PROTOCOL

TITLE:	A Multicenter, Randomized, Double-blind, Placebo-controlled Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Combination with Rituximab versus Placebo in Combination with Rituximab in Treatment Naïve Subjects with Follicular Lymphoma
PROTOCOL NUMBER:	PCYC-1141-CA
STUDY DRUG:	Ibrutinib (PCI-32765)
IND NUMBER:	102,688
EU CT NUMBER:	2023-507271-21-00
SPONSOR MEDICAL MONITOR:	[redacted] MD AbbVie Phone: [redacted] Email: [redacted]
SPONSOR:	Pharmacyclics LLC, an AbbVie company 1000 Gateway Boulevard South San Francisco, CA 94080 United States of America
DATE FINAL:	04 August 2016
Amendment 1:	30 January 2018
Amendment 2:	10 March 2021
Amendment 3:	10 October 2022
Amendment 4:	07 February 2023
Amendment 5:	10 May 2024

PROTOCOL APPROVAL PAGE

Study Title: A Multicenter, Randomized, Double-blind, Placebo-controlled Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Combination with Rituximab versus Placebo in Combination with Rituximab in Treatment Naïve Subjects with Follicular Lymphoma

Study Number: PCYC-1141-CA

Protocol Date: 04 August 2016

Amendment 1: 30 January 2018

Amendment 2: 10 March 2021

Amendment 3: 10 October 2022

Amendment 4: 07 February 2023

Amendment 5: 10 May 2024

I have carefully read Protocol PCYC-1141-CA entitled "A Multicenter, Randomized, Double-blind, Placebo-controlled Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Combination with Rituximab versus Placebo in Combination with Rituximab in Treatment Naïve Subjects with Follicular Lymphoma." I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements. Furthermore, I understand that the Sponsor, Pharmacyclics, and the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) must approve any changes to the protocol in writing before implementation.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational product and processes or methods of Pharmacyclics. All data pertaining to this study will be provided to Pharmacyclics. The policy of Pharmacyclics LLC requires that any presentation or publication of study data by clinical Investigators be reviewed by Pharmacyclics, before release, as specified in the protocol.

Principal Investigator's Signature Date

Print Name

The following Pharmacyclics LLC representative is authorized to sign the protocol and any amendments:

Medical Monitor's Signature Date

[redacted] MD

Imbruvica Global Development, AbbVie

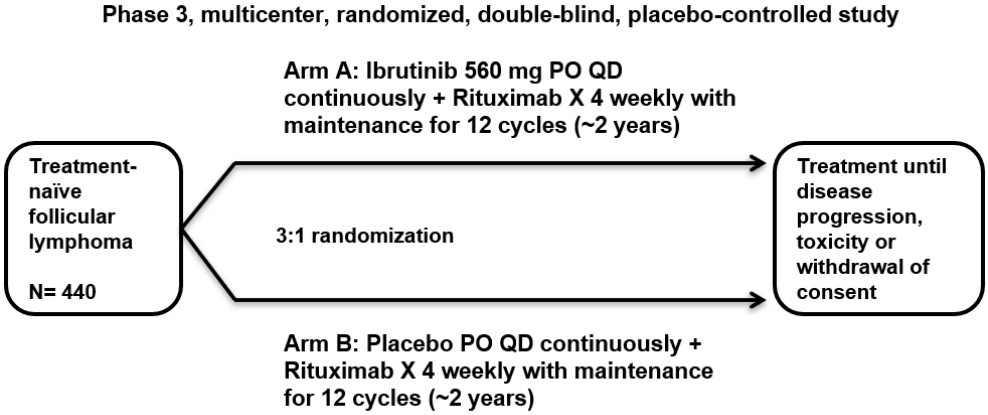
TABLE OF CONTENTS

LIST OF APPENDICES

LIST OF IN-TEXT TABLES AND FIGURES

Figures

SYNOPSIS

Title:	A Multicenter, Randomized, Double-blind, Placebo-controlled Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Combination with Rituximab versus Placebo in Combination with Rituximab in Treatment Naïve Subjects with Follicular Lymphoma
Protocol number:	PCYC-1141-CA
Phase:	3
Subject population:	Treatment naïve subjects with follicular lymphoma (Grade 1-3A) meeting Groupe d'Etude des Lymphomes Folliculaire (GELF) criteria for therapy and are: 70 years of age or older or 60-69 years of age with comorbidities (see Inclusion/Exclusion criteria for additional details)
Study drug and comparator:	Study drug: ibrutinib PO hard gelatin capsule in combination with rituximab Comparator: placebo PO hard gelatin capsule in combination with rituximab
Primary objective:	To evaluate whether the addition of ibrutinib to rituximab will result in prolongation of progression-free survival (PFS) when compared with rituximab alone in treatment naïve subjects with follicular lymphoma.
Study design:	This is a randomized, double-blind, placebo-controlled Phase 3 study designed to assess the efficacy and safety of ibrutinib in combination with rituximab compared to placebo in combination with rituximab in treatment naïve subjects with follicular lymphoma.  **Stratification factors:** Age (60-69 vs. ≥ 70 years) FLIPI-1 score low vs. intermediate/high ECOG performance status 0/1 vs. 2

	Approximately 440 subjects will be enrolled (estimate based on an accrual assumption of 30 months). Subjects will be randomized at a 3:1 (Arm A: Arm B) ratio. Subjects will be stratified on the basis of: • Age (60-69 vs. ≥70 years) • Follicular Lymphoma-specific International Prognostic Index (FLIPI)-1 (low vs. intermediate/high), and • Eastern Cooperative Oncology Group (ECOG) performance status score (0/1 vs. 2) Subjects randomized to the investigational arm (Arm A) will receive ibrutinib 560 mg by mouth (PO) (4 capsules) daily until disease progression or unacceptable toxicity. Subjects randomized to the control arm (Arm B) will receive placebo PO (4 capsules) daily until disease progression or unacceptable toxicity. Primary analysis for PFS will be conducted when 200 PFS events are observed, or if pre-specified boundaries are crossed at an interim analysis. The final analysis for OS will be conducted when 165 OS events are observed or five years after enrollment of the last subject, whichever is earlier. Subjects in both arms (Arms A and B) will also receive rituximab 375 mg/m^2 intravenous (IV) once weekly for the first 4 weeks of study treatment (Cycle 1: Days 1, 8, 15, and 22). Beginning with Cycle 3, Day 1, rituximab will be given as maintenance therapy administered as a single 375 mg/m^2 IV dose every 8 weeks for up to 12 additional doses (approximately 2 years) or until disease progression or unacceptable toxicity, whichever comes first. A Response Evaluation Visit including local imaging assessments will be performed every 16 weeks through Cycle 37 and then every 24 weeks thereafter and copies of the images will be stored at a central location for independent review-based assessment. The details of the analyses will be specified in a separate document. Blinded study treatment administration will continue until disease progression, unacceptable toxicity or study termination. Subjects who discontinue study treatment due to any reason will be followed for OS every 24 weeks. Subsequent anticancer therapies, best response to therapy, and information about other malignancies will be collected.

Inclusion/ Exclusion Criteria:	**Inclusion Criteria** *Disease-Related* 1. Subjects with histologically documented follicular lymphoma (Grade 1, 2 or 3a) according to World Health Organization (WHO) criteria and Ann Arbor Stage II, III or IV disease. 2. At least one two-dimensionally measurable lesion ≥2.0 cm in the longest diameter (LDi) by contrast-enhanced CT scan. Lesions in anatomical locations (such as extremities or soft tissue lesions) that are not well visualized by CT may be measured by MRI instead. 3. Subjects 70 years of age or older; OR subjects 60-69 years of age who have **one or more** comorbidities that make them a candidate to receive single -agent rituximab therapy: • Creatinine clearance 30-59 mL/min (by Cockcroft-Gault or creatinine clearance calculated based on 24-hour urine collection). • ECOG performance status score of 2 4. In need of systemic therapy as evidenced by meeting **one or more** of the following Groupe d'Etude des Lymphomes Folliculaire (GELF) criteria (Solal-Céligny 1998, Chen 2012): • Involvement of ≥3 nodal sites, each with a diameter of >3 cm • Any nodal or extranodal tumor mass with a diameter of >7 cm or risk of local compressive symptoms that may result in organ compromise • B symptoms (ie, fever, night sweats or weight loss) • Splenomegaly • Pleural effusions or peritoneal ascites • Thrombocytopenia (platelet count <100 x 10^9/L) • Peripheral blood involvement (>5.0 x 10^9/L malignant cells) *Laboratory* 5. Adequate hematologic function defined as: • Hemoglobin ≥8.0 g/dL • Platelet count ≥50 x 10^9/L (50,000 cells/mm^3) • Absolute neutrophil count ≥1.0 x 10^9/L (1,000 cells/mm^3) 6. Adequate renal and hepatic function defined as: • Estimated creatinine clearance ≥30 mL/min (Cockcroft-Gault) • Serum aspartate transaminase (AST) and alanine transaminase (ALT) ≤3.0 x upper limit of normal (ULN) • Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome such that bilirubin ≤3 x ULN or is of non-hepatic origin) 7. PT/ INR <1.5 x ULN (unless treated with warfarin or other vitamin K antagonists such that INR ≤3.0) and PTT (aPTT) <1.5 x ULN. *Demographic* 8. Eastern Cooperative Oncology Group (ECOG) performance status score of 0-2.

	Ethical/Other 9. Female subjects of reproductive potential must have a negative urine/serum pregnancy test upon study entry. Female subjects who are of nonreproductive potential (ie, post-menopausal by history - no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy) are exempt from pregnancy testing. 10. Male and female subjects of reproductive potential who agree to use both a highly effective method of birth control (eg, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence[1], or sterilized partner) and a barrier method (eg, condoms, cervical ring, sponge, etc) during the period of therapy. For female subjects, these birth control requirements must be adhered to for 90 days after the last dose of ibrutinib/placebo and 12 months after the last dose of rituximab, whichever is later. For male subjects, these birth control requirements must be adhered to for 90 days after the last dose of ibrutinib/placebo. 11. Subjects must not be incarcerated and must be freely willing and able to provide informed consent (e.g., adults under legal protection measure [e.g., under guardianship/curatorship] or unable to express their consent and select adults under psychiatric care). Investigator discretion should be applied.
	Exclusion criteria Any potential subject who meets any of the following criteria will be excluded from participating in the study. *Disease-Related* 1. Transformed lymphoma; if clinical evidence of transformed lymphoma is present (high lactate dehydrogenase [LDH] and/or high maximum standard uptake value [SUV_{max}] of a lymph node/lesion on positron emission tomography [PET] scanning, LDH and SUV_{max} level cut off per investigator's clinical judgement), transformation should be ruled out by biopsy of the suspicious lymph node/lesion. 2. Prior treatment for follicular lymphoma (eg, systemic anti-cancer therapy or involved site radiotherapy). 3. Medically apparent central nervous system lymphoma or leptomeningeal disease. *Concurrent conditions* 4. History of other malignancies, except: • Malignancy treated with curative intent and with no known active disease present for ≥3 years before the first dose of study treatment and felt to be at low risk for recurrence by treating physician. • Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease. • Adequately treated carcinoma in situ without evidence of disease.

[1] Complete abstinence is a highly effective method only if defined as refining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. http://www.hma.eu/fileadmin/dateien/Human Medicines/01 About HMA/Working Groups/CTFG/2014 09 HMA CTFG Contraception.pdf

	5. Concurrent systemic immunosuppressant therapy (eg, cyclosporine A, tacrolimus, etc., or chronic administration of >20 mg/day of prednisone or equivalent) within 28 days of the first dose of study treatment. For indications other than lymphoma or management of lymphoma-related symptoms, the following are **exceptions** to this criterion: • Intranasal, inhaled, topical corticosteroids or local corticosteroid injections (eg, intra-articular injection) • Systemic corticosteroids at doses not to exceed 20 mg/day of prednisone or its equivalent • Corticosteroids as pre-medication for hypersensitivity reactions (eg, computed tomography [CT] scan pre-medication) 6. Vaccinated with live, attenuated vaccines within 4 weeks of the first dose of study treatment. 7. Known bleeding disorders (eg, von Willebrand's disease or hemophilia). 8. History of stroke or intracranial hemorrhage within 6 months prior to enrollment. 9. Known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded. In equivocal cases, hepatitis B or C PCR may be performed and must be negative for enrollment. 10. Any uncontrolled active systemic infection or recent infection requiring intravenous antibiotic treatment that was completed ≤14 days before the first dose of study treatment. 11. Major surgery within 4 weeks of first dose of study treatment. 12. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk. 13. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization.

	14. Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction. 15. Known anaphylaxis or IgE-mediated hypersensitivity to murine proteins or to any component of rituximab. 16. Prior use of an anti-CD20 agent or an inhibitor of Bruton's tyrosine kinase (BTK) (eg, rituximab, ibrutinib). (*NOTE: use of any prior treatment for follicular lymphoma is not permitted per protocol*) 17. Any investigational drug within 4 weeks prior to randomization or concurrent enrollment in another therapeutic investigational clinical treatment study. 18. Subject who received systemic administration of a strong cytochrome P-450 (CYP) 3A inhibitor within 7 days prior to the first dose of ibrutinib or subject who requires continuous treatment with a strong CYP3A inhibitor (see Appendix D). 19. Currently active, clinically significant hepatic impairment Child-Pugh class B or C according to the Child Pugh classification (see Appendix G). 20. Lactating or pregnant. 21. Unwilling or unable to participate in all required study evaluations and procedures. 22. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).
Endpoints:	***Primary Endpoint*** • Progression-free survival (PFS) ***Secondary Endpoints*** • Overall response rate (ORR) (Cheson 2014) • Overall Survival (OS) • Infusion-related reaction rate (Arm A vs. Arm B) • Duration of response (DOR) as assessed by investigator • Frequency, severity, seriousness, and relatedness of adverse events (AEs) ***Exploratory Endpoints*** • Health-related quality of life (QOL) as measured by the Functional Assessment of Cancer Therapy- Lymphoma (FACT- Lym) • Pharmacokinetic parameters or metrics of systemic exposure of ibrutinib and rituximab • Evaluation and/or identification of relevant patient populations defined by biomarker(s) Minimal residual disease (MRD)-negative rate defined as the proportion of follicular lymphoma subjects who achieve a CR and who reach MRD-negative disease status • Complete response rate at 30 months (CR30) as defined by the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma (Cheson 2014)

Study treatment:	Subjects randomized to the investigational arm (Arm A) will receive ibrutinib 560 mg PO daily continuously in combination with rituximab 375 mg/m^2 IV once weekly for the first 4 weeks of study treatment (Cycle 1: Days 1, 8, 15, and 22) and as maintenance therapy beginning Cycle 3, Day 1 given as a single dose of 375 mg/m^2 IV every 8 weeks for up to 12 additional doses (approximately 2 years). In the control arm (Arm B) subjects will receive placebo PO daily continuously in combination with rituximab 375 mg/m^2 IV once weekly for the first 4 weeks of study treatment (Cycle 1: Days 1, 8, 15, and 22), and as maintenance therapy beginning with Cycle 3, Day 1 given as a single dose of 375 mg/m^2 IV every 8 weeks up to 12 additional doses (approximately 2 years). Rituximab is not given in Arms A and B in Cycle 2 unless as specified in Section 5.3.2. Administration of study treatment will continue until disease progression or unacceptable toxicity. Subjects who discontinue study treatment in the absence of disease progression will continue to be followed for response. Subjects who discontinue study treatment, due to any reason and have not withdrawn consent for follow up, will be followed for overall survival. Subsequent anticancer therapies, best response to therapy, and information about other malignancies will be collected.
Select Concomitant therapy:	**Permitted Concomitant Therapy** Antiemetics are permitted if clinically indicated. Standard supportive care medications are permitted including prophylaxis for infusion-related reactions. Corticosteroids for non-cancer-related medical reasons at doses equivalent to ≤ 20 mg per day or its equivalent are permitted. Corticosteroids as pre-medication for hypersensitivity reactions (eg, CT scan pre-medication) are also permitted. Short courses (< 14 days) of corticosteroid treatment for non-cancer-related medical reasons (eg, asthma, rash, etc.) at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted. Corticosteroid treatment courses of 14 days or more may be considered after consultation with the Medical Monitor. For purposes of premedication or management of rituximab infusion reactions only, 100 mg of prednisone (or its equivalent) treatment per day may be exceeded. **Prohibited Concomitant Therapy** Any chemotherapy, anti-cancer immunotherapy, corticosteroids (used for cancer-related medical reasons) or corticosteroids for non–cancer-related medical reasons at doses >20 mg/day of prednisone or equivalent for 14 days or more, (unless approved by Medical Monitor), experimental therapy, and radiotherapy are prohibited while the subject is receiving ibrutinib/placebo.

