTCAE will be summarized for both criteria (low and high). Subjects will be counted only once for each criterion/direction. The same subject can be counted for both criteria if the subject has laboratory values that meet each criterion. Subjects who meet the criteria for Grade 1 or higher for the high direction will be summarized under Grade 0 for summarization of the low direction and vice versa.

Hematology and serum chemistry values from local labs will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range of the following values that are derived for each patient:

(P v z'– z(v' z(

(a –¬„ „ (ww z'– z(v' z(v y(x z y– ≤(x≥v ≤z(• „ (ww z'– z(

(a v –¬„ „ (ww z'– z(v' z(v y(x z y– ≤(change from baseline

(] v (ww z'– z(v' z(v y(x z y– ≤(x≥v ≤z(• „ (ww z'– z(

In addition, incidence of the most extreme treatment-emergent postbaseline abnormal laboratory parameters will be summarized upon request. A treatment-emergent laboratory abnormality is defined as a laboratory value at least 1 grade higher than the baseline grade.

Additional analysis of Lymphocytosis for the CLL/SLL patients will be conducted upon request.

8.5.6. Vital Signs

The following vital signs were measured at screening and at periodic time points (including end of treatment and safety follow-up) following the initiation of LOXO-305:

(g '–x(v y(y–v '–x(w' y(z z

(Vzv (v z

(f z –v – (v z(

(P y (z„ z v z

Each of these vital signs will be listed by visit. Blood pressures will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range of the following values that are derived for each patient:

Baseline value

(a –¬„ „ (ww z'– z(v' z(v y(x z y– ≤(x≥v ≤z(• „ (ww z'– z(

(a v –¬„ „ (ww z'– z(v' z(v y(x z y– ≤(x≥v ≤z(• „ (ww z'– z(

[] v (ww z'– z(v' z(v y(x z y– ≤(x≥v ≤z(• „ (ww z'– z(

8.5.7. Body Weight

Body weight was measured at screening and at periodic time points following the initiation of LOXO-305. Changes in body weight will be summarized in a descriptive manner.

8.5.8. ECOG Performance Status

Performance status is graded according to the ECOG. Shift table analysis of baseline vs worst/last score will be presented.

8.5.9. Electrocardiograms

The ECGs were performed at screening and at periodic time points throughout LOXO- 305 treatment. The findings and related AEs will be summarized for each time point. Since triplicate ECGs are performed during screening, C1D1 and C1D8. At these time points, the ECG of a patient will be considered performed if at least one ECG is performed and a finding of adverse event or medical history will be considered if at least one ECG has a finding.

8.6. Secondary Endpoint Analyses (PRO)

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).

The EORTC QLQ-C30 consists of 30 total items (questions) 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).

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

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 Symptom Assessments: EORTC IL63, which consists of additional symptom items: Night sweats, Fever/Chills, Fatigue (3 items), and Bloating of the abdomen.

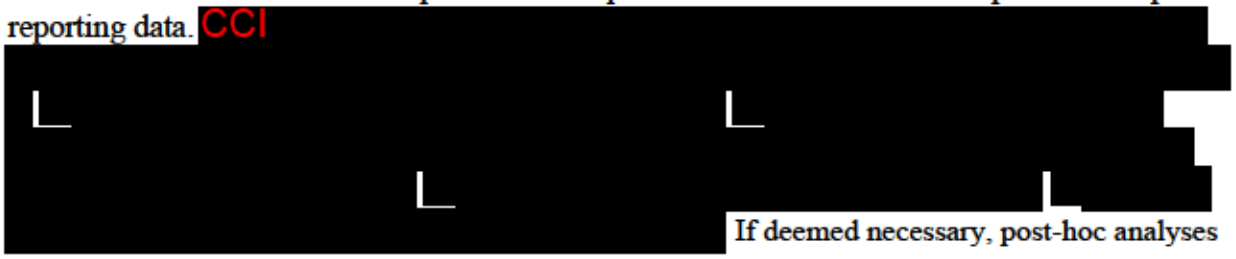
Following the scoring instructions given by the EORTC Quality of Life Study Group, the raw EORTC QLQ-C30 and EORTC IL63 subscale scores will be linearly transformed to 0-100. Missing values will be handled as outlined in the EORTC QLQ-C30 and EORTC IL63 scoring manual if at least 50% of the items on a scale or subscale are reported; no values will be imputed.