Statistical methods:	This study evaluates ibrutinib + rituximab (Arm A) vs. placebo + rituximab (Arm B) with 2 interim analyses planned and a primary analysis for PFS when the study observes 200 PFS events, or if pre-specified boundaries are crossed at an interim analysis. The final analysis for OS is planned when 165 OS events are observed or five years after enrollment of the last subject, whichever is earlier. **Statistical Analysis:** **Primary Analysis of PFS** Progression Free Survival, as assessed by the investigator, will be analyzed in the intent-to-treat (ITT) population, comparing the 2 treatment arms at an overall 1-sided 0.025 significance level using a log-rank test stratified by the randomization factors including age (60-69, ≥70 years), FLIPI-1 score and ECOG performance status score. Two interim analyses are planned. First interim analysis will be conducted for futility when approximately 55% of the 200 PFS events have occurred. The second interim analysis will be carried out for efficacy when approximately 75% of the PFS events have occurred and after the last subject has been enrolled, with approximately 90% of the subjects reaching at least 1 year of study follow-up. Kaplan-Meier (KM) estimates for PFS will be summarized by treatment arm. The estimate of the hazard ratio and its corresponding 95% confidence interval (CI) will be computed using a Cox proportional hazards model stratified by the age group, FLIPI-1 score, and ECOG performance status score. **ORR and OS:** These two secondary endpoints will be tested sequentially with ORR ranked first followed by OS, once the primary analysis of PFS has demonstrated statistical significance. Details will be specified in the SAP. ORR in the two treatment arms will be compared using the Cochran-Mantel-Haenszel (CMH) chi-square test, stratified by the age group, FLIPI-1 score, and ECOG performance status score. The OS analysis will use the same statistical method as defined for PFS. **Safety Analysis:** Details of safety data (AEs, clinical laboratory tests and other safety endpoints) will be summarized by treatments that subjects in the Safety population actually receive.
Safety plan:	This study will be monitored by an independent Data Monitoring Committee (DMC) and in accordance with the Sponsor's Pharmacovigilance procedures. An independent DMC of at least 2 medical experts in the relevant therapeutic area and at least 1 statistician will be established to monitor unblinded data on an ongoing basis to ensure the safety of the subjects enrolled in this study. At least three safety review meetings are planned that will occur approximately 1 month after 88 subjects have been randomized (20% of expected enrollment), 1 month after 220 subjects have been randomized (50% of expected enrollment), and 1 month after all subjects have been randomized. The safety review will focus on deaths, treatment discontinuations, serious adverse events, Grade ≥3 events, and events of special interest. Based on the results from these scheduled safety review meetings, the DMC chair may request additional safety interim analyses and more frequent monitoring. Two interim analyses are planned and both will be performed by the DMC as described below. The plan for monitoring subject safety and the roles and responsibilities of the DMC will be detailed in the DMC Charter.

Interim analysis:	An interim futility analysis will be conducted when approximately 55% of the 200 PFS events have occurred., An interim efficacy analysis will be carried out for PFS with a separate futility assessment for OS when approximately 75% of the 200 PFS events have occurred and after the last subject has been enrolled with approximately 90% of the subjects reaching at least 1 year of study follow-up. An interim efficacy analysis for OS will be conducted when 200 PFS events have occurred.
Sample size determination:	Approximately 440 subjects will be randomized into 2 groups (Arms A, and B) at a 3:1 (Arm A: Arm B) ratio. A sample size of approximately 440 subjects will be randomized to Arms A and B to evaluate whether Arm A will result in prolongation of PFS when compared to Arm B in treatment naïve subjects with follicular lymphoma. The sample size is determined according to the Group Sequential Design. For this calculation, the references used for the assumptions were Hainsworth 2002, Ghielmini 2004, Zucca 2019, and Fowler 2020. Assuming exponential survival distribution for the PFS events and 66.7% improvement in median PFS of Arm A over Arm B (a hazard ratio [HR] of 0.60), the study has ~ 87% power with 200 observed PFS events using an overall 1-sided significance level of 0.025. Two interim analyses are planned. The first interim analysis (IA1) of futility will be conducted when approximately 55% of the 200 PFS events have occurred. The second interim analysis (IA2) for efficacy is planned after approximately 75% of the 200 events (150 PFS events) are observed and after the last subject has been enrolled. The futility boundary is based on a Rho parameter of 5 and the efficacy boundary is based on the unequally weighted Bonferroni method allocating 1-sided alpha of 0.001 to IA2 and 0.024 to primary analysis (PA).

ABBREVIATIONS

AE	adverse event
AESI	Adverse Events of Special Interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	antibody to hepatitis B core antigen
anti-HBs	antibody to hepatitis B surface antigen
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCL-2	B-cell lymphoma
BCR	B-cell receptor
BTK	Bruton's tyrosine kinase
BR	bendamustine and rituximab
BUN	blood urea nitrogen
CLL	chronic lymphocytic leukemia
CMH	Cochran-Mantel-Haenszel
COVID–19	Coronavirus Disease – 2019
CR	complete response
CR30	complete response rate at 30 months
CrCl	creatinine clearance
CRF	case report form (paper or electronic as appropriate for this study)
CT	computed tomography
CTCAE	NCI Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DMC	Data Monitoring Committee
DOR	duration of response
DSUR	Development safety update report
DTP	Direct-to-patient
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMR	electronic medical record
ESMO	European Society of Medical Oncology
EU	European Union
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-Lym	Functional Assessment of Cancer Therapy - Lymphoma

FDA	Food and Drug Administration
FCR	fludarabine, cyclophosphamide, and rituximab
FDG	fluorodeoxyglucose
FFPE	formalin-fixed, paraffin-embedded
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GCP	Good Clinical Practice
GELA	Group d'Etude des Lymphomes de l'Adulte
GELF	Group d'Etude des Lymphomes Folliculaire
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
IB	Investigator's Brochure
IBR	ibrutinib
IC_{50}	concentration that inhibits a process by 50%
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IIA	Investigator Information and Agreement
ILD	interstitial lung disease
IMP	Investigational medicinal product
INR	International normal ratio
IRB	Institutional Review Board
ITT	intent to treat
IUD	intrauterine device
IV	intravenous
IWG	International Working Group
IXRS	interactive voice and web response system
KM	Kaplan-Meier
LDH	lactate dehydrogenase
LDi	longest diameter
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease

MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression free survival
P-gp	P-glycoprotein
PI	prescribing information
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PO	per os; by mouth
PR	partial response
PRO	patient-reported outcome(s)
(a)PTT	(activated) partial thromboplastin time
PT	prothrombin time
QOL	Quality of life
R-CHOP	rituximab-cyclophosphamide, doxorubicin, vincristine and prednisone
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
REB	Research Ethics Board
SAR	Serious Adverse Reaction
SLL	small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
SPD	sum of the product of the greatest diameters
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV_{max}	maximum standard uptake value
$t_{1/2}$	half-life
T_{max}	time to maximum plasma concentration
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
ULN	upper limit of normal
US	United States

USPI	United States Prescribing Information
WHO	World Health Organization

1. BACKGROUND

1.1. Follicular Lymphoma

Follicular lymphoma (FL) is one of the most common types of Non-Hodgkin's Lymphoma (NHL) accounting for approximately 22% of cases and for about 70% of indolent lymphomas (Dreyling 2014). Follicular lymphoma is characterized by an indolent clinical course, typical morphology, and the presence of a chromosomal translocation, t(14;18)(q32;q21) or variant in 85% of patients (Relander 2010), which can result in the overexpression of the BCL-2 protein, a member of a family of proteins that blocks apoptosis. The overall incidence of B-cell lymphoid neoplasms in the United States (US) is estimated at 26.13/100,000 person-years (Morton 2006), with FL accounting for 3.18 new cases per 100,000 persons each year in the US and 5 to 7 new cases per 100,000 persons each year in the European Union (EU) (Dreyling 2014). The neoplastic lymphocytes in FL express pan-B markers CD19, CD20, CD22, and CD79a; as well as antigens of the germinal center (including CD10 and BCL-6). Histologically, the follicular form of NHL is composed mainly of centrocytes with an admixture of centroblasts. Grading is based on the number of large transformed cells in 10 malignant follicles viewed at high power (Martinez 2007). Follicular lymphoma is generally subdivided into 3 grades (Freedman 2014). However, Grade 3 is often further divided into 2 subgroups, 3a and 3b; with 3b considered more aggressive (Hans 2003).

Follicular lymphoma is diagnosed at a median age of 60 years with the majority of patients diagnosed at advanced stages of III and IV (Freedman 2014). Since FL is slow growing, it may take years for the disease to progress, during which time treatment may not be necessary. The indications for treatment often include the presence of symptomatic disease including B symptoms (fevers, night sweats, and weight loss), bulky lymphadenopathy or splenomegaly or both, compromise of normal organ function, the presence of cytopenias resulting from bone marrow involvement, or rapid disease progression (Freedman 2014; Gribben 2007).

The Groupe pour l'Etude de Lymphome Folliculaire (GELF) criteria have been developed from studies of the Groupe d'Etude des Lymphomes de l'Adulte (GELA) (Solal-Céligny 1998, Solal-Céligny 1993, Chen 2012) to evaluate risk factors and determine indications for initiating therapy in patients with treatment naïve FL Grade 1, 2 or 3a. The GELF criteria consider the number of involved nodal sites, diameter of nodal or extranodal tumor mass, presence of B symptoms, splenomegaly, pleural effusions/ascites, cytopenias, and presence of malignant cells in the peripheral blood. The presence of just one of the criteria (Table 1) justifies initiation of therapy (Férme 2005) since these factors are thought to represent clinically significant disease burden.

Table 1. The Groupe pour l'Etude de Lymphome Folliculaire (GELF) Criteria

GELF criteria
Involvement of ≥ 3 nodal sites, each with a diameter of >3 cm
Any nodal or extranodal tumor mass with a diameter of >7 cm or risk of local compressive symptoms that may result in organ compromise
B symptoms
Splenomegaly
Pleural effusions or peritoneal ascites
Cytopenias (leukocytes <1.0 x 10^9/L and/or platelets <100 x 10^9/L)
Leukemia (>5.0 x 10^9/L circulating malignant cells)

From: GELF criteria: A guide for the need for treatment of indolent lymphoma (Solal Céligny 1993, Chen 2012).

While the indications for treatment are based on GELF criteria, the choice of agent(s) depends on stage of disease as well as age and co-morbidities. Notably, the introduction of monoclonal antibodies, and of rituximab in particular, into FL therapy has resulted in substantial improvement in clinical outcomes (NCCN 2020, Dreyling 2014, Salles 2010).

1.1.1. Current Treatment Options

Treatment guidelines provided by both the National Comprehensive Cancer Network (NCCN) (NCCN 2020) and the European Society for Medical Oncology (ESMO) (Dreyling 2014) provide similar evidence-based recommendations for standard first-line and consolidation therapy for patients with advanced stage FL. These recommendations include rituximab with or without chemotherapy or radioimmunotherapy (NCCN 2020; Dreyling 2014). For additional information on treatments, tolerability, and clinical outcomes in FL please refer to Section 1.4.

1.2. Ibrutinib Overview

Ibrutinib (Imbruvica®) is a first-in-class, potent, orally administered, covalently binding inhibitor of Bruton's tyrosine kinase (BTK) co-developed by Pharmacyclics LLC and Janssen Research & Development LLC (collectively referred to as the Sponsor) for the treatment of B-cell malignancies.

Ibrutinib has been approved in many regions, including the US and EU, for indications including treatment of patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy, patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), including CLL with a deletion of the short arm of chromosome 17 (del17p), patients with Waldenström's macroglobulinemia, patients with Marginal Zone Lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy and for patients

with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy.

For the most up to date and comprehensive nonclinical and clinical information regarding ibrutinib background, safety, in vitro and in vivo preclinical activity, and toxicology of ibrutinib, refer to the latest version of the ibrutinib Investigator's Brochure (IB) and/or the applicable regional labeling information.

1.2.1. Summary of Nonclinical Data

1.2.1.1. Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of the BTK (Pan 2007). In vitro, ibrutinib is a potent inhibitor of BTK activity (IC_{50} 0.39 nM). The irreversible binding of ibrutinib to cysteine-481 in the active site of BTK results in sustained inhibition of BTK catalytic activity and enhanced selectivity over other kinases that do not contain a cysteine at this position. When added directly to human whole blood, ibrutinib inhibits signal transduction from the BCR and blocks primary B-cell activation (IC_{50} 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression (Herman 2011).

For more detailed and comprehensive information regarding nonclinical pharmacology and toxicology, please refer to the current ibrutinib IB.

1.2.1.2. Safety Pharmacology and Toxicology

No treatment-related effects were observed in the central nervous system or respiratory system in rats at any dose tested. Further, no treatment-related corrected QT interval (QTc) prolongation effect was observed at any tested dose in a cardiovascular study using telemetry-monitored dogs. Based on data from rat and dog including general toxicity studies up to 13 weeks duration, the greatest potential for human toxicity with ibrutinib is predicted to be in lymphoid tissues (lymphoid depletion) and the gastrointestinal tract (soft feces/diarrhea with or without inflammation). Additional toxicity findings seen in only one species with no observed human correlate in clinical studies to date include pancreatic acinar cell atrophy (rat), minimally decreased trabecular and cortical bone (rat) and corneal dystrophy (dog). In studies in pregnant rats and rabbits, ibrutinib administration was associated with malformations (teratogenicity) at ibrutinib doses that result in approximately 14 and 2 times the exposure (area under the concentration-time curve [AUC]) in patients administered the dose of 560 mg daily, respectively. Fetal loss and reduced fetal body weights were also seen in treated pregnant animals. Carcinogenicity studies have not been conducted with ibrutinib. In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. No effects on fertility or reproductive capacities were observed in a study in male and female rats.

For the most comprehensive information regarding nonclinical safety pharmacology and toxicology, please refer to the current ibrutinib IB.

1.2.2. Summary of Clinical Data

For the most comprehensive clinical information regarding ibrutinib, please refer to the current version of the ibrutinib IB.

1.2.2.1. Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging from 420 to 840 mg/day, exposure to ibrutinib increased proportionally to increasing doses with substantial intersubject variability. The mean half-life ($t_{1/2}$) of ibrutinib ranged from 4 to 13 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Taking into account the approximate doubling in mean systemic exposure when dosed with food and the favorable safety profile, ibrutinib can be dosed with or without food. Ibrutinib is extensively metabolized primarily by cytochrome P450 (CYP) 3A4. The on-target effects of metabolite PCI-45227 are not considered clinically relevant. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure. Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with creatinine clearance (CrCl) >30 mL/min. Patients with severe renal impairment or patients on dialysis have not been studied. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. A higher proportion of Grade 3 or higher adverse reactions were reported in patients with B-cell malignancies (CLL, MCL and WM) with mild hepatic impairment based on NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction compared to patients with normal hepatic function. For the most comprehensive information on pharmacokinetics (PK) and ibrutinib metabolism, please refer to the current version of the ibrutinib IB.

1.2.3. Summary of Clinical Safety

For comprehensive safety information please refer to the current version of the ibrutinib IB. Additional safety information may be available for approved indications in regional prescribing labels where the study is conducted (eg, Imbruvica® US Prescribing Information [USPI], Imbruvica® Summary of Product Characteristics [SmPC]).

1.2.4. Ibrutinib Risks

For more comprehensive risk information please refer to the current version of the ibrutinib IB and/or the applicable regional labeling information.

1.2.4.1. Bleeding-related Events

There have been reports of hemorrhagic events in patients treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria. Use of ibrutinib in patients requiring other

anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Patients with congenital bleeding diathesis have not been studied. See Section 6.2.3 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 6.4 for guidance on ibrutinib management with surgeries or procedures.

1.2.4.2. Cardiac Arrhythmias

Atrial fibrillation, atrial flutter, and cases of ventricular tachyarrhythmia including some fatal events, have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmia. Periodically monitor subjects clinically for cardiac arrhythmia. Subjects who develop arrhythmic symptoms (eg, palpitations, lightheadedness, syncope, chest discomfort or new onset of dyspnea) should be evaluated clinically and, if indicated, have an ECG performed. For cardiac arrhythmias which persist, consider the risks and benefits of ibrutinib treatment and follow the dose modification guidelines (see Section 5.3.1.4).

1.2.4.3. Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in patients treated with ibrutinib.

1.2.4.4. Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 5.3.1.4).

1.2.4.5. Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections. Although causality has not been established, cases of progressive multifocal leukoencephalopathy and hepatitis B reactivation have occurred in subjects treated with ibrutinib. Cases of hepatitis E, which may be chronic, have occurred in patients treated with ibrutinib. Subjects should be monitored for signs and symptoms (such as fever, chills, weakness, confusion, vomiting and jaundice, and abnormal liver function tests) and appropriate therapy should be instituted as indicated.

1.2.4.6. Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in patients treated with ibrutinib. Monitor patients for pulmonary symptoms indicative of ILD. Should symptoms develop follow the protocol dose modification guidelines (see Section 5.3.1.4).

1.2.4.7. Non-Melanoma Skin Cancer

Non-melanoma skin cancers have occurred in patients treated with ibrutinib. Monitor subjects for the appearance of non-melanoma skin cancer.

1.2.4.8. Rash

Rash has been commonly reported in patients treated with either single agent ibrutinib or in combination with chemotherapy. In a randomized Phase 3 study (PCYC-1112-CA), rash occurred at a higher rate in the ibrutinib arm than in the control arm. Most rashes were mild to moderate in severity.

1.2.4.9. Tumor Lysis Syndrome

There have been reports of tumor lysis syndrome (TLS) events in patients treated with single-agent ibrutinib or in combination with chemotherapy. Patients at risk of TLS are those with comorbidities and/or risk factors such as high tumor burden prior to treatment, increased uric acid (hyperuricemia), elevated lactate dehydrogenase (LDH), bulky disease at baseline, and pre-existing kidney abnormalities.

1.3. Rituximab Overview

1.3.1. Summary of Nonclinical Data

Rituximab (Rituxan®, Mabthera®) is a chimeric murine/human monoclonal antibody that is directed specifically against the B-cell antigen CD20 (Tedder and Engel 1994). In preclinical studies, rituximab was shown to induce both complement-mediated and antibody-dependent, cell mediated lysis of $CD20^+$ cells (Reff 1994). Rituximab also induces apoptosis in vitro and sensitizes drug-resistant human B-cell lymphoma cell lines to the cytotoxic effects of some chemotherapeutic agents (Maloney 1996, Demidem 1996).

1.3.2. Summary of Clinical Safety

In patients with NHL receiving rituximab monotherapy, NCI-CTC Grade 3 and 4 cytopenias were reported in 48% of patients. These included lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1-588 days) and of neutropenia was 13 days (range, 2-116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following rituximab therapy occurred during the single-arm studies. In studies of monotherapy, rituximab-induced B-cell depletion occurred in 70% to 80% of patients with NHL. Decreased IgM and IgG serum levels occurred in 14% of these patients (Rituxan® USPI 2021).

Specific safety considerations regarding the use of rituximab detailed in the rituximab regional prescribing information are described below (MabThera® SmPC 2023, Rituxan® USPI 2021).

1.3.2.1. Infusion Reactions

Rituximab can cause severe, including fatal, infusion reactions. Severe reactions typically occurred during the first infusion with time to onset of 30-120 minutes. Rituximab-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death. Premedicate patients with an antihistamine and acetaminophen prior to dosing.

In the majority of patients with NHL, infusion reactions consisting of fever, chills/rigors, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension occurred during the first rituximab infusion. Infusion reactions typically occurred within 30 to 120 minutes of beginning the first infusion and resolved with slowing or interruption of the rituximab infusion and with supportive care (diphenhydramine, acetaminophen, and intravenous saline). The incidence of infusion reactions was highest during the first infusion (77%) and decreased with each subsequent infusion.

1.3.2.2. Mucocutaneous Reactions

Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with rituximab.

These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has been variable and includes reports with onset on the first day of rituximab exposure.

1.3.2.3. Hepatitis B Reactivation with Fulminant Hepatitis

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including rituximab. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation also has occurred in patients who appear to have resolved hepatitis B infection (ie, HBsAg negative, anti-HBc positive and hepatitis B surface antibody [anti-HBs] positive).

1.3.2.4. Progressive Multifocal Leukoencephalopathy

John Cunningham virus (JCV) infection resulting in PML and death can occur in rituximab-treated patients with hematologic malignancies or with autoimmune diseases. The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant.

1.3.2.5. Tumor Lysis Syndrome

Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, some fatal, can occur within 12-24 hours after the first infusion of rituximab in patients with NHL. A high number of circulating malignant cells ($\geq$25,000/mm^3) or high tumor burden confers a greater risk of TLS.

1.3.2.6. Infections

Serious infections, including fatalities, can occur during therapy with rituximab. Serious infections (NCI CTCAE Grade 3 or 4), including sepsis, occurred in less than 5% of patients with NHL in the single-arm studies.

1.3.2.7. Cardiac Disorders

Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after all infusions of rituximab for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina.

1.3.2.8. Renal Toxicity

Severe, including fatal, renal toxicity can occur after rituximab administration in patients with NHL. Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy during clinical trials. Monitor closely for signs of renal failure and discontinue rituximab in patients with a rising serum creatinine or oliguria.

1.3.2.9. Bowel Obstruction and Perforation

Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in patients receiving rituximab in combination with chemotherapy. In postmarketing reports, the mean time to documented gastrointestinal perforation was 6 (range 1-77) days in patients with NHL. Evaluate if symptoms of obstruction such as abdominal pain or repeated vomiting occur.

For additional clinical safety information for rituximab, please refer to the current regional prescribing information.

1.4. Study Rationale

1.4.1. Preclinical

Bruton's Tyrosine Kinase is a central mediator of BCR signaling and is essential for normal B-cell development. Aberrant signaling of the B-cell receptor pathway has been linked to the development and maintenance of B-cell malignancies. Subtypes of NHL may be dependent on chronic activation of the BCR pathway and primary FL cells have been found to maintain enhanced signaling when compared to normal B-cells (Irish 2006).

1.4.2. Study PCYC-04753

Because of the central role of BCR signaling, the restricted expression of BTK within B lymphocytes, and promising preclinical activity, ibrutinib was evaluated in study PCYC-04753, a first-in-human, Phase 1, dose-escalating study of ibrutinib in subjects with recurrent B-cell lymphoma including NHL, CLL, FL, MCL, and WM (Advani 2013). Five sequential cohorts of subjects received ibrutinib from 1.25 to 12.5 mg/kg/day for 28 days of a 35-day cycle and 2 additional cohorts received a continuous ibrutinib dose of 8.3 mg/kg/day or a 560-mg fixed dose. Sixty-six (66) subjects were enrolled including 16 subjects with FL. Of the 16 subjects with FL, 13 (81.5%) were evaluable for response. The ORR for these 13 subjects was 46%, with 3 complete responses (CR, 23.1%) and 3 partial responses (PR, 23.1%). Four (30.8%) of the seven remaining subjects had stable disease (SD). The most common AEs (>20% of subjects) in this population were diarrhea, nausea/vomiting, fatigue, muscle spasms/myalgia, cough, decreased appetite and pyrexia (Advani 2013). Subjects with stable disease or better, who received therapy for 6 months, continued ibrutinib at a fixed dose of 560 mg/day in the extension study (PCYC-1103-CA) until progression or unacceptable toxicity.

1.4.3. Study PCYC-1125-CA

Study PCYC-1125-CA was an open-label, multicenter Phase 2 study designed to assess the efficacy and safety of ibrutinib combined with rituximab in treatment naïve subjects with FL (ClinicalTrials.gov identifier NCT01980654). The study was fully enrolled with 80 subjects in two separate treatment arms with 61 subjects in the main clinical study arm (Arm 1) (60 received study drug) and 20 subjects in the exploratory biomarker study arm (Arm 2) (Fowler 2020). Arm 2 used a different dosing regimen than the main study arm and was designed to explore biomarkers that may predict sensitivity or resistance to ibrutinib.

This phase 2 study evaluated the activity and safety of ibrutinib plus rituximab in adults with previously untreated FL. Patients received once-daily ibrutinib 560 mg continuously plus once-weekly rituximab 375 mg/m2 for 4 weeks beginning Week 1 (Arm 1, n 60) or Week 9 (following an 8-week ibrutinib lead-in) to explore biomarkers (Arm 2, n 20). The primary endpoint was the best overall response rate (ORR). The median age was 58 years; most had an ECOG Performance Status of 0 (74%) and Stage III/IV disease (84%). At a median study follow-up of 34 months in Arm 1 and 29 months in Arm 2, ORRs were 85% [95% confidence interval (CI) 73 93] and 75% (95% CI 51 91), respectively, with complete responses in 40% and 50%. The median duration of response was not reached in either arm; 30-month progression-free and overall survival rates were 67% and 97% (Arm 1) and 65% and 100% (Arm 2). The most common adverse events were fatigue, diarrhoea and nausea. Higher grade (Grade 3 or 4) haematological, haemorrhagic and cardiac events occurred infrequently. Ibrutinib plus rituximab was active and tolerable in first-line follicular lymphoma (Fowler 2020).

In conclusion, the combination of ibrutinib with four weekly infusions of rituximab demonstrated clinical activity and durable responses in first-line FL. This combination was well

tolerated, with a manageable overall safety profile consistent with those of single-agent ibrutinib or rituximab (Fowler 2020).

1.4.4. Overall Rationale for Study PCYC-1141-CA

Despite the improvements in the treatment of FL, the disease remains incurable; thus, there is a continued need to optimize treatment outcomes. Given the toxicity seen with standard combination treatment regimens in patients who are elderly or infirm, an initial chemotherapy-free regimen such as rituximab and ibrutinib may be an attractive treatment option if found to be well tolerated and to have significant anti-tumor activity. Data from clinical trials in high-risk CLL and MCL have shown that the combination of ibrutinib and rituximab has a favorable safety profile with enhanced efficacy (Burger 2014, Wang 2014). The clinical efficacy and tolerability observed in the Phase 2 study of ibrutinib in combination with rituximab in treatment naïve FL (PCYC-1125-CA) serves as the basis for study PCYC-1141-CA, a randomized, double-blind, placebo-controlled, multicenter Phase 3 study to evaluate the efficacy and safety of ibrutinib in combination with rituximab versus placebo in combination with rituximab in treatment naïve subjects with FL.

To date, ibrutinib administration in an indolent lymphoma setting has been daily treatment until disease progression.

1.4.4.1. Study Population and Treatment Rationale

Treatment guidelines provided by both the National Comprehensive Cancer Network (NCCN) (NCCN 2020) and the European Society for Medical Oncology (ESMO) (Dreyling 2014) provide similar evidence-based recommendations for standard first-line and maintenance therapy for patients with advanced-stage FL. These recommendations include rituximab with or without chemotherapy, or radio-immunotherapy (NCCN 2020; Dreyling 2014). In the treatment naïve population, rituximab-based chemo-immunotherapy regimens have demonstrated overall response rates in excess of 85% with complete remissions in the range of 20-60% with subsequent periods of median progression-free survival exceeding 4 to 5 years (Rummel 2012, Marcus 2007, Czuczman 2005, Hiddemann 2005, Peterson 2003) when administered to a population with a median age less than 65 years with good performance status (Flinn 2014, Rummel 2013, Salles 2010). To date, no comparative randomized studies have shown superiority of one chemo-immunotherapy regimen over another with regards to overall survival outcomes. Addition of rituximab as maintenance treatment improves the response rate and disease-free interval (Salles 2010; Hainsworth 2003, Colombat 2001).

Data are available to support a comparable survival advantage for older patients whose initial therapy is less intense, such as with rituximab monotherapy (Casulo 2015). Age-defined, risk-factor adjusted, subgroup analyses conducted using a prospective, multicenter registry that enrolled 2,652 FL patients from 2004 to 2007 (the National LymphoCare Study) have shown no difference in overall survival (OS) among patients 71-80 and >80 years of age who received rituximab monotherapy compared to those who received rituximab plus chemotherapy

(Casulo 2015). In the cohort of patients 61-70 years of age, representing approximately 25% of the study population (Nabhan 2012), the overall survival appears to favor rituximab monotherapy in the front-line setting (Casulo 2015).

PFS was similar between the cohorts of patients 71-80 and >80 years of age who received rituximab plus chemotherapy compared to rituximab monotherapy. Among the cohort of patients 61-70 years of age, there was a trend toward improved PFS outcomes with rituximab plus chemotherapy compared to rituximab monotherapy (Casulo 2015). Overall, the efficacy findings in this study regarding PFS and OS support the use of rituximab monotherapy followed by maintenance as a reasonable treatment option for patients 60 years of age and older.

Clinical practice guidelines acknowledge that chemo-immunotherapy regimens may not be tolerable for all patients. Patients 60-69 years of age with diminished performance status (eg, ECOG 2) or decreased renal function are at risk of toxicity and have inferior outcomes on standard chemo-immunotherapy regimens (Beumer 2016, Fischer 2012, Hurria 2005). For elderly or infirm (for whom the aforementioned regimens are not expected to be tolerable in the opinion of the treating physician), rituximab monotherapy is a preferred choice over single-agent alkylators with or without rituximab in part due to the lower rates of nonhematologic and hematologic toxicity (NCCN 2020). Rituximab monotherapy has significant clinical activity in treatment naïve patients with indolent NHL with response rates of 47-73% in newly diagnosed FL following four weekly doses of 375 mg/m^2 (Hainsworth 2002, Colombat 2001). Additional exposure to rituximab as maintenance therapy given at a dose of 375 mg/m^2 weekly for four weeks every six months, further improves response rates and complete remission rates with a median PFS following the addition of maintenance rituximab dosing reaching 34 months (Hainsworth 2002). Similarly, rituximab maintenance given at a dose of 375 mg/m^2 every 2 months for four doses resulted in a median event-free survival of 36 months (Ghielmini 2004).

Treatment with maintenance rituximab after a response to induction therapy appears to be an effective and tolerable approach for extending the duration of disease remission including event-free and progression-free survival. Various dosing schedules for maintenance treatment have been investigated including a single dose given every 2 or 3 months and once-weekly dosing for 4 weeks every 6 months for up to 2 years following induction therapy. In a meta-analysis of all randomized trials, similar improvements in response were seen regardless of the maintenance schedule used with no one regimen being clearly superior (Vidal 2011, Vidal 2009).

While there are a number of available therapies for patients with previously untreated FL, these regimens are typically chemo-immunotherapy, which may not be well-tolerated by all patients and none of these are curative, highlighting the need for novel, effective treatment options with a favorable toxicity profile. Thus, there is a medical need for treatments that can be combined with existing therapies to provide durable clinical benefit without added toxicities.

A new, chemotherapy-free treatment combination was tested by SAKK 35/10 (Swiss Group for Clinical Cancer Research) and the Nordic Lymphoma Group (NLG) comparing single-agent

rituximab and rituximab plus lenalidomide as first-line treatment for symptomatic grade 1 3a FL patients in need of systemic therapy. Patients were randomized to rituximab (375 mg/m2 IV on day 1 of weeks 1-4 and repeated during weeks 12-15 in responding patients) or rituximab (same schedule) in combination with lenalidomide (15 mg orally daily for 18 weeks). Primary end point was complete response (CR)/un-confirmed CR (CRu) rate at 6 months. In total, 77 patients were allocated to rituximab monotherapy and 77 to the combination (47% poor-risk Follicular Lymphoma International Index score in each arm). A significantly higher CR/CRu rate at 6 months was documented in the combination arm by the investigators (36%; 95% confidence interval [CI],26%-48% vs 25%; 95% CI, 16%-36%) and confirmed by an independent response review of computed tomography scans only (61%; 95% CI, 49%-72% vs 36%; 95% CI, 26%-48%). After a median follow-up of 4 years, significantly higher 30-month CR/CRu rates and longer progression-free survival (PFS) (5.0 vs 2.3 years; HR, 0.60 [95% CI: 0.38-0.97], p 0.035) and time to next treatment (TTNT) were observed for the patients in the combination arm. Overall survival (OS) rates were similar in both arms (≥ 90%). Toxicity grade ≥ 3 was more common in the combination arm (56% vs 22% of patients), mainly represented by neutropenia (23% vs 7%). Addition of lenalidomide to rituximab significantly improved CR/CRu rates, PFS, and TTNT, with expected higher, but manageable toxicity. The excellent OS in both arms suggests that chemotherapy-free strategies should be further explored (Zucca 2019).

The choice of rituximab as background therapy in the frontline treatment of FL is based on the recommendations in the NCCN and ESMO guidelines (NCCN 2020, Dreyling 2014). In these guidelines, rituximab is considered the treatment of choice for patients who are elderly or infirm (NCCN 2020, Dreyling 2014). In addition, the previously described Phase 2 study (PCYC-1125-CA) adding rituximab to ibrutinib demonstrates robust clinical activity with a high overall response rate in treatment naïve patients with FL; here the combination was well tolerated for the eligible population (Fowler 2020).

1.4.4.2. Dose Selection Rationale

The dose for ibrutinib in study PCYC-1141-CA is 560 mg (4 x 140-mg capsules) administered once daily without interruption. The 560 mg daily dose of ibrutinib was selected as the recommended dose in combination with rituximab based on clinical data. In the Phase 1 study (PCYC-04753 including similar mg/kg/day doses), the extension study (PCYC-1103-CA), and Phase 2 study (PCYC-1125-CA), the 560 mg dose administered once daily appeared safe and led to favorable responses in subjects with FL (Advani 2013, Fowler 2020). The dose for rituximab in cycle 1 is 375 mg/m^2 administered intravenously once weekly for 4 weeks. This dose was given in two single-arm studies that form the basis for the NCCN guidelines for rituximab in the first-line setting (Hainsworth 2002, Colombat 2001). Beginning with cycle 3, rituximab maintenance is given as a 375 mg/m^2 intravenous dose every 8 weeks up to 12 doses (approximately 2 years) or until disease progression. This dose and frequency is consistent with the FDA and EMA-approved labeling (MabThera® SmPC 2023, Rituxan® USPI 2021).

The assessment of pharmacokinetics is important in understanding both safety and efficacy in this patient population. The study includes a sparse pharmacokinetic sampling strategy for population pharmacokinetic purposes, which will serve as a means to derive the individual subject's ibrutinib exposure. In addition to determination of subject-covariates that influence the pharmacokinetics of ibrutinib, this may provide supportive evidence for the efficacy and safety analyses, and identify at-risk subjects who require a dose-adaptation. Furthermore, rituximab exposure with or without ibrutinib combination treatment will also be examined.

2. STUDY OBJECTIVE

2.1. Primary Objective

- To evaluate whether the addition of ibrutinib to rituximab will result in prolongation of progression-free survival (PFS) when compared with rituximab alone in treatment naïve subjects with follicular lymphoma

2.2. Secondary Objective(s)

- Evaluate whether the addition of ibrutinib to rituximab will result in improvement in investigator-assessed ORR when compared with rituximab alone in treatment naïve subjects with follicular lymphoma
- To evaluate whether the addition of ibrutinib to rituximab will result in a reduction in infusion-related reactions
- To evaluate whether the addition of ibrutinib to rituximab will result in prolongation of OS
- To evaluate whether the addition of ibrutinib to rituximab will result in prolongation of duration of response (DOR)
- To evaluate the safety and tolerability of ibrutinib combined with rituximab compared to rituximab alone in treatment naïve subjects with follicular lymphoma

2.3. Exploratory Objective(s)

- To compare treatment groups with regards to patient reported lymphoma symptoms and health-related QOL as measured by the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym)
- To characterize the pharmacokinetics of ibrutinib and rituximab and explore the potential relationships between ibrutinib metrics of exposure with relevant clinical or biomarker information
- To evaluate and/or identify patient populations defined by relevant biomarker(s)
- To evaluate the minimal residual disease (MRD)-negative rate defined as the proportion of follicular lymphoma subjects who achieve a CR and who reach MRD-negative disease status

- To evaluate whether the addition of ibrutinib to rituximab will result in improvement of the investigator-assessed CR30 when compared with rituximab alone in treatment naïve subjects with follicular lymphoma

The statistical analysis methods and final set of exploratory endpoints are detailed in the Statistical Analysis Plan (SAP); if there are any variances between both documents the SAP takes precedence.

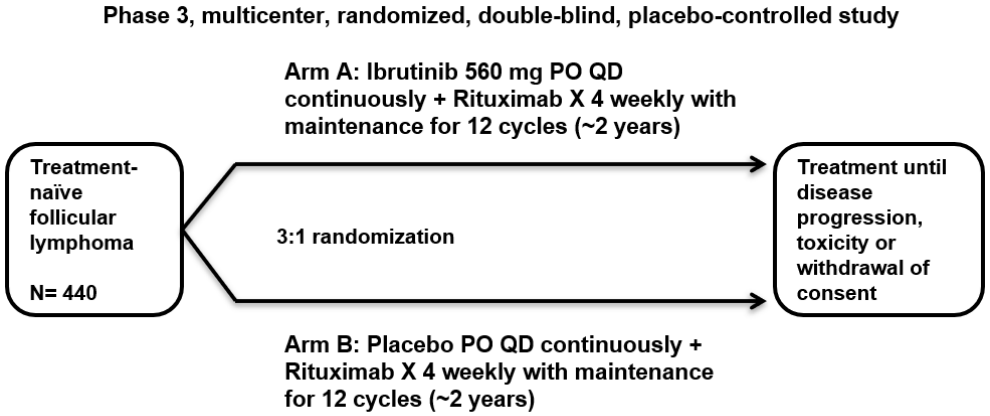
3. STUDY DESIGN

3.1. Overview of Study Design

The rationale for the study concept is provided in Section 1.4.