The raw score will be computed if at least 50% of the items on a scale or subscale are complete. The scoring for EORTC QLQ-C30 and EORTC IL63 is detailed in Appendix 1.

Descriptive analyses will report median/quartile, mean/standard deviation (SD), and will include mean change/standard error (SE) from baseline for each subscale at each study visit for the predefined analysis sets. Similar descriptive analyses will be conducted for each kind of best of response by IRC which the MCL patients received to evaluate the improvement in cancer-related symptoms and physical function among MCL patients associated with BOR.

For each subscale, mean scores across time will be presented in a line plot. For all change-from-baseline measures, the analysis set will include all treated patients who have baseline and at least one post-baseline PRO assessment.

The number and percentage of patients improving, stable and worsening relative to their own baseline measurement will be reported at each post-baseline clinic visit time point for all patients reporting data. CCI



If deemed necessary, post-hoc analyses which use different criteria to define worsening and improvement may be conducted for exploratory purpose.

Time to first improvement and to first worsening, respectively, will be evaluated using Kaplan-Meier method. For time to first improvement, patients who did not improve will be censored at the date of their last EORTC assessment; Similarly, for time to first worsening, patients who did not worsen will be censored at the date of their last EORTC assessment.

Questionnaire compliance will be summarized. Compliance rates will be calculated at each assessment time point. Compliance at an assessment time point is defined as the number of patients who were assessed divided by the expected number of patients at that time point.

A patient who answers at least one item at a time point is considered to have been assessed.

8.7. Other Analyses

8.7.1. Demographic and Other Baseline Characteristics (MCL)

Baseline characteristics of patients will be summarized in a tabular manner for the following factors:

(Rz,, ≤ v ≥ (

(P v z'– z(y– zv z(x≥v vx z – –x (

(d – (xv xz (zv ,, z (

Demography and Baseline Characteristics

The following variables will be summarized across patients to describe the demographics at enrollment:

(O≤z(v (z ’’,, z (- summarized as a continuous variable in years relative to the date informed consent is signed. Age will also be summarized categorically based on the following age groups:

- < 50 years
- 50 to < 65 years
- 65 to < 75 years
- 75 to < 85 years
- (85 years
- < 65 vs (CB(zv (
- < 75 vs (75 years
- < 85 vs (85 years

(gz (3,, v'z7(•z,, v'z4

(Vz–<> (3x,, 4(

(k z–<> (3'’≤4(

Baseline Disease Characteristics

The following variables will be summarized across patients:

(Sv z (Q z v – z(c x ’ ≤ (Group (ECOG) performance status (0, 1, 2)

(h–,, z(3,, ≥ 4(• ,, (– –-v'(y–v≤ –((•– (y z(

(O (O w (v≤– ≤(• (’ ,, ≥ ,, v

Simplified MCL International Prognostic Index (s-MIPI) score (low risk, intermediate risk, high risk)

(h ,, (w ’’’(3I B(x,, , 5 cm, unknown)

(S v yv'(y– zv z((yes, no, unknown)

(P z(,, v (– ’ z,, z ((yes, no, unknown)

(a Q] (≥– ’ ≤ (3w’v –y7(non-blastoid)

(R– zv z(z’v zy(,, ,, (3 z–<> (’ 7(•z z 7(–<> (zv 7(•v –≤ z4

Additional baseline disease variables may be included.

Prior Cancer Treatments

The following variables will be summarized across patients to characterize the extent of prior cancer treatments:

(h z(•(– (z,, –x(≥z v –z (

(d – (’– z (•(z,, –x ≥z v –z (3<7(=7(>7((A4(

(d – (’– z (•(z,, –x(≥z v –z (3,, zv (ogRr7(,, zy–v 7(e <7(e >7(,, – (v y(,, v 4(

(] – z (•(– (Ph[(– ≥–w– (3; 7(<7(=7((>4

(Best overall response to most recent prior systemic regimen

(Best overall response to most recent prior BTKi

(f zv (• (y– x – v – (• ,, (≥z(,, (zxz (– (Ph[(– ≥–w– (3dR7(intolerance, complete treatment, subject decision or other)

(f zv (• (y– x – v – (• ,, (v (– (Ph[(– ≥–w– ((PD, intolerance, complete treatment, subject decision or other)

(d – (vy– ≥z v (3 z 7(4(

(d – (xv xz -related surgery (yes, no)

Subsequent anticancer therapy and cancer-related surgery will be presented as listings.

8.7.2. Demographic and Other Baseline Characteristics (CLL/SLL)

Demography and Baseline Characteristics

The same sets of variables as MCL will be summarized.

Baseline Disease Characteristics

The following variables will be summarized across patients:

(Sv z (Q z v – z(c x ’ ≤ (U (3SQc U4(z • ,, v xz(v (3; 7(<7(=4(

(h–,, z(3,, ≥ 4(• ,, (– –v’(y–v≤ –((•– (y z(

(V– ’ ≤ (3Q]] 7(g]] 4(

(f v-(v≤z(3; 7(W(WW(WWW(v y(W 4(

(P ”” (y– zv z(3I (B(x,, (((B(x,, I(I (<; (x,, (((<; (x,, , unknown)

IGHV mutation (mutated, unmutated, unknown)

(h dB>(,, v – (3,, v zy7(,, v zy, unknown)

(Q ,, 'z ("v z(3 z 7(, unknown)

(Q ≤z z –x(•zv z (3•' z xz xz(– (– (≥ w –y– v – (oTWgVr(v z'4G

- 17p deletion presence (yes, no, unknown)
- 11q deletion presence (yes, no, unknown)

(V–≤(–"(•zv z G

- 17p deletion and/or TP53 mutation (yes, no, unknown)
- 17p deletion and TP53 mutation (yes, no, unknown)

(Q z –v(v (ww z'– zG

- Neutropenia - absolute neutrophil count (ANC) < 1.5 x 10^9/L (yes, no)
- Anemia - hemoglobin (Hgb) < 11 g/dL (yes, no)
- Thrombocytopenia - platelet counts < 100 x 10^9/L (yes, no)
- Any of the above (yes, no)

(R– zv z(z'v zy(,, ,, (3 z–≤ (' 7(•z z 7(–≤ (zv 7(•v –≤ z4(

Prior Cancer Treatments

The same sets of variables as MCL will be summarized.

8.7.3. Pre-Existing Conditions and Medical History

General pre-existing conditions and medical history data will be coded per Medical Dictionary for Regulatory Activities (MedDRA 25.0), summarized by system organ class (SOC) and preferred term (PT), and presented as a patient listing.

8.7.4. Study Drug Exposure

Exposure to LOXO-305 will be summarized based on the following:

(R z(– z ––z (

(R v≤z(,, y–•–xv –

(Time on Treatment

Dose Intensities

LOXO-305 dose intensities will be summarized descriptively as actual dose intensity (ADI), planned dose intensity (PDI) and relative dose intensity (RDI).

The ADI of LOXO-305 (mg/day) will be calculated as the actual cumulative dose of LOXO-305 (mg) received divided by the time from first dose to EOT (days).