This is a randomized, double-blind, placebo-controlled Phase 3 study designed to assess the efficacy and safety of ibrutinib in combination with rituximab compared to placebo in combination with rituximab in treatment naïve subjects with follicular lymphoma. The methodology used for these analyses is outlined in the Statistical methods (Section 10).

Figure 1. Study Design



Stratification factors:
Age (60-69 vs. ≥ 70 years)
FLIPI-1 score low vs. intermediate/high
ECOG performance status 0/1 vs. 2

Approximately 440 subjects will be enrolled (estimate based on an accrual assumption of 30 months). Subjects will be randomized at a 3:1 ratio to Arm A and B, respectively. Subjects will be stratified on the basis of: (a) age (60-69 vs. ≥70 years), (b) Follicular Lymphoma-specific International Prognostic Index (FLIPI)-1 score (low vs. intermediate/high) and (c) ECOG performance status score (0/1 vs. 2).

Subjects randomized to the investigational arm (Arm A) will receive ibrutinib 560 mg PO daily until disease progression or unacceptable toxicity. Subjects randomized to the control arm (Arm B) will receive placebo PO (4 capsules) daily until disease progression or unacceptable toxicity.

Subjects in both arms (Arm A and B) will also receive rituximab 375 mg/m^2 IV once weekly for the first 4 weeks of study treatment (Cycle 1: Days 1, 8, 15, and 22). Beginning with Cycle 3, Day 1, rituximab will be given as maintenance therapy administered as a single dose of 375 mg/m^2 IV every 8 weeks up to 12 additional doses (approximately 2 years) or until disease progression or unacceptable toxicity, whichever comes first. Two interim analyses are planned: the first interim analysis (IA1) is for futility and is planned at approximately 55% information; and the second interim analysis (IA2) is for efficacy and is planned after approximately 75% information (150 PFS events) is observed and after the last subject has been enrolled.

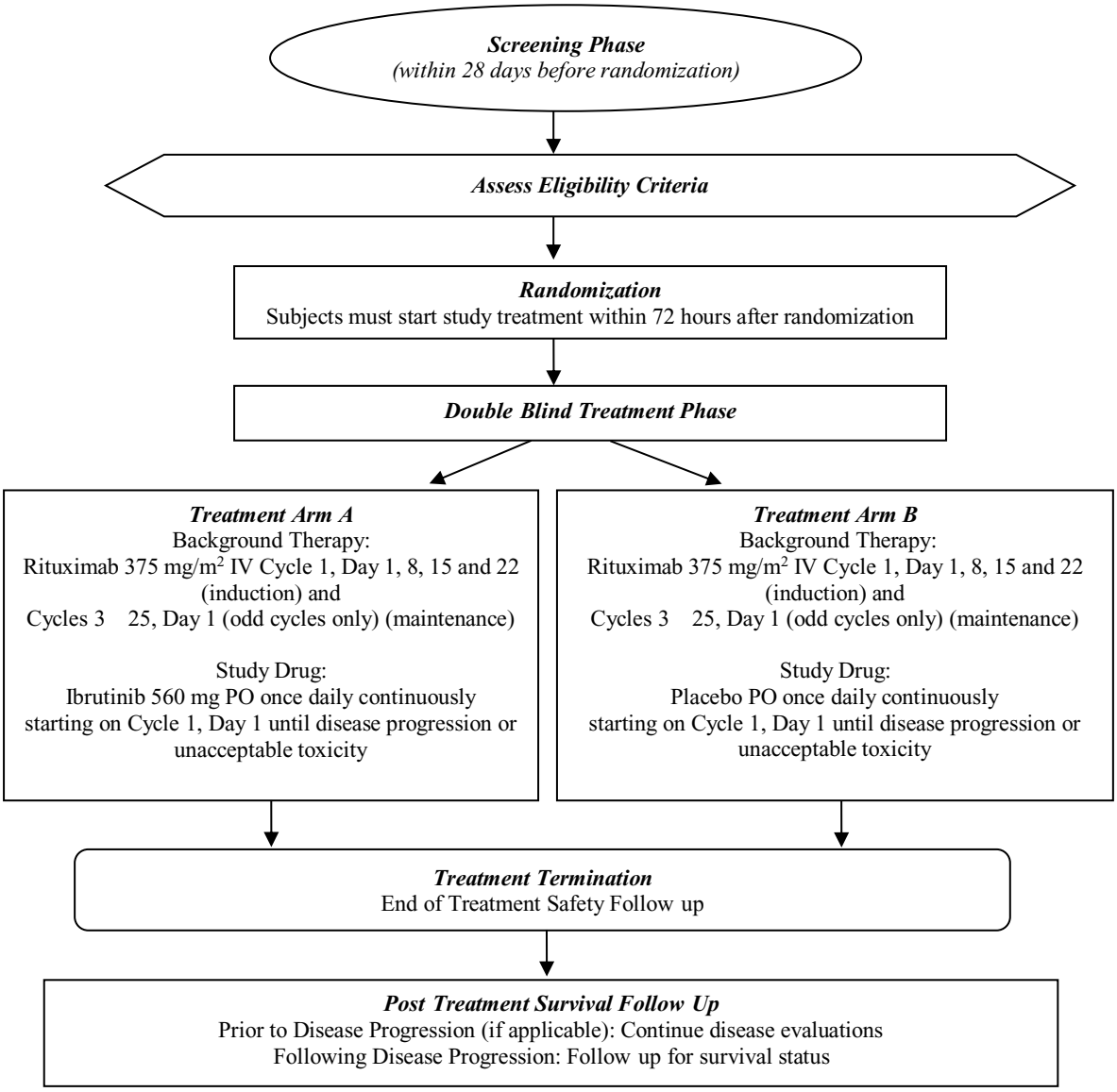
Primary analysis for PFS will be conducted when 200 PFS events are observed, or if pre-specified boundaries are crossed at an interim analysis. The final analysis for OS is planned when 165 OS events are observed or five years after enrollment of the last subject, whichever is earlier.

A Response Evaluation Visit including local imaging assessments will be performed every 16 weeks through Cycle 37 and then every 24 weeks thereafter and copies of the images will be stored at a central location for independent review-based assessment. The detail of the analyses will be specified in a separate document. Blinded study treatment administration will continue until disease progression, unacceptable toxicity, withdrawal of consent or study termination.

Subjects who discontinue study treatment due to any reason other than withdrawal of consent for follow-up will be followed for overall survival every 24 weeks. Subsequent anticancer therapies, best response to therapy, and information about other malignancies will also be collected.

Assessment of tumor response and progression, safety and tolerability, and pharmacokinetics and biomarkers will be evaluated at time points throughout the study. Please refer to Section 7 and Section 8 and the Schedule of Assessments (Appendix A) for details.

3.2. Study Schema



4. SUBJECT SELECTION

Screening for eligible subjects will be performed within 28 days before randomization. Computed tomography/magnetic resonance imaging (CT/MRI) and PET may be performed up to 60 days before randomization. Bone marrow aspirate and biopsy may be performed up to 60 days before randomization, at the latest prior to the first dose of study treatment.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. Investigators must ensure that all inclusion and exclusion criteria have been satisfied at Screening. Retesting during the Screening Period is allowed. A subject is considered eligible if the last observation before randomization and first study treatment dose satisfies the inclusion and exclusion criteria. If a subject's status changes (including laboratory results or receipt of additional medical records) after Screening but before randomization or first study treatment dose such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before obtaining randomization for a subject in the study. The eligibility in question will be confirmed by the appropriate sponsor representative prior to randomization.

Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 12.6, Study Files and Record Retention.

4.1. Inclusion Criteria

Prior to randomization each potential subject must satisfy all of the following inclusion criteria.

Disease-Related

1. Subjects with histologically documented follicular lymphoma $CD20^+$ (Grade 1, 2 or 3a) according to World Health Organization (WHO) criteria; Ann Arbor Stage II, III or IV disease.
   - Prior to randomization, diagnosis must be confirmed by local pathology report stating a diagnosis of follicular lymphoma. If the report from the local laboratory is not available or insufficient (if not including all the following information: FL diagnosis, $CD20^+$ and Grade), the diagnosis must be confirmed by the central pathology laboratory (Section 7.1.1.5).
2. At least one two-dimensionally measurable lesion ≥2.0 cm in longest diameter (LDi) by contrast-enhanced CT scan. Lesions in anatomical locations (such as extremities or soft tissue lesions) that are not well visualized by CT may be measured by MRI instead.
3. Subjects 70 years of age or older; OR subjects 60-69 years of age who have **one or more** comorbidities that make them a candidate to receive single-agent rituximab therapy:

- Creatinine clearance 30-59 mL/min (by Cockcroft-Gault). Alternatively, creatinine clearance may be calculated based on a 24-hour urine collection.
- ECOG performance status score of 2

4. In need of systemic therapy as evidenced by meeting **one or more** of the following Groupe d'Etude des Lymphomes Folliculaire (GELF) criteria (Solal-Céligny 1998, Chen 2012):

- Involvement of ≥3 nodal sites, each with a diameter of >3 cm
- Any nodal or extranodal tumor mass with a diameter of >7 cm or risk of local compressive symptoms that may result in organ compromise
- B symptoms (ie, fever, night sweats or weight loss)
- Splenomegaly
- Pleural effusions or peritoneal ascites
- Thrombocytopenia (platelet count <100 x 10^9/L)
- Peripheral blood involvement (>5.0 x 10^9/L malignant cells)

Laboratory

5. Adequate hematologic function defined as:

- Hemoglobin ≥8.0 g/dL
- Platelet count ≥50 x 10^9/L (50,000 cells/mm^3)
- Absolute neutrophil count (ANC) ≥1.0 x 10^9/L (1,000 cells/mm^3)

6. Adequate renal and hepatic function defined as:

- Estimated Creatinine Clearance ≥30 mL/min (Cockcroft-Gault)
- Serum aspartate transaminase (AST) and alanine transaminase (ALT) ≤3 x upper limit of normal (ULN)
- Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome such that bilirubin ≤3 x ULN or is of non-hepatic origin)

7. PT/INR <1.5 x ULN (unless treated with warfarin or other vitamin K antagonists such that INR ≤3.0) and PTT (aPTT) <1.5 x ULN

Demographic

8. Eastern Cooperative Oncology Group (ECOG) performance status score of 0-2.

Ethical/Other

9. Female subjects of reproductive potential must have a negative urine/serum pregnancy test upon study entry. Female subjects who are of non-reproductive potential (ie, post menopausal by history - no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy) are exempt from pregnancy testing.

10. Male and female subjects of reproductive potential who agree to use both a highly effective method of birth control (eg, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence[2], or sterilized partner) and a barrier method (eg, condoms, cervical ring, sponge, etc) during the period of therapy. For female subjects, these birth control requirements must be adhered to for 90 days after the last dose of ibrutinib/placebo and 12 months after the last dose of rituximab, whichever is later. For male subjects, these birth control requirements must be adhered to for 90 days after the last dose of ibrutinib/placebo.
11. Subjects must not be incarcerated and must be freely willing and able to provide informed consent (e.g., adults under legal protection measure [e.g., under guardianship/curatorship] or unable to express their consent and select adults under psychiatric care). Investigator's discretion should be applied.

4.2. Exclusion Criteria

To be enrolled in the study, potential subjects must meet NONE of the following exclusion criteria:

Disease-Related

1. Transformed lymphoma; if clinical evidence of transformed lymphoma is present (high lactate dehydrogenase [LDH] and/or high maximum standard uptake value [SUV_{max}] of a lymph node/lesion on positron emission tomography [PET] scanning, LDH and SUV_{max} level cutoff per investigator's clinical judgement), transformation should be ruled out by biopsy of the suspicious lymph node/lesion.
2. Prior treatment for follicular lymphoma (eg, systemic anti-cancer therapy or involved site radiotherapy).
3. Medically apparent central nervous system lymphoma or leptomeningeal disease.

Concurrent Conditions

4. History of other malignancies, except:
   - Malignancy treated with curative intent and with no known active disease present for ≥3 years before the first dose of study treatment and felt to be at low risk for recurrence by treating physician.
   - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.

[2] Complete abstinence is a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. http://www.hma.eu/fileadmin/dateien/Human Medicines/01 About HMA/Working Groups/CTFG/2014 09 HMA CTFG Contraception.pdf

- Adequately treated carcinoma in situ without evidence of disease.

5. Concurrent systemic immunosuppressant therapy (eg, cyclosporine A, tacrolimus, etc., or chronic administration of >20 mg/day of prednisone or equivalent) within 28 days of the first dose of study treatment. For indications other than lymphoma or management of lymphoma-related symptoms, the following are **exceptions** to this criterion:
   - Intranasal, inhaled, topical corticosteroids or local corticosteroid injections (eg, intra-articular injection)
   - Systemic corticosteroids at doses not to exceed 20 mg/day of prednisone or its equivalent
   - Corticosteroids as pre-medication for hypersensitivity reactions (eg, CT scan pre-medication)
6. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study treatment.
7. Known bleeding disorders (eg, von Willebrand's disease or hemophilia).
8. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
9. Known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded. In equivocal cases, hepatitis B or C PCR may be performed and must be negative for enrollment.
10. Any uncontrolled active systemic infection or recent infection requiring intravenous antibiotic treatment that was completed ≤14 days before the first dose of study treatment.
11. Major surgery within 4 weeks of first dose of study treatment.
12. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.
13. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization.
14. Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.
15. Known anaphylaxis or IgE-mediated hypersensitivity to murine proteins or to any component of rituximab.

16. Prior use of an anti-CD20 agent or an inhibitor of Bruton's tyrosine kinase (BTK) (eg, rituximab, ibrutinib) (NOTE: use of any prior treatment for follicular lymphoma is not permitted per protocol).
17. Any investigational drug within 4 weeks prior to randomization or concurrent enrollment in another therapeutic investigational clinical treatment study.
18. Subject who received systemic administration of a strong cytochrome P (CYP) 450 3A inhibitor within 7 days prior to the first dose of ibrutinib or subject who requires continuous treatment with a strong CYP 450 3A inhibitor (see Appendix C).
19. Currently active, clinically significant hepatic impairment Child-Pugh class B or C according to the Child Pugh classification (see Appendix F).
20. Lactating or pregnant.
21. Unwilling or unable to participate in all required study evaluations and procedures.
22. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).

5. TREATMENT OF SUBJECTS

5.1. Treatment Allocation and Blinding

5.1.1. Randomization, Stratification and Placebo Control

Central randomization will be implemented in this study. Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Two randomization schemes will be generated: one for each geographic region (North America versus Rest of World). Under each scheme, subjects will be randomized based on the following stratification factors:

- Age 60-69 vs. ≥70 years
- FLIPI-1 score at Screening (low vs. intermediate/high)
- ECOG performance status score (0/1 vs. 2)

Subjects will be randomized at a 3:1 ratio to receive either Treatment Arm A (ibrutinib/rituximab) or Treatment Arm B (placebo/rituximab) within each randomization stratum. A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment.

Subjects who discontinue study treatment due to any reason other than withdrawal of consent for follow-up will be followed for overall survival. Subsequent anticancer therapies, best response to therapy, and information about other malignancies will be collected.

The interactive voice or web response system (IXRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study treatment kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IXRS, and will then provide the relevant subject details to uniquely identify the subject.

5.1.2. Blinding

Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints. This is a double-blind study; therefore, subjects, investigators, and the Sponsor's study team members will remain blinded to treatment assignment. The investigator will not be provided with randomization codes.

Data that may potentially unblind the treatment assignment (i.e., study drug plasma concentrations) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This may include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and/or unblinding.

Under normal circumstances, the blind should not be broken. The blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IXRS. It is recommended that the investigator contact the sponsor or its designee, if possible, to discuss the particular situation before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in the source documents. The documentation received from the IXRS indicating the code break must be retained with the subject's source documents in a secure manner. A subject whose treatment assignment has been unblinded may continue the study treatment if receiving clinical benefit and the subject should continue to return for scheduled study evaluations. The single-blind (i.e., subject remains blinded to treatment assignment) should be maintained provided the subject's safety is not compromised.

Subjects, investigators, and the sponsor's study team members will remain blinded to treatment assignment until the primary analysis is completed. Examples of personnel who may be unblinded during the study are:

- The independent DMC, and the independent biostatistician and statistical programmers from an independent Statistical Support Group who are responsible for preparing interim tables, listings, and graphs for DMC review. Unblinding procedures and the control of the unblinded data are described in the DMC charter.
- Sponsor's representative responsible for pharmacokinetics testing and analysis.
- Sponsor safety representative to fulfill regulatory reporting requirements for suspected unexpected serious adverse events.

- In case of an urgent safety concern, site personnel and the sponsor may be unblinded, if treatment assignment information is needed to determine further actions to address the urgent safety concern (e.g., life-threatening event, medication error, such as an accidental overdose).

5.2. Study Treatment

- All eligible subjects for randomization will be treated with rituximab in combination with either ibrutinib (Arm A) or matching placebo (Arm B) according to the dose and schedule outlined in Table 2.
- Treatment with ibrutinib or placebo, referred to as study drug, will continue until disease progression, unacceptable toxicity, withdrawal of consent for treatment, or study end, whichever comes first. All subjects treated in this study will follow guidelines for dosing and toxicity management as described in Section 5.3.1 and Section 5.3.2 of the protocol for study drug (ibrutinib/placebo) and rituximab, respectively.

5.2.1. Route and Schedule

Table 2. Treatment, Dose, and Schedule of Administration for Study Treatment

Study Treatment	Dose and Schedule of Administration
Study drug (ibrutinib/placebo)	4 x 140 mg capsules (560 mg ibrutinib or placebo) orally administered daily beginning from Cycle 1, Day 1 (at least 24 cycles).
Rituximab	375 mg/m^2 IV per regional prescribing information administered weekly for four consecutive weeks, beginning from Cycle 1, Day 1, followed by maintenance rituximab administered every 8 weeks up to 12 doses (approximately 2 years) beginning Cycle 3, Day 1.
	Rituximab administration days: Cycle 1, Days 1, 8, 15, 22 and Cycle 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23 and 25 on Day 1 (a total of 16 doses of rituximab will be given during the study). NOTE: No rituximab will be given in Cycle 2.