The PDI of LOXO-305 (mg/day) will be as follows:

• For QD dosing schedule, the PDI (mg/day) = assigned dose level (mg/day) = CCI

The RDI is the percentage of dose received relative to the planned dose through to treatment discontinuation and is defined as follows:

CCI

Dosage Modifications

The number and percentage of patients with dose reductions, dose interruptions, and dose increases will be tabulated with the reason for each dose modification.

Time on Treatment

Time on treatment (TOT) will be summarized descriptively. For patients who permanently discontinued LOXO-305 as of the data cutoff date, TOT will be calculated as follows:

CCI

The last dose date reported on the Last Dose CRF will be used.

For patients continuing to receive LOXO-305 as of the data cutoff date, TOT will be calculated as follows:

CCI

8.7.5. Concomitant Medications

The reported medication term will be assigned to a preferred term using the World Health Organization Drug Dictionary (March 2023 Global Version). The number and percentage of patients taking these concomitant medications will be summarized.

8.7.6. COVID-19 Impact

A listing of protocol deviations (both important and non-important) caused by COVID-19 will be provided. A table which summarizes the number of patients missing visits or tumor assessments due to COVID-19, conducting tumor assessments by a local hospital due to COVID-19, with visits replaced by telephone visits due to COVID-19, receiving IP by direct to patient (DTP) IP delivery and with visit window extension due to COVID-19 will be provided. A sensitivity analysis which excludes tumor assessments by local hospitals from the tumor assessments of each patient will be conducted on the PAS. Treatment-emergent adverse events will be summarized for each reported PTs under the SMQ of COVID-19.

8.7.7. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

- Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and "Other" AEs are summarized by treatment arms and by MedDRA PT.

O (OS(– (x –yz zy(gz – (≥z ≥z (((–(– (v(h SOS9

O (OS(– (x –yz zy(– (≥z(c ≥z (xv z≤ (•(–(– (w ≥(v(h SOS(and is not serious.

T (zvx≥(gOS(v y(c ≥z (OS7(• (zvx≥(z „ (v y(zv „ z (arms, the following are provided:

- the number of participants at risk of an event
- the number of participants who experienced each event term, and
- the number of events experienced.

Consistent with www.ClinicalTrials.gov requirements, a threshold for frequency of c ≥z (OS (xv (wz(–„ ’z„ z zy(v ≥z (≥v (z z –≤(v’’(c ≥z (OS 9(T (z v„ ’z7(c ≥z (OS (≥v (xx (– (•z z (≥v (B0 (•(v –z (– (v (zv „ z (arms may not be included if a 5% threshold is chosen. The frequency threshold must be less than or equal to the allowed maximum of 5%.

AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

8.8. Interim Analyses and Data Monitoring

The primary analysis will be performed after all enrolled patients have been followed for sufficient amount of time (6 months). No interim analysis is planned. However, the primary analysis may be updated upon request from regulatory authorities at any time during the study.

No data monitoring committee is planned for this study.

8.9. Unbinding Plan

Since this study is an open-label, single-arm study, no blinding will be applied when patients are enrolled in the Interactive Web Response System (IWRS).

9. References

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85(5):365-376.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes inhealth-related quality-of-life scores. *Journal of clinical oncology* 1998; 16, no. 1: 139-144.

10. Appendices

Appendix 1. Scoring for the EORTC QLQ-C30 and EORTC IL63 Questionnaire Version 3.0

EORTC QLQ-C30 and EORTC IL63 will be scored according to the scoring manual including transforming the raw score to the transformed score and handling of missing item responses as follows:

· Missing Data:

If there are missing items, raw scores derived from more than one question can be prorated so long as the respondent completed >50% of the items on a given subscale:

a) For status/scales/items derived from an odd total number of questions:

[(Number of questions answered+1)/2] questions must be answered

b) For status/scales/items derived from an event total number of questions:

[Number of questions answered/2] questions must be answered

Prorated raw score = [Sum of answered item scores] / [Number of items answered]

If any subscale has >50% missing items, then the subscale total score will be missing.

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