5.3. Study Medications

5.3.1. Ibrutinib/Placebo (Study Drug)

For the purposes of this study, study drug refers to both ibrutinib and placebo, the blinded label study drug. All subjects will follow the guidelines for ibrutinib dosing and toxicity management. Ibrutinib/placebo should be administered as described in Table 2 until one or more of the discontinuation criteria in Section 9.2 are met.

5.3.1.1. Ibrutinib/Placebo: Formulation/Packaging/Storage

Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib IB for a list of excipients.

Matching placebo capsules are provided as a hard gelatin capsule and look identical to ibrutinib capsules.

The ibrutinib and placebo capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. Study drug (ibrutinib/placebo) will be dispensed in child-resistant packaging.

Refer to the Pharmacy Manual/site investigational product manual for additional guidance on study drug storage, preparation and handling.

5.3.1.2. Ibrutinib/Placebo: Dose and Administration

Study drug (ibrutinib/placebo) is recommended to be self-administered on an outpatient basis. Blinded study medication will be administered for continuous daily dosing.

Study drug (4 capsules) is administered orally once daily. The capsules are to be taken around the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study (Section 6.2.1 and Appendix C).

If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose.

The first dose will be delivered in the clinic on Cycle 1, Day 1, after which subsequent dosing will be self-administered daily by the subjects typically on an outpatient basis. Please refer to Table 3 and Section 8 for oral dose and administration instructions on pharmacokinetic visits; on these days, study drug will be administered in clinic as soon as the subject comes into clinic and after pre-dosing procedures. Pre-medications and rituximab will then be administered as outlined in Section 5.3.2.2.

Study drug will be dispensed to subjects in bottles. Unused study drug must be returned to the site and drug accountability records (Section 12.8) updated. Returned capsules must not be redispensed to anyone.

Study drug is continuous (without interruptions) throughout the Treatment Phase. If rituximab infusion is delayed due to scheduling conflicts or toxicity, study drug dosing should continue.

Table 3. Study Drug (Ibrutinib/Placebo) Administration

Study Drug	**Ibrutinib/placebo**
Schedule of Administration	Daily
Route/Regimen	Oral In-clinic dosing days (Cycle 1, Day 1 and 22; Cycle 3, Day 1): supervised by site staff; given as soon as the subject comes into clinic and after pre-dosing procedures. Pre-medications and rituximab will then be administered. Home administration days: self-administered by subject.
Dose	560 mg (4 x 140 mg capsules) or placebo
Dosing Instructions	Take the study drug around the same time each day with approximately 8 ounces of water. Swallow capsules whole (shouldn't open, break, or chew). A missed dose is taken as soon as possible on the same day, with a return to the normal schedule the following day. Extra capsules to make up for a missed dose should not be taken. For days with rituximab scheduled but not in-clinic dosing days as indicated above, take the study drug prior to clinic visit.

COVID-19 Pandemic-Related Direct-to-Patient Shipments

If a subject is unable to come to the study site to pick up their study drug due to COVID-19, study drug may be shipped from the study site directly to the study subject's home via a direct-to-patient (DTP) shipment if the following criteria are met:

- DTP shipment of study drug is allowed by local regulations and the relevant ethics committee
- Subject agrees to have the study drug shipped directly to their home.

Of note:

- Shipments may also include other study supplies (e.g., drug dosing diaries, paper copies of PROs).
- Instructions will be provided by AbbVie as to how a study site can initiate a DTP shipment using Marken, a global vendor selected by AbbVie to provide this service when necessary. Shipments of study drugs from the study site to a subject's home will be appropriately temperature controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; due to COVID-19-related social distancing, this may be provided by the courier after delivery. Documentation of the shipment is to be retained by the clinical site.
- AbbVie will not receive subject identifying information related to these shipments, as the site will work directly with the courier.

The study site is responsible for meeting IRB/IEC reporting requirements related to DTP shipments of study drug, and for obtaining consent to provide delivery information to the courier and documenting this consent in source documents.

5.3.1.3. Ibrutinib/Placebo: Overdose

There is no specific experience in the management of ibrutinib overdose in subjects. No maximum tolerated dose (MTD) was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1400 mg/day). Healthy subjects were exposed up to single dose of 1680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Subjects who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment (ibrutinib IB).

Refer to Section 11.3 for further information regarding special reporting situations as a result of overdose.

5.3.1.4. Ibrutinib/Placebo: Dose Modification for Ibrutinib/Placebo-Related Adverse Reactions

For an ibrutinib/placebo-related adverse reaction, the recommendations for dose modification of ibrutinib/placebo are provided in Table 4 and Table 5 if any of the following hematologic or non-hematologic toxicities occur:

- Grade 3 or greater neutropenia with infection or fever
- Grade 4 neutropenia (ANC<500/µL) for more than 7 days. See Section 6.1 for instructions regarding the use of growth factor support.
- Grade 3 thrombocytopenia (platelets<50,000/µL) in the presence of clinically significant bleeding events.
- Grade 4 thrombocytopenia (platelets<25,000/µL).
- Grade 3 or greater non-hematological toxicity (Note: Table 5 recommendations for Grade 3 or higher cardiac failure and cardiac arrhythmias)
- Grade 2 cardiac failure (Table 5)
- Any other Grade 4 or unmanageable Grade 3 hematological toxicity.

If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation (Section 6.2.3).

For other grade 3 or 4 AEs, and grade 2 AEs that are deemed per the investigator potentially manageable by dose reduction, these can be managed with a one dose level dose reduction.

In the event that the investigator feels deviation from the recommendations above is required, please consult the Medical Monitor to discuss.

If administration of study drug is delayed or discontinued for toxicity that does not require rituximab to be held for toxicity, rituximab dosing should continue at the investigator's discretion.

Study drug should be discontinued in the event of a toxicity considered to be related to study drug requiring a dose hold lasting more than 28 days, unless reviewed and approved by the Medical Monitor.

Dose changes must be recorded in the Dose Administration eCRF.

Table 4. Ibrutinib/Placebo: Study Drug Dose Modifications for Events not Specified in Table 5

Occurrence	Action to be Taken
First	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at original dose level (ie, 4 capsules [560 mg/day])[a]
Second	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (ie, 3 capsules [420 mg/day])
Third	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (ie, 2 capsules [280 mg/day])
Fourth	Discontinue study drug

a. When resuming treatment, restart at the same or lower dose based on benefit risk evaluation. If the toxicity reoccurs, reduce daily dose by 140 mg.

For required dose modification for hepatic impairment refer to Section 5.3.1.5 and for concomitant treatment with CYP3A inhibitors refer to Section 6.2.1. If a subject is being dosed at 280 mg due to hepatic impairment or concurrent CYP3A inhibitor administration, dose level is to be reduced by one capsule to 140 mg at the second occurrence of AEs as described above.

Table 5. Ibrutinib Dose Modifications for Cardiac Failure or Cardiac Arrhythmias

Events	Occurrence	Action
Grade 2 cardiac failure	First	Hold study drug until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (3 capsules [ie, 420 mg daily])
	Second	Hold study drug until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (2 capsules [ie, 280 mg daily])
	Third	Discontinue study drug
Grade 3 cardiac arrhythmias	First	Hold study drug until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (3 capsules [ie, 420 mg daily])[a]
	Second	Discontinue study drug
Grade 3 or 4 cardiac failure Grade 4 cardiac arrhythmias	First	Discontinue study drug

a. Evaluate the benefit risk before resuming treatment.

5.3.1.5. Ibrutinib/Placebo: Dose Modification for Hepatic Impaired Subjects

Ibrutinib is metabolized in the liver and therefore subjects with clinically significant hepatic impairment at the time of Screening (Child-Pugh class B or C) are excluded from study participation. For subjects who have at enrollment or develop mild liver impairment while on study (Child-Pugh class A), the recommended dose reduction for ibrutinib/placebo is to a level of 280 mg daily (two capsules). For subjects who develop moderate liver impairment while on study (Child-Pugh class B), the recommended dose reduction is to a level of 140 mg daily (one capsule). Subjects who develop severe hepatic impairment (Child-Pugh class C) must hold study drug until resolved to moderate impairment (Child-Pugh class B) or better. Monitor subjects for signs of toxicity and follow dose modification guidance as needed (refer to Appendix F).

5.3.2. Rituximab

Rituximab (Rituxan®) is indicated for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent (MabThera® SmPC 2023, Rituxan® USPI 2021). In addition, rituximab, as a single-agent is currently a recommended therapy for elderly or infirm patients with previously untreated FL per clinical guidelines (NCCN 2020, Dreyling 2014).

All subjects in Arms A and B will receive rituximab and will follow the regional labeling information for rituximab premedication, dosing and toxicity management (MabThera® SmPC 2023, Rituxan® USPI 2021).

5.3.2.1. Rituximab: Formulation/Package/Storage

Rituximab is a highly purified 1328-amino acid antibody with an approximate molecular weight of 145 kd. The chimeric mouse/human anti-CD20 antibody is a glycosylated IgG1 immunoglobulin containing murine light- and heavy-chain variable regions and human γ1 heavychain and κ light-chain constant regions. Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration. Rituximab is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for IV administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Sterile Water for Injection. The pH is adjusted to 6.5 (MabThera® SmPC 2023, Rituxan® USPI 2021).

Rituximab vials should be stored refrigerated between 2°C to 8°C (36°F to 46°F). Vials should be protected from light. Do not freeze or shake.

For more information regarding stability and storage refer to the Pharmacy Manual and regional labeling information (MabThera® SmPC 2023, Rituxan® USPI 2021).

5.3.2.2. Rituximab: Dose and Administration

The first dose of rituximab will be administered IV beginning on Cycle 1, Day 1 in the Induction portion (Cycle 1) of the Treatment Phase. Rituximab will continue to be administered at the clinical site weekly for a total of four consecutive weekly doses. Rituximab doses during induction may be adjusted within a 3-day window due to scheduling conflicts. A minimum of 5 days between doses of rituximab is required.

Maintenance administration of rituximab will begin on Cycle 3, Day 1 of the Treatment Phase (5 weeks ± 3 days after the last induction treatment on Cycle 1, Day 22) and continue every 8 weeks for a total of 12 doses (Cycle 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, and 25 on Day 1). Rituximab doses during Cycle 3 may be adjusted within a 3-day window. For Cycle 5 and beyond, rituximab maintenance administration visits may be adjusted within a 7-day window due to scheduling conflicts.

Dosage calculations for rituximab will be based on the subject's body surface area (BSA) based on height and weight obtained at the Screening visit. Actual body weight will be used for dose calculations. If the height and weight were not recorded at Screening, they may be obtained on Cycle 1, Day 1 and used for the dose calculations. Dose modification for changes in a subject's weight are not required per protocol but may be performed per institutional standard.

Rituximab will be administered IV by clinic staff according to the regional prescribing information. Premedication consisting of an analgesic/antipyretic (e.g., acetaminophen or paracetamol) and an antihistamine (e.g., diphenhydramine) should always be administered before each infusion of rituximab as outlined in the regional product information

(MabThera® SmPC 2023, Rituxan® USPI 2021). Premedication will be given prior to each administration. Rituximab should not be mixed or diluted with other drugs.

In the event of an infusion reaction, institute medical management (e.g., glucocorticoids, epinephrine, bronchodilators, or oxygen), as appropriate. If hypersensitivity (non-IgE-mediated) or an infusion reaction develops, the infusion should be temporarily slowed or interrupted.

Depending on the severity of the infusion reaction and the required interventions, treatment with rituximab may be temporarily or permanently discontinued. See Section 5.3.2.5 for further instructions.

Some individual subjects may require close monitoring during the first and all subsequent infusions, e.g., subjects who have pre-existing cardiac or pulmonary conditions, prior clinically significant cardiopulmonary AEs or high numbers of circulating malignant cells (≥25,000/mm^3) with or without evidence of high tumor burden.

Unused rituximab must be disposed of according to the sites drug disposal policy and drug accountability records updated.

5.3.2.3. Rituximab: Overdose

There has been no experience with overdose in human clinical trials. The highest intravenous dose of rituximab tested in humans to date is 5000 mg (2250 mg/m^2), tested in a dose escalation study in subjects with chronic lymphocytic leukemia. No additional safety signals were identified (MabThera® SmPC 2023).

Subjects who experience overdose should have immediate interruption of their infusion and be closely monitored (MabThera® SmPC 2023).

In the postmarketing setting, five cases of rituximab overdose have been reported. Three cases had no reported adverse event. The two adverse events that were reported were flu-like symptoms, with a dose of 1.8 g of rituximab and fatal respiratory failure, with a dose of 2 g of rituximab (MabThera® SmPC 2023).

Refer to Section 11.3 for further information regarding special reporting situations as a result of overdose.

5.3.2.4. Rituximab: Dose Modification for Rituximab-Related Adverse Reactions

At the investigator's discretion, the rituximab dose should be held for any unmanageable, potentially rituximab-related toxicity that is consistent with the regional prescribing information and the rules outlined in this section. Rituximab should be held for any rituximab-related Grade 4 toxicity or for any, clinically significant, unmanageable potentially rituximab-related non-hematological Grade 3 adverse events. Rituximab may be held for a maximum of 28 consecutive days for a rituximab-related toxicity, unless reviewed and approved by the Medical Monitor.

The dose of rituximab should be modified according to the dose modification guidelines in Table 6 if any Grade 4 or unmanageable non-hematologic Grade 3 toxicity attributed to rituximab occurs. Dose modifications of rituximab must be recorded in the case report form (CRF).

Table 6. Rituximab: Dose Modification for Toxicity

Occurrence	Action to be Taken
First, Second, Third	Withhold rituximab until recovery to Grade ≤1 or baseline; may restart at original dose level
Fourth	Discontinue rituximab[a]

a. If rituximab is discontinued for toxicity prior to the completion of induction treatment (Cycle 1), the subject will discontinue study drug and be followed for progression. If rituximab is discontinued for toxicity during the maintenance phase, the subject may continue on study drug.

Note: for guidance on management of rituximab in relation to infusion reactions see Section 5.3.2.5.

A missed dose of rituximab during the induction phase in Cycle 1 for any reason will not be made up (i.e., the dose will be skipped) during Cycle 1; the visit window for Cycle 1 is ± 3 days.

- If the subject skips dosing of rituximab during Cycle 1 due to reasons other than not being able to tolerate rituximab, subject can make up the induction phase dosing as soon as possible during Cycle 2 as long as there is a minimum of 5-day window between doses and 5-day window prior to Cycle 3 Day 1.
- If induction phase cannot be completed prior to 5 days of Cycle 3 Day 1, subject can begin maintenance rituximab dosing according to the protocol schedule if only one induction phase dose is missed. If more than one induction phase dose is missed, please contact PCYC Medical Monitors for further guidance.

A missed dose of rituximab during the maintenance phase in Cycles 3-25 may be given within the defined visit window (i.e., ± 3 days for Cycle 3 and ± 7 days for Cycles 5-25).

If rituximab dosing is delayed for toxicity that does not require study drug (ibrutinib/placebo) to be held for toxicity, administration of study drug should continue at the investigator's discretion. If a rituximab infusion is delayed due to scheduling delays, administration of study drug should continue.

Any other clinically important events where dose delays may be considered appropriate by the Investigator must be discussed with the Medical Monitor.

Upon recovery, subjects should resume the protocol-specified treatment schedule as soon as possible.

5.3.2.5. Rituximab: Dose Interruption for Infusion-Related Reactions

Modify administration of rituximab for infusion-related reactions of any severity as described below.

- For Grade 1 and 2 infusion-related reactions, slow the infusion rate by a minimum of 50% and monitor subject closely. Provide medical intervention as indicated. If symptoms resolve, complete the infusion at the decreased rate. If symptoms do not improve, or worsen, discontinue the infusion.
- For Grade 3 infusion-related reactions, interrupt the infusion, provide medical intervention as appropriate. Monitor subject closely and if symptoms resolve resume the infusion at 50% or less of the previous rate. If there is no return of symptoms, then complete the infusion at the decreased rate. If symptoms do not improve, or worsen, discontinue the infusion.
- For Grade 4 infusion-related reactions, stop the infusion. Provide appropriate medical intervention. Contact the Medical Monitor prior to re-challenge or if permanent discontinuation of rituximab is necessary.

5.3.2.6. Rituximab: Dose Reduction

There will be no dose reductions for rituximab. Particular attention should be paid to the Warnings and Precautions sections of the product label.

5.3.2.7. Rituximab: Dose Discontinuation

Rituximab should be discontinued in the event of a rituximab toxicity requiring a dose hold lasting more than 28 days, unless reviewed and approved by the Medical Monitor. If rituximab is discontinued for toxicity prior to the completion of induction treatment (Cycle 1), the subject will discontinue study drug (ibrutinib/placebo) and be followed for progression. If rituximab is discontinued for toxicity during the maintenance phase, the subject may continue on study drug.

5.4. Study Treatment Compliance

5.4.1. Study Drug (Ibrutinib/Placebo) Compliance

The study drug (ibrutinib/placebo) is to be prescribed only by the Principal Investigator or a qualified physician or other licensed prescriber listed as a Sub-Investigator on the Form FDA 1572/Investigator Information and Agreement (IIA). The study site personnel must maintain all study drug records in the study file, and record all study drug's dispensing and returning on the drug accountability form and in the subject's source documents. The study drug must not be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing. The IXRS will be used to assign study drug kits for each subject enrolled with each cohort assignment.

Drug supplies for each subject will be inventoried and accounted for throughout the study by the site personnel. Subjects will be provided with a subject diary card at the beginning of Day 1 of each cycle to record daily dosing. The site personnel must instruct the subjects to bring the completed subject diary card along with any used and unused study drug to each study visit. The site personnel must reconcile and document the returned capsules from the study subjects at each study visit to ensure compliance with study drug administration. Instructions for self-administration and storage conditions of study drug will be provided to the subjects by the site personnel. Precautions associated with the use of study drug and prohibited concomitant medications must be reviewed with the study subjects by the Investigator or qualified study site personnel. The site staff will provide additional instruction to re-educate any subject who is not compliant with the study drug dosing schedule.

5.4.2. Rituximab Compliance

Rituximab treatment will be administered by qualified study-site personnel. The site pharmacist or designee must document all rituximab treatment and premedications prepared for the infusion and administration in the subject's source documents. Drug supplies for each subject will be inventoried and accounted for throughout the study by the site personnel as appropriate. The infusion will be administered to the study subjects according to the approved prescribing information per protocol and/or institutional guidelines.

5.5. Criteria for Permanent Discontinuation of Study Treatment

Investigators are encouraged to keep a subject who is experiencing clinical benefit in the study unless significant toxicity puts the subject at risk or routine noncompliance puts the study outcomes at risk. For a complete list of criteria for permanent discontinuation of study treatment, refer to Section 9.2.

An End of Treatment Safety Follow up visit (Section 8.2.3) is required for all subjects except for those subjects who have withdrawn full consent.

5.6. Replacement of Subjects

If a subject discontinues study treatment at any time, the subject will not be replaced.

6. CONCOMITANT MEDICATIONS/PROCEDURES

Concomitant therapies must be recorded from the time of ICF signing and recorded continuously from the time of signing the ICF to 30 days after the last dose of study treatment.

6.1. Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) including prophylaxis for infusion-related reactions are permitted. Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is

permitted per institutional policy, in accordance with the ASCO guidelines (Smith 2006) or local/regional guidelines. Transfusions may be given in accordance with institutional policy.

After consultation with the Medical Monitor the following may be considered: hormonal or bone sparing treatment for non-B-cell malignancies, or localized radiotherapy for medical conditions other than the underlying B-cell malignancies.

Corticosteroids for non-cancer-related medical reasons at doses equivalent to ≤20 mg per day of prednisone or its equivalent are permitted. Corticosteroids as pre-medication for hypersensitivity reactions (e.g., CT scan pre-medication or infusion-related reaction) are also permitted. Short courses (less than 14 days) of corticosteroid treatment for non-cancer-related medical reasons (e.g., joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted. Corticosteroid treatment courses of 14 days or more may be considered after consultation with the Medical Monitor. For purposes of premedication or management of rituximab infusion reactions only, 100 mg prednisone (or its equivalent) per day may be exceeded.

COVID-19 Pandemic-Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., mRNA, non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during screening, the treatment period, or follow up, as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine is encouraged, but should be based on local guidance and an individual discussion between the treating physician and the subject.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine details eCRF. Refer to Section 11.4.9 for instructions on reporting any adverse events associated with the COVID-19 vaccine.

6.2. Medications to be Used with Caution

6.2.1. CYP3A Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A4. Concomitant use of ibrutinib and drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure and strong CYP3A inhibitors should be avoided.

- Strong inhibitors of CYP3A (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone, and cobicistat) should be avoided and an alternative with less CYP3A inhibitory potential should be considered. If the benefit outweighs the risk and a strong CYP3A inhibitor must be used, see recommended dose modifications in the table below.

- If a moderate CYP3A inhibitor (e.g., fluconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib, verapamil, amiodarone, dronedarone) is indicated, reduce ibrutinib dose as per recommended dose modifications in the table below. Avoid grapefruit and Seville oranges during ibrutinib/placebo treatment, as these contain moderate inhibitors of CYP3A (see Section 5.3.1.2).
- No dose adjustment is required in combination with mild inhibitors.

Recommended dose modifications are described below:

Patient Population	**Co-administered Drug**	**Recommended Ibrutinib Dose for the Duration of the Inhibitor Use**[a]
B-Cell Malignancies	• Mild CYP3A inhibitors	560 mg once daily per indication. No dose adjustment required.
	• Moderate CYP3A inhibitors	280 mg once daily.
	• Voriconazole • Posaconazole at doses less than or equal to suspension 200 mg BID	140 mg once daily.
	• Other strong CYP3A inhibitors • Posaconazole at higher doses[b]	• Avoid concomitant use and consider alternative with less CYP3A inhibitory potential. • If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib. • If the benefit outweighs the risk, and long-term dosing with a CYP3A inhibitor is required (more than seven days), reduce ibrutinib dose to 140 mg once daily for the duration of the inhibitor use.

a. Monitor for adverse reactions to ibrutinib and interrupt or modify dose as recommended (see Dosage and Administration).

b. Posaconazole at higher doses (posaconazole suspension 200 mg three times daily or 400 mg twice daily, posaconazole IV injection 300 mg once daily, posaconazole delayed release tablets 300 mg once daily).

Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

A list of common CYP3A inhibitors and inducers is provided in Appendix C. For further information, please refer to the current version of the ibrutinib IB and examples of inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

6.2.2. Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor. Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There are no clinical data available. Therefore, to avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin should be taken at least 6 hours before or after study drug.

6.2.3. Antiplatelet Agents and Anticoagulants

Warfarin or other vitamin K antagonists as well as supplements such as fish oil and vitamin E preparations should be avoided if possible. Use ibrutinib with caution in subjects requiring anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. Study drug should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding (see Section 6.4).

For subjects requiring the initiation of therapeutic anticoagulation therapy (eg, atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib/placebo should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. No dose reduction is required when study drug is restarted. Subjects should be observed closely for signs and symptoms of bleeding.

6.3. Prohibited Concomitant Medications

Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy is prohibited while the subject is receiving study treatment. See Section 6.1 for limited exceptions.

Corticosteroids for the treatment of the underlying malignancy are prohibited. Corticosteroids for non-cancer-related medical reasons at doses >20 mg per day of prednisone or equivalent for 14 days or longer are prohibited, unless approved by the Medical Monitor. See Section 6.1 for limited exceptions following consultation with the Medical Monitor.

The Medical Monitor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.4. Guidelines for Ibrutinib Management with Surgeries or Procedures

Ibrutinib may increase the risk of bleeding with invasive procedures or surgery. The following guidance should be applied to the use of ibrutinib in the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving study drug.

6.4.1. Minor Surgical Procedures

For minor procedures (such as a central line placement, needle biopsy, lumbar puncture [other than shunt reservoir access], thoracentesis, or paracentesis) study drug should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on study drug, it is not necessary to hold study drug.

6.4.2. Major Surgical Procedures

For any surgery or invasive procedure requiring sutures or staples for closure, study drug should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.

6.4.3. Emergency Procedures

For emergency procedures, study drug should be held as soon as possible until the surgical site is reasonably healed or for at least 7 days after the urgent surgical procedure, whichever is longer.

7. STUDY EVALUATIONS

7.1. Description of Procedures

7.1.1. Assessments

Screening clinical and laboratory assessments must be performed within 28 days of and prior to randomization.

7.1.1.1. Informed Consent

The subject must read, understand, and sign the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) approved ICF confirming his or her willingness to participate in this study before any study-specific screening procedures are performed. Subjects must also grant permission to use protected health information per the Health Insurance Portability and Accountability Act (HIPAA) or similar local requirement. In addition, subjects must sign all approved ICF amendments per the site IRB/REB/IEC guidelines during the course of the study.

7.1.1.2. Confirm Eligibility

All necessary procedures and evaluations must be performed to document that the subject meets all of the inclusion criteria and none of the exclusion criteria and prior to first dose on Day 1 (Section 4).

7.1.1.3. Medical History and Demographics

The subject's relevant medical history through review of medical records and by interview will be collected and recorded. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis will be recorded.

7.1.1.4. Follicular Lymphoma International Prognostic Index-1 (FLIPI-1)

The FLIPI-1 is a validated prognostic scoring system based on five adverse factors (Solal-Céligny 2004). The parameters include age, Ann Arbor stage, and number of nodal areas involved, hemoglobin levels and serum LDH levels (Table 10). Each of these adverse factors is assigned one point if positive, the points are totaled to give the final FLIPI-1 score and lymphoma prognoses are based on this score. See Appendix D.

7.1.1.5. Diagnostic Tissue Block(s) or Slides

Sites will be required to submit diagnostic biopsy materials (formalin-fixed, paraffin-embedded [FFPE] tissue block(s) or minimum 10 slides, preferably of lymph node origin) to a central laboratory for confirmation of diagnosis of FL. If an archived specimen is not available or contains insufficient material, a fresh tumor biopsy will be required. A portion of the FFPE tissue block or slides collected for confirmation of disease may be used for the assessment of molecular and genetic biomarkers. Prior to randomization, a copy of the report confirming the diagnosis of FL from the local laboratory may be acceptable to demonstrate a diagnosis of FL. This report, confirming the diagnosis of FL, may contain morphology, expression of B-cell lymphoma-2 (Bcl-2) in association with other relevant markers (e.g., CD10 and CD19) or evidence of t(14;18) as assessed by cytogenetics, fluorescent in situ hybridization (FISH), or polymerase chain reaction. A copy of the report containing this information must be sent to the central laboratory along with the diagnostic biopsy material. For subjects who do not have this diagnostic report available, a tumor tissue block or slides must be sent to the central laboratory and confirmation of FL diagnosis must be obtained from the central laboratory prior to enrollment.

7.1.1.6. Prior and Concomitant Medications

All active medications from the signing of ICF through 30 days after the last dose of study treatment will be documented.

7.1.1.7. Adverse Events

The accepted regulatory definition for an adverse event (AE) is provided in Section 11.1. The occurrence of AEs at the time the ICF is signed until the first dose of study treatment should be entered in the medical history in the eCRF. Any medical occurrence after the first dose with study treatment until 30 days after the last dose of study treatment that meet the AE definition must be recorded as an AE in the eCRF. Laboratory abnormalities designated clinically

significant by the investigator will also be documented as AEs. Additional important requirements for AE and SAE reporting are explained in Section 11.4

7.1.1.8. Physical Examination

The Screening and End of Treatment Safety Follow-up visit physical examination will include, at a minimum, the general appearance of the subject, height (Screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen and extremities, musculoskeletal system, nervous system, and lymphatic system. A limited symptom-directed physical examination is required at Day 1 of Cycle 1 and 2, Day 15 of Cycle 1, as well as Day 1 of each odd cycle starting at Cycle 3, Response Evaluation Visits and Treatment Termination and should include assessment of the lymphatic system, liver and spleen. See time points as specified in the Schedule of Assessments (Appendix A)

7.1.1.9. Eye-related Symptom Assessment

The subjects will be asked about eye-related symptoms at Screening and during each physical examination. See time points as specified in the Schedule of Assessments (Appendix A).

If there are any eye-related symptoms of severity Grade ≥2 at Screening or if the subject develops any eye-related symptoms of severity Grade ≥2 while on study treatment, an ophthalmologic evaluation/consult must be performed and the outcome must be reported on the ophthalmologic eCRF.

7.1.1.10. B-Symptoms

The subject will be asked about the occurrence of B-symptoms at Screening and at every Response Evaluation Visit. See time points as specified in the Schedule of Assessments (Appendix A). At Screening, collection of B-symptoms will include unexplained weight loss >10% within the last 6 months, unexplained fever >38°C for at least 3 consecutive days within the last 3 months, and drenching night sweats within the last 3 months. At every Response Evaluation Visit, collection of B-symptoms will include unexplained weight loss >10% within the last month, unexplained fever >38°C for at least 3 consecutive days within the last month, and drenching night sweats within the last month. Any new or worsening of a pre-existing B-symptom should be recorded as an AE.

7.1.1.11. ECOG

The ECOG performance status index is provided in Appendix B. The ECOG performance status will be assessed at time points specified in the Schedule of Assessments (Appendix A).

7.1.1.12. Vital Signs

Vital signs will include blood pressure, heart rate, and body temperature and will be assessed at time points specified in the Schedule of Assessments (Appendix A). Blood pressure should be obtained after the subject has been resting in the sitting position for at least 3 minutes.

7.1.1.13. Patient Reported Outcomes (PRO)

The PRO instrument FACT-Lym (Appendix H), will be administered to all randomized subjects in this study. These questionnaires are to be completed by the subject prior to any other study procedures at time points specified in the Schedule of Assessments (Appendix A).

The purpose of the FACT-Lym questionnaire is to provide an assessment of the subject's own functional status, well-being and lymphoma symptoms over time. The FACT-Lym was originally developed to assess functional status and well-being of patients with non-Hodgkin lymphoma (Eremenco 2004). Reliability and validity have been assessed in non-Hodgkin lymphoma (Webster 2005). The FACT-Lym consists of the Functional Assessment of Cancer Therapy - General (FACT-G) and a lymphoma specific additional concerns subscale (Lym). Responses to all items are rated on a 5-point scale ranging from 0 "not at all" to 4 "very much". The FACT-G consists of three 7 item subscales scored 0 to 28 (physical well-being, social well-being, and functional well-being) plus one 6 item subscale (emotional well-being) scored 0 to 24. The recall period is the past 7 days. The lymphoma scale includes 15 items and scores range from 0 to 60. Two summary scores may also be calculated: the FACT-Lym total score (FACT-G plus Lym) and the FACT-Lym trial outcome index (TOI) score (physical wellbeing+functional well-being+lymphoma). The subscale of most interest in this study will be the Lym subscale. Carter et al (Carter 2008) and Cella et al (Cella 2005) reported a minimal important change score for the Lym subscale in a relapsed/refractory MCL population range from approximately 2.9 to 5.4. Therefore, a 5-point change in the Lym subscale was selected as a conservative estimate of clinically meaningful deterioration in lymphoma symptoms. Time to complete the FACT-Lym is approximately 7 to 12 minutes. All translations not currently available will be completed according to best practices guidelines (Wild 2005).

7.1.2. Laboratory

7.1.2.1. Hematology

Hematology parameters will include a complete blood count: white blood cells, red blood cells, hemoglobin, hematocrit, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils. Hematology parameters will be evaluated using a central laboratory at time points specified in the Schedule of Assessments (Appendix A).

7.1.2.2. Chemistry (Serum)

Serum chemistry parameters will include sodium, potassium, chloride, blood urea nitrogen (BUN)/ urea, creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline

phosphatase, total bilirubin, LDH, phosphate, bicarbonate and uric acid. Serum chemistry parameters will be evaluated using a central laboratory at time points specified in the Schedule of Assessments (Appendix A).

7.1.2.3. Coagulation Studies

Measurement of PT/INR and aPTT will be evaluated using a central laboratory at time points specified in the Schedule of Assessments (Appendix A).

7.1.2.4. Hepatitis Serologies

Hepatitis serologies include hepatitis C antibody, hepatitis B surface antigen, and hepatitis B core antibody and will be evaluated using a central laboratory. If hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody is positive, then PCR to quantitate hepatitis B DNA or hepatitis C RNA must be performed and must be negative prior to randomization. In equivocal cases, hepatitis B or C PCR will be performed using a central laboratory and must be negative for enrollment.

7.1.2.5. Urinalysis

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. Urinalysis will be performed using a local laboratory at time points specified in the Schedule of Assessments (Appendix A).

7.1.2.6. Pregnancy Test

Serum or urine pregnancy test will be required at Screening by local laboratory only for women of reproductive potential. A serum or urine pregnancy test will also be performed on Day 1 prior to first dose. If positive, pregnancy must be ruled out by ultrasound to be eligible. A urine pregnancy test will be conducted using a local laboratory at time points specified in the Schedule of Assessments (Appendix A); if a time point is missed this can be performed at next visit. This test may be performed more frequently if required by local regulatory authorities.

7.1.3. Diagnostics/Procedures

7.1.3.1. Electrocardiograms (ECGs)

Electrocardiograms (ECGs) should be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (e.g., palpitations, lightheadedness, atrial fibrillation) or new onset dyspnea.

During visits in which both ECGs and blood draws are performed, ECGs should be performed first. At Screening and at the End of Treatment Safety Follow-up visit, a 12-lead ECG will be done in triplicate (≥1 minute apart). Subjects should be in a supine position and resting for at

least 10 minutes before obtaining the ECGs. Abnormalities noted at Screening should be included in the medical history.

7.1.3.2. Radiographic Imaging Assessments (CT/MRI)

Pretreatment tumor assessment will be performed within 60 days before randomization, at the latest prior to the first dose of study treatment. A CT scan (with contrast unless contraindicated) of the neck, chest, abdomen, and pelvis and any other disease sites **and** a PET scan are required for the pretreatment tumor assessment. Information on extranodal involvement (e.g., gastric or ocular disease) will also be recorded in the source documents. Lesions in anatomical locations that are not well visualized by CT may be measured by MRI instead.

In the case where CT with contrast is contraindicated, an alternative would be MRI with gadolinium contrast of the abdomen and pelvis and CT of the chest and neck without contrast. In this case, neck nodes cannot be used as target lesions. Subjects who have baseline target lesions identified by neck CT obtained with contrast and then cannot receive contrast for a post-dose neck CT will have the involved target lesions included in the response assessment.

NOTE: PET/CT hybrid scanners may be used to acquire the required CT images only if the CT produced by the scanner is of diagnostic quality, adheres to the specified slice thickness/scan parameters, and includes the use of intravenous (IV) contrast. Additionally, the CT images must be separated from the PET data prior to submitting the data to the imaging vendor, and cannot be transmitted as fused CT/PET images.

If using a hybrid machine to acquire both PET and CT, the PET must be performed prior to the CT with IV contrast as to not compromise PET results.

If independent CT and PET scanners are used, and the subject is receiving both scans on the same day, the PET must be performed prior to the CT with IV contrast.

De-identified copies of all scans and radiology reports (including those from Screening) must be provided to the Sponsor or designee (e.g., central imaging vendor). At the Sponsor's discretion, the Sponsor or its designee may conduct an independent review of the scans for disease response evaluation.

7.1.3.3. Positron Emission Tomography (PET) Scan

Whole body FDG-PET scan (skull base to the proximal femur) will be performed for Screening purpose up to 60 days before randomization, at the latest prior to the first dose of study treatment and should be considered at the time of maximal tumor reduction to confirm CR if the scan was positive or indeterminate at Screening.

Assessment of PET results is based on published criteria (Cheson 2014).

7.1.3.4. Tumor Tissue Biopsy (Optional)

It is strongly recommended that a fresh tumor biopsy (excision, core needle biopsy, or fine needle aspiration) should be collected at disease progression for biomarker assessments.

7.1.3.5. Bone Marrow Biopsies and Aspirate for Bone Marrow Involvement

At Screening or up to 60 days before randomization or prior to first study treatment dose at the latest, a unilateral bone marrow core biopsy must be obtained and a sample should be sent to the local laboratory for bone marrow involvement assessment and to the central laboratory if samples are available. In cases where the bone marrow core biopsy cannot be obtained due to access related or patient condition related issues the bone marrow aspirate sample should be obtained instead. The Screening bone marrow biopsy/aspirate will be assessed at a local pathology laboratory (by the site) to determine bone marrow involvement with lymphoma.

To confirm CR if bone marrow involvement was positive or indeterminate at Screening, bone marrow core biopsy, or aspirate if biopsy not possible, assessments should be performed in a local laboratory. A sample of the bone marrow biopsy or aspirate should be sent to the central laboratory for central review if available. It is preferable that the bone marrow biopsy or aspirate be performed within 30 days of initial documentation of CR.

The following material will be sent to the central laboratory at Screening for all subjects and to confirm CR if bone marrow was positive at Screening:

- Any remaining bone marrow core biopsy for potential confirmation of bone marrow involvement
- Any remaining bone marrow aspirate for potential confirmation of bone marrow involvement
- Copies of redacted pathology reports for contemporaneous samples reviewed locally

Refer to the laboratory manual for instructions on collecting and processing of these samples.

7.1.3.6. Bone Marrow Aspirate and Blood Samples for Minimal Residual Disease (MRD)

Assessment of MRD in bone marrow aspirate

In subjects with positive bone marrow involvement by histology at baseline (Screening), samples of bone marrow aspirate will be collected for MRD analysis. The bone marrow aspirates (bone marrow core biopsies are not suitable for MRD analysis due to calcification) will be sent to a central laboratory for MRD analysis. Bone marrow aspirates for MRD will be collected as follows: 1) At Screening or up to 60 days before randomization or prior to the first study treatment dose at the latest; 2) At the time of radiographic complete response (CR), preferably within 30 days of initial documented CR.

Assessment of MRD in peripheral blood

Samples of peripheral blood will be collected for MRD analysis for all enrolled subjects. The peripheral blood samples will be sent to a central laboratory for MRD analysis. Peripheral blood for MRD analysis will be collected as follows: 1) At Screening or Cycle 1 Day 1 Pre-dose; 2) At clinical complete response (CR); 3) At every disease assessment visit (every 16 weeks until Cycle 37, then every 24 weeks thereafter) after first CR visit.

Peripheral blood MRD samples should also be collected in patients who meet the criteria for a CR based on CT scan (clinical complete response), however, are unable to undergo a bone marrow biopsy in order to analyse MRD after potential CR as per Appendix G.

MRD-negative is defined as undetectable MRD in a bone marrow aspirate and/or peripheral blood from each subject who has achieved a clinical complete response.

MRD-positive relapse is defined as a detectable increase in disease, in a peripheral blood and/or bone marrow aspirate sample.

Refer to the laboratory manual for instructions on collecting and processing of these samples.

7.1.4. Pharmacokinetics/Biomarkers

7.1.4.1. Pharmacokinetics

Plasma concentrations of ibrutinib and metabolite PCI-45227 and serum concentrations of rituximab will be determined using validated analytical methods. Other potential metabolites of ibrutinib may be explored. Refer to the Schedule of Assessments (Appendix A) and the Pharmacokinetic Sample Schedules (Table 7 and Table 8). Refer to the laboratory manual for instructions on collecting and processing these samples.

On the days of study drug PK sampling, the clinical staff will instruct the subject to not take their study drug before arrival at the clinic (i.e., Cycle 1, Day 22 and Cycle 3, Day 1). Study drug intake will be observed by clinic staff. The actual time (versus requested time) that each sample is drawn must be recorded using a 24-hour format. The same clock should be used for recording the time of dosing.

Table 7. Pharmacokinetic Sample Schedule for Study Drug (Ibrutinib/Placebo)

Arms	Cycle	Day	Pre-dose[a]	Time After Dosing[b]		
				1h ± 15 min	2 h ± 15 min	4 h ± 30 min
A and B	1	22	X	X	X	X
	3	1	X			

a. Pre dose samples should be collected prior to the administration of ibrutinib/placebo and rituximab

b. Time after dosing of ibrutinib/placebo

Table 8. Pharmacokinetic Sample Schedule for Rituximab

Arms	Cycle	Day(s)	Pre-dose[b]
A and B	1	1[a], 8, 15, 22[a]	X
	3	1[a]	X
	5	1	X
	7	1	X
	9	1	X
	11	1	X

a. Pre dose samples should be collected prior to the administration of ibrutinib/placebo and rituximab

b. Pre dose samples should be collected prior to the administration of rituximab

7.1.4.2. Exploratory Genetic and Molecular Biomarkers

Peripheral blood samples and a buccal swab will be collected and sent to the central laboratory at selected timepoints specified in the Schedule of Assessments (Appendix A). Tumor cells from peripheral blood, bone marrow and/or tumor tissue may be studied for gene and/or protein expression profiling including but not limited to Bcl-2 gene and protein expression, as well as gene sequencing to identify genomic alterations in BTK and other related kinases or critical genes. These efforts may identify biomarkers that could support the understanding of the disease and that could associate with response/resistance to ibrutinib treatment.

Biological specimens collected at specified time points during the study may be used for pharmacodynamic and biomarker assessments including kinase activity, sequencing expression analysis, immunophenotyping (T cell repertoire) and secreted protein analyses.

Samples collected in this study may be stored at a central lab for up to 10 years (or according to local regulations) for additional research. Samples will only be used to better understand the effects of ibrutinib and rituximab, to understand FL, to understand sensitivity or resistance to the investigational products tested in this study, and to develop tests/assays related to ibrutinib and rituximab and FL. The research may begin at any time during the study or the post-study storage period. Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers.

7.2. Efficacy Evaluations

Eligible subjects must have at least 1 measurable site of disease by radiological assessment (Cheson 2014). Efficacy evaluations will be conducted as specified in the Schedule of Assessments (Appendix A) and may include the following: computed tomography (CT) scans, magnetic resonance imaging (MRI), positron emission tomography (PET) using [18F]-fluorodeoxyglucose (FDG), bone marrow aspirate and biopsy, physical examination including lymphoma B symptoms, or other procedures as necessary. These assessments should be

performed throughout the study at each time point using the same method of assessment used to assess disease at baseline. If study drug (ibrutinib/placebo) is held before a scheduled response assessment, then the response assessment can be delayed up to 2 weeks to allow re-initiation of study drug prior to the scheduled response assessment. Images will be sent to a central imaging vendor. Subject self-reported lymphoma related symptoms and concerns will be measured by the lymphoma subscale of the FACT-Lym (Appendix H).

Response assessments will be completed by the investigator using the revised criteria for malignant lymphoma described by the International Working Group for NHL (Cheson 2014). At Screening, up to six target lesions will be selected and will be followed for the duration of the study. All target lesions must be followed and mentioned in the radiology report at all subsequent response assessments.

Lesions in anatomical locations that are not well visualized by CT may be measured by MRI instead.

Caution must be exercised not to confuse a possible tumor flare with progressive disease. Delayed responses after a tumor flare have been reported in follicular lymphoma. In order to accommodate the potential for immune flare (pseudoprogression), treatment with study drug (ibrutinib/placebo) and/or rituximab (if ongoing) may continue between the initial assessment of suspected progression and confirmation of progression. Subjects with radiographic PD who, in the Investigator's opinion, continue to receive clinical benefit from their treatment may continue to receive study treatment as dictated in the protocol after consultation with the Medical Monitor and at the Investigator's discretion. In the absence of clinically significant deterioration, a CT scan or biopsy may be performed at least 4 weeks later to confirm PD. If PD is confirmed at the later time point, PD should be assigned to the prior time point at which PD criteria were also met. Study treatment should be discontinued if there is confirmed PD per Revised Criteria for Response Assessment of Malignant Lymphoma (Cheson 2014).

Refer to Appendix G for response criteria.

7.3. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in source documents for transcription to the eCRF or laboratory requisition form. Refer to the Schedule of Assessments (Appendix A) for the timing and frequency of all sample collections.

Instructions for the collection, handling, and shipment of samples are found in the Laboratory Manual.

7.4. COVID-19 Pandemic and Geo-Political Conflict in Ukraine and Surrounding Impacted Countries Provisions

The COVID-19 pandemic and geo-political conflict in Ukraine and surrounding impacted regions have posed significant challenges in performing protocol-specified procedures. To ensure the safety of study participants and minimize risks to the integrity of the study, alternative methods for study assessments, activities, data collection, or study drug shipments are being implemented for impacted sites and study participants in these regions/countries as needed.

Alternative methods or protocol modifications that may be employed include the following:

Study Drug Interruption or Discontinuation:

Delays in study drug dosing must be discussed with the sponsor medical contact, along with the possibility of premature discontinuation from study drug. The investigator should contact the sponsor medical contact before discontinuing a subject from the study for a reason other than described in the protocol to ensure all acceptable mitigation steps have been explored.

Study Drug Dispensation and/or Administration:

If a subject is unable to come to the study site to pick up their study drug, a DTP study drug shipment to the subject may be made if allowed by local regulations. Follow the instructions in Section 5.3.1.2 for DTP shipments.

Study Visits:

Study visits may be impacted and include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted, discuss the next steps with the sponsor medical contact.

Blood Chemistry and Hematology:

If subjects cannot have blood drawn for laboratory testing at the study site (i.e., due to travel restrictions, changes in local regulations, etc.), if possible, arrange for subjects to have laboratory work done at a local laboratory, hospital, or other facility. Local laboratory results should be obtained along with reference ranges and kept within the subjects' source documentation. The investigator should review local laboratory results as soon as possible.

If laboratory samples cannot be obtained, study drug administration may be continued, provided the investigator has reviewed all prior laboratory results and confirms and discusses with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current laboratory results.

8. STUDY PROCEDURES

The study is divided into a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Schedule of Assessments (Appendix A) summarizes the frequency and timing of efficacy, PK, and safety measurements applicable to this study. All subjects enrolled will undergo the same study procedures throughout the study unless otherwise noted.

Screening procedures will be performed up to 28 days before randomization, unless otherwise specified. All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be randomized. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the screening window. Central laboratory results will be used for confirmation of eligibility. Only in the event of unresulted analyses will local laboratory results be acceptable to confirm eligibility.

8.1. Screening/Consenting Visit

The ICF must be signed before any study-specific screening procedures are performed. The following procedures will be performed during the Screening Visit within 28 days prior to randomization, unless otherwise noted:

- Medical history including demographic information
- Determination of FLIPI-1 score
- Obtain a bone marrow aspirate and core biopsy if not performed within 60 days prior to the randomization for bone marrow involvement and MRD testing as described in Section 7.1.3.5 and Section 7.1.3.6. The procedure can be performed prior to first dose of study treatment at the latest.
- Collect blood sample for MRD baseline. The procedure can be performed prior to first dose of study treatment at the latest.
- Complete physical exam including height and weight (may use prior height measurement if available in source documents)
- Eye-related symptom assessment
- B-symptoms assessment
- Obtain vital signs (including blood pressure, heart rate, and body temperature) after the subject has rested in the sitting position for ≥ 3 minutes
- Evaluation of ECOG performance status
- Obtain triplicate 12-lead ECG (≥1 minute apart) after the subject has been in a supine position and resting for at least 10 minutes
- Record prior medication history including over-the-counter drugs, vitamins and herbs
- Record any adverse events since signing the ICF

- Imaging by CT or other modality as described in Section 7.1.3.2 if not performed within 60 days prior to randomization
- Imaging by PET as described in Section 7.1.3.3 if not performed within 60 days prior to randomization
- Collect blood and urine samples for the following clinical laboratory tests:
  - Hematology
  - Serum chemistry
  - Coagulation (PT/INR, aPTT)
  - Serum or urine pregnancy test (for women of reproductive potential only)
  - Hepatitis serologies
  - Urinalysis
- Calculation of creatinine clearance using Cockcroft-Gault or creatinine clearance calculated based on 24-hour urine collection. The 24-hour urine collection may be evaluated by a local laboratory.
- Obtain tumor tissue biopsy for confirmation of diagnosis may be archival. Slides or tumor block may be either new or from a previous biopsy and any remaining sample may be used for biomarker evaluation. See Section 7.1.3.4 for additional details.
- Confirm eligibility (per inclusion/exclusion criteria in Section 4) and randomize subject via the IXRS. Dosing should occur within 72 hours of randomization.

8.2. Treatment Phase

Following completion of the Screening Visit and once eligibility has been confirmed, subjects will be randomized via an automatic IXRS or alternative system provided by the Sponsor. Randomization should occur as close to the time of the expected first dose as possible and not more than 72 hours prior to expected first dose of study treatment.

Study treatment should be continued until disease progression, unacceptable treatment-related toxicity, or other reasons outlined in Section 9.2 and Section 9.3. Local laboratory results may be used to guide all dosing-related decisions. In the event of clinically suspected disease progression, the subject should continue to receive study treatment until disease progression is confirmed by Investigator using the revised criteria for malignant lymphoma described by the International Working Group for NHL (Cheson 2014).

Refer to the Schedule of Assessments (Appendix A) for a complete list of procedures to be performed at each scheduled study visit.

8.2.1. Treatment Visits

8.2.1.1. Cycle 1, Day 1

The last measurements taken on Day 1 of Cycle 1 before administration of study treatment or at Screening (whichever value is last) will be defined as baseline for safety assessments and

treatment decisions. Screening evaluations and laboratory values that were obtained prior to Day 1 of Cycle 1 may be used as baseline assessments if they were collected within 7 days of the start of study treatment.

Pre-dose

- PRO assessment
- Limited symptom-directed physical exam including weight and eye-related symptom assessment and evaluation of lymphatic system, liver and spleen.
- Evaluation of ECOG performance status
- Vital signs including blood pressure, heart rate, and body temperature
- Review of concomitant medications
- Collect blood and urine samples for the following clinical laboratory tests (This applies to clinical laboratory tests in all visits):
  - Hematology
  - Serum chemistry
  - Serum or urine pregnancy test (for women of reproductive potential only)
- Obtain research laboratory samples for:
  - Buccal swab
  - Blood sample for rituximab PK
  - Blood sample for MRD baseline if not done during Screening

Dosing and Post-Dose

- Dispense study drug (ibrutinib/placebo)
- In-clinic administration of study drug as soon as the subject comes into clinic and after pre-dosing procedures. Pre-medications and rituximab will then be administered.
- In-clinic administration of rituximab
- Record any AEs and concomitant medications

8.2.1.2. Cycle 1, Day 8

Pre-dose

- Review of AEs and concomitant medications
- Collect blood samples for the following clinical laboratory tests:
  - Hematology
  - Serum chemistry
- Obtain research laboratory blood samples for:
  - Rituximab PK

Dosing and Post-Dose

- In-clinic administration of rituximab
- Review of AEs and concomitant medications

8.2.1.3. Cycle 1, Day 15

Pre-dose

- Limited symptom-directed physical exam including weight and eye-related symptom assessment and evaluation of lymphatic system, liver and spleen.
- Evaluation of ECOG performance status
- Vital signs
- Review of AEs and concomitant medications
- Collect blood samples for the following clinical laboratory tests:
  - Hematology
  - Serum chemistry
- Obtain research laboratory blood samples for:
  - Rituximab PK

Dosing and Post-Dose

- In-clinic administration of rituximab
- Review of AEs and concomitant medications

8.2.1.4. Cycle 1, Day 22

Pre-dose

- Review of AEs and concomitant medications
- Collect blood samples for the following clinical laboratory tests:
  - Hematology
  - Serum chemistry
- Obtain research laboratory blood samples collected for:
  - Study drug (ibrutinib/placebo) PK
  - Rituximab PK

Dosing and Post-Dose

- In-clinic administration of study drug as soon as the subject comes into clinic and after pre-dosing procedures. Pre-medications and rituximab will then be administered.
- In-clinic administration of rituximab

- Obtain research laboratory blood samples collected for:
  - Study drug pharmacokinetics (1, 2 and 4 hours after administration of study drug). See Table 7 in Section 7.1.4.1 for additional details.
- Review of AEs and concomitant medications

8.2.1.5. Cycle 2, Day 1

Pre-dose

- Limited symptom-directed physical exam including weight and eye-related symptom assessment and evaluation of lymphatic system, liver and spleen.
- Evaluation of ECOG performance status
- Vital signs
- Collect blood samples for the following clinical laboratory tests:
  - Hematology
  - Serum chemistry
- Review of AEs and concomitant medications
- Drug accountability
- Dispense study drug

8.2.1.6. Cycle 3, Day 1

Pre-dose

- PRO assessment
- Limited symptom-directed physical exam including weight and eye-related symptom assessment and evaluation of lymphatic system, liver and spleen.
- Evaluation of ECOG performance status
- Vital signs
- Review of AEs and concomitant medications
- Collect blood and urine samples for the following clinical laboratory tests:
  - Hematology
  - Serum chemistry
  - Urine pregnancy test (every 8 weeks from Day 1 [or at the closest associated visit] for women of reproductive potential only)
- Obtain research laboratory blood samples collected for:
  - Study drug pharmacokinetics
  - Rituximab pharmacokinetics

Dosing and Post-Dose

- Drug accountability
- In-clinic administration of study drug as soon as the subject comes into clinic and after pre-dosing procedures. Pre-medications and rituximab will then be administered.
- In-clinic administration of rituximab
- Review of AEs and concomitant medications

8.2.1.7. Cycle 5, Day 1: First Response Evaluation Visit

Pre-dose

- PRO assessment
- Limited symptom-directed physical exam including weight and eye-related symptom assessment and evaluation of lymphatic system, liver and spleen.
- Evaluation of ECOG performance status
- Vital signs
- B-symptom assessment
- Review of AEs and concomitant medications
- Collect blood and urine samples for the following clinical laboratory tests:
  - Hematology
  - Serum chemistry
  - Urine pregnancy test (every 8 weeks from Day 1 [or at the closest associated visit] for women of reproductive potential only)
- Obtain research laboratory blood samples collected for:
  - Rituximab pharmacokinetics
- Imaging by CT/MRI
- Overall Response Assessment
- To confirm a suspected CR:
  - Imaging by PET to confirm CR if screening PET was positive
  - Bone marrow core biopsy or aspirate if biopsy not possible, to confirm CR (local testing and if samples available, potentially central) as well as aspirate for central MRD assessment, if there was evidence of lymphoma involvement in the bone marrow at baseline by histology
- For subjects achieving a CR, research laboratory blood sample collected for:
  - Determination of MRD by peripheral blood assessment is repeated at each response evaluation visit

Dosing and Post-Dose

- Drug accountability
- Dispense study drug

- In-clinic administration of rituximab
- Review of AEs and concomitant medications

8.2.1.8. Cycles 7 – 25 (odd cycles only), Day 1

Pre-dose

- Limited symptom-directed physical exam including weight and eye-related symptom assessment and evaluation of lymphatic liver and spleen.
- Evaluation of ECOG performance status
- Vital signs
- Review of AEs and concomitant medications
- Collect blood and urine samples for the following clinical laboratory tests:
  - Hematology
  - Serum chemistry
  - Urine pregnancy test (every 8 weeks from Day 1 [or at the closest associated visit] for women of reproductive potential only)
- (Cycle 7, 9, and 11 only) Obtain research laboratory blood samples collected for:
  - Rituximab pharmacokinetics

Dosing and Post-Dose

- Drug accountability
- Dispense study drug
- In-clinic administration of rituximab
- Review of AEs and concomitant medications

NOTE: For cycle visits aligning with response assessment visits, see also Section 8.2.1.10 for the full list of assessments to be completed. Assessments are to be performed only one time for a given visit (i.e., only one set of vital signs needs to be obtained if a regularly scheduled visit is also a response evaluation visit).

8.2.1.9. Cycles 27 until Treatment Termination (odd cycles only), Day 1

- Limited symptom-directed physical exam including weight and eye-related symptom assessment and evaluation of lymphatic system, liver and spleen.
- Evaluation of ECOG performance status
- Vital signs
- Review of AEs and concomitant medications
- Collect blood and urine samples for the following clinical laboratory tests:
  - Hematology
  - Serum chemistry

  - Urine pregnancy test (every 8 weeks from Day 1 [or at the closest associated visit] for women of reproductive potential only)
- Drug accountability
- Dispense study drug

NOTE: For cycle visits aligning with response assessment visits, see also Section 8.2.1.10 for the full list of assessments to be completed. Assessments are to be performed only one time for a given visit (i.e., only one set of vital signs needs to be obtained if a regularly scheduled visit is also a response evaluation visit).

8.2.1.10. Response Evaluation Visits

Response assessments will be performed every 4 Cycles or 16 weeks (±7 days) starting at Cycle 5 until completion of the Cycle 37 Visit and then every 6 Cycles or 24 weeks (±7 days) thereafter until Treatment Termination. All visits will be scheduled in relation to Cycle 1 Day 1. Visit windows are relative to the Cycle 1 Day 1 visit date.

Response assessment visits on an every 16-week schedule will occur as follows: Cycle 5, 9, 13, 17, 21, 25, 29, 33, and 37. Response assessment visits on an every 24-week schedule will begin with Cycle 43 and continue every 6 cycles as follows: Cycle 49, 55, 61, 67, 73, 79, 85, 91, 97, 103, etc.

The following procedures will be performed:

- PRO assessment
- Limited symptom-directed physical exam including weight and eye-related symptom assessment and evaluation of lymphatic system, liver and spleen.
- Evaluation of ECOG performance status
- Vital signs
- B-symptom assessment
- Review of AEs and concomitant medications
- Collect blood and urine samples for the following clinical laboratory tests:
  - Hematology
  - Serum chemistry
  - Urine pregnancy test (every 8 weeks from Day 1 [or at the closest associated visit] for women of reproductive potential only)
- Drug accountability
- Dispense study drug
- Imaging by CT/MRI
- Overall response assessment
- To confirm a suspected CR:
  - Imaging by PET to confirm CR if screening PET was positive

  - Bone marrow core biopsy, or aspirate if core biopsy not possible, to confirm CR (local testing and if samples available, potentially central) as well as aspirate for central MRD assessment, if there was evidence of lymphoma involvement in the bone marrow at baseline by histology
- For subjects achieving a CR, research laboratory blood sample collected for:
  - Determination of MRD by peripheral blood assessment is repeated at each response evaluation visit after CR is achieved

8.2.2. Suspected PD and/or Treatment Termination Visit

The suspected PD or treatment termination visit should be performed at any time during the study, if based on clinical evaluation, the investigator suspects PD, or if the subject discontinues treatment for any other reason. If the subject comes in for a regular study visit and the investigator wants to discontinue treatment at that time, the regular visit will become the termination visit. Any additional procedures that would not be performed for the regular study visit should be performed for the treatment termination visit. The suspected PD visit may be repeated during the course of the study if PD is not confirmed. Each subject will have only one treatment termination visit.

The following procedures will be performed:

- PRO assessment
- Limited symptom-directed physical exam including weight and eye-related symptom assessment and evaluation of lymphatic system, liver and spleen.
- Evaluation of ECOG performance status
- Vital signs
- Review of AEs and concomitant medications
- Collect blood samples for the following clinical laboratory tests:
  - Hematology
  - Serum chemistry
  - Coagulation
- Optional tumor tissue biopsy (Section 7.1.3.4): It is strongly recommended that a fresh tumor tissue biopsy (excision, core needle biopsy, or fine needle aspiration) should be collected at disease progression for biomarker assessments.
- CT or MRI (if clinically indicated)
- Overall response assessment
- Drug accountability
- For subjects achieving a CR, research laboratory blood sample collected for:
  - Determination of MRD by peripheral blood assessment for subjects terminating treatment for reasons other than disease progression.

8.2.3. End of Treatment Safety Follow-up Visit

A Safety Follow-up visit should occur 30 days (±7 days) from the last dose of study treatment **or** prior to the start of a new anticancer treatment. If the subject starts a new anticancer treatment less than 7 days after the treatment termination visit, only those procedures not conducted at the treatment termination visit should be performed at the Safety Follow-up visit.

Subjects who withdraw consent to treatment may still participate in Safety Follow-up.
The following procedures will be performed at the Safety Follow-up visit:

- Complete physical exam including weight and eye-related symptom assessment
- Evaluation of ECOG performance status
- Vital signs
- Review of AEs and concomitant medications
- 12-lead ECG (in triplicate [≥1 minute apart])
- Collect blood samples and urine for the following clinical laboratory tests:
  - Hematology
  - Serum chemistry
  - Coagulation
  - Urine pregnancy test (for women of reproductive potential only)
  - Urinalysis

8.3. Follow-up Phase

Once a subject has completed the End of Treatment Safety Follow-up visit they will enter the Follow-up Phase. Subjects that discontinue treatment for reasons other than progressive disease and full withdrawal of consent will participate in ongoing response follow-up.

8.3.1. Response Follow-up

Subjects who discontinue the study for reasons other than PD through Cycle 37 will be followed every 16 weeks until the date that would have corresponded to the planned Cycle 37 and then every 24 weeks (±7 days) from the last CT or MRI scan until PD, up to the end of the study. Subjects who discontinue the study for reasons other than PD after Cycle 37 will be followed every 24 weeks (±7 days) from last CT or MRI scan until PD, up to the end of the study. During this period, scans and related response evaluation assessments will be carried out as follows: CT scan for target, non-target, and new lesion assessment, radiographic spleen and liver assessment, and overall disease assessment. In cases where the subject is being evaluated for CR, the following should also be performed: PET scan to confirm CR; bone marrow disease assessment to confirm CR; and MRD central lab upon CR.

8.3.2. Survival Follow-Up, Subsequent Anticancer Therapy Collection, and Long-term Surveillance of Other Malignancies

Once a subject progresses (for subjects who have not withdrawn consent for follow-up), he/she will be contacted approximately every 24 weeks (±7 days) from the last dose by clinic visit or telephone to assess survival for up to the end of the study. Subsequent anticancer therapies, best response to therapy, and information about other malignancies will be collected. Subjects will be contacted until death, subject withdrawal, lost to follow-up, or study termination by the Sponsor, whichever occurs first.

8.3.3. Missed Evaluations

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Completion

A subject will be considered to have completed the study if he or she has died before the end of the study, has not been lost to follow up, or has not withdrawn consent before the end of study.

9.2. Withdrawal from Study Treatment

Study treatment will be discontinued in the event of any of the following events:

- Progressive disease
- Unacceptable toxicity: an intercurrent illness or AE that prevents further administration of study treatment or completion of rituximab dosing during induction phase
- Withdrawal of consent for treatment by subject
- Investigator decision (such as chronic noncompliance, significant protocol deviation, or best interest of the subject)
- Study termination by Sponsor
- Subject becomes pregnant

All subjects, regardless of reason for discontinuation of study treatment will undergo an End of Treatment Visit and be followed for progression and/or survival.

The investigator should notify the Sponsor within 24 hours if a subject discontinues study treatment (ibrutinib/placebo and/or rituximab) due to disease progression and should provide documentation of disease progression for review by the Medical Monitor. If a subject shows signs of disease progression on physical examination or laboratory assessment, the subject

should continue study treatment until disease progression is confirmed by the investigator using the revised criteria for malignant lymphoma described by the International Working Group for NHL (Cheson 2014). These subjects should stay in the study to be followed for survival.

9.3. Withdrawal from Study

Withdrawal from study (including all follow-up) will occur under the following circumstances:

- Withdrawal of consent for follow-up observation by the subject
- Lost to follow-up
- Study termination by Sponsor
- Death

If a subject is lost to follow-up, every reasonable effort should be made by the study site personnel to contact the subject. The measures taken to follow up should be documented.

When a subject withdraws before completing the study, the following information should be documented in the source documents:

- Reason for withdrawal
- Whether the subject withdraws full consent (i.e., withdraws consent to treatment and all further contact) or partial consent (i.e., withdraws consent to treatment but agrees to participate in follow-up visits).

10. STATISTICAL METHODS AND ANALYSIS

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

This study evaluates ibrutinib + rituximab (Arm A) vs. placebo + rituximab (Arm B) with 2 interim analyses and the primary analysis planned when the study observes 200 PFS events, or if pre-specified boundaries are crossed at an interim analysis. The final analysis for OS is planned when 165 OS events are observed or five years after enrollment of the last subject, whichever is earlier.

10.1. Subject Information

10.1.1. Intent-to-Treat (ITT) Population

The ITT population consists of all subjects randomized. The ITT population will be the primary population for all efficacy analyses. All the subjects will be analyzed according to the treatment arms to which they are randomized.

10.1.2. Safety Population

The Safety population consists of all subjects who received at least 1 dose of study treatment (rituximab, ibrutinib/placebo).

10.1.3. Pharmacokinetic Population

All subjects who received at least 1 dose of study treatment and had at least one post-treatment sample obtained.

10.2. Endpoints

10.2.1. Primary Endpoint

- Progression-free survival (PFS)

10.2.2. Secondary Endpoints

- Overall response rate (ORR) (Cheson 2014)
- Overall survival (OS)
- Infusion-related reaction rate (Arm A vs. Arm B)
- Duration of response (DOR) as assessed by investigator
- Frequency, severity, seriousness, and relatedness of adverse events (AEs)

10.2.3. Exploratory Endpoints

- Health-related quality of life (QOL) as measured by the FACT-Lym
- Pharmacokinetic parameters or metrics of systemic exposure of ibrutinib and rituximab
- Evaluation and/or identification of relevant patient populations defined by biomarker(s)
- Minimal residual disease (MRD)-negative rate defined as the proportion of FL subjects who reach MRD-negative disease status
- Complete response rate at 30 months (CR30) as defined by the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma (Cheson 2014)

10.3. Sample Size Determination

Sample Size Consideration for PFS

A sample size of approximately 440 subjects will be randomized to Arms A and B to evaluate whether Arm A will result in prolongation of progression-free survival (PFS) when compared to Arm B in treatment naïve subjects with follicular lymphoma. The sample size is determined according to the Group Sequential Design. For this calculation, the references used for the assumptions were Hainsworth 2002, Ghielmini 2004, Zucca 2019, and Fowler 2020. Assuming exponential survival distribution for the PFS events and 66.7% improvement in median PFS of Arm A over Arm B (a hazard ratio [HR] of 0.60), the study has ~ 87% power with 200 observed

PFS events using an overall 1-sided significance level of 0.025. For the sample size calculation, a median PFS of 28 months in the control arm, the actual enrollment rates using the 3-month average until November 2020, and a projected enrollment rate of 8 subjects per month afterwards were used. Two interim analyses are planned with the first interim analysis (IA1) for futility and the second interim analysis (IA2) for efficacy. The first interim analysis (IA1, futility) will be conducted when approximately 55% of the 200 PFS events have occurred. The futility boundary is based on a Rho parameter of 5. The second interim analysis (IA2) for efficacy is planned after approximately 75% of the 200 PFS events (ie, 150 PFS events) are observed and after the last subject has been enrolled, with approximately 90% of the subjects reaching at least 1 year of study follow-up. The efficacy boundary is based on the unequally weighted Bonferroni method allocating 1-sided alpha of 0.001 to IA2 and 0.024 to the primary analysis (PA) (Table 9).

Table 9. Futility and Efficacy Boundaries for Interim Analysis for PFS

Look #	Info. Fraction	Events	Cum. 1-sided α Spent	Boundary (1-sided p-value)	
				Efficacy	Futility
1	0.55	110	0	NA	0.5596
2	0.75	150	0.001	0.001	NA
3	1	200	0.025	0.024	0.024

Power Consideration for ORR

For ORR if we assume a response rate of 0.57 (Zucca 2019) in Arm B and a response rate of 0.73 (PCYC-1125-CA;Fowler 2020) in Arm A, then the power will be approximately 85% for a 1-sided alpha of 0.025 and sample size of 440.

Power Consideration for OS

The final analysis for OS is planned when 165 OS events are observed or five years after enrollment of the last subject, whichever is earlier. The study has ~80% power for the OS analysis at an overall 1-sided alpha of 0.025 when 165 OS events have occurred. An interim analysis for OS will be conducted at the time of the primary analysis of PFS when the superiority boundaries for PFS and ORR are crossed. It is anticipated that 140 and 165 OS events in total will be observed at the interim analysis (at ~77 months, corresponding to the timing of the PFS PA) and the final analysis (at ~91 months), respectively. This is based on the assumption that the 36-month OS landmark estimate is 73% for Arm B (Batlevi 2020) and 82.8% for Arm A (PCYC-1125-CA; Fowler 2020), i.e., a HR of 0.6 and control arm median OS of 79.29 months. The 1-sided alpha boundaries are 0.015 and 0.0207 at the interim analysis and final analysis, respectively, based on Lan-DeMets spending function with O'Brien-Fleming boundary ensuring control of overall type-1 error. In addition, a separate futility analysis without spending alpha is planned for OS at the second interim analysis, and details will be described in the SAP. The Sponsor may consider extending follow-up to attain more OS events to account for the impact of COVID-19.

The futility and efficacy interim analyses will be performed by the DMC. The Sponsor will remain blinded to the data and interim results if the study will continue. Exact alpha boundary will be calculated using the actual events observed at the interim analyses. Details will be included in the SAP.

10.4. Efficacy Analysis Methods for Primary and Secondary Endpoints

10.4.1. Analysis Study

10.4.1.1. Primary Endpoint PFS

Progression Free Survival, as assessed by the investigator, will be analyzed in the ITT population, comparing the 2 treatment arms (Arm A and Arm B) at an overall 1-sided 0.025 significance level using the log-rank test stratified by the randomization stratification factors: age group, FLIPI-1 score and ECOG performance status score. Distribution of PFS will be summarized for each treatment arm using the Kaplan-Meier (KM) method. The estimate of the hazard ratio between the two arms and its corresponding 95% CI will be computed using a Cox proportional hazards model stratified by the randomization stratification factors. In stratified efficacy analysis, small strata are combined to form bigger strata with ≥10 events and ≥40 patients in each stratum.

PFS is defined as duration from the date of randomization to the date of first documentation of disease progression or date of death due to any cause, whichever is first reported, prior to the use of subsequent anti-cancer therapy. Subjects who initiated subsequent anti-cancer therapy before disease progression or death will be censored at the last adequate disease assessment before the use of subsequent anti-cancer therapy. Subjects who are progression-free and alive, or have unknown status will be censored at the last adequate disease assessment. Subjects with no postbaseline disease assessment will be censored at randomization date. Adequate disease assessment is defined as having sufficient evidence to correctly indicate that progression has or has not occurred.

Supplementary/sensitivity analyses may be conducted using different censoring rules and will be described in the SAP.

10.4.1.2. Secondary Endpoints ORR and OS

If the primary endpoint comparison of PFS between Arms A and Arm B has demonstrated statistical significance, then secondary endpoints will be tested sequentially following a hierarchical order with ORR ranked first followed by OS.

ORR of the two treatment arms will be compared using the Cochran-Mantel-Haenszel (CMH) chi-square test, stratified by the randomization stratification factors, under the hierarchical procedure.

Overall survival is defined as the interval between the date of randomization and the date of the subject's death from any cause. If a subject is not known to have died (this includes subject with unknown death date), OS will be censored at the date the subject was last known to have been alive. Subjects who are known to be alive as of their last known status will be censored at their date of last contact. Subjects who are lost to follow-up will be censored at the date the subject is last known to have been alive. The last known alive date will be determined by selecting the last available date of any study procedures.

OS will be analyzed using the same method as for PFS.

The details of estimand framework, stratification factors used in the stratified analysis, and other statistical details will be specified in the SAP.

10.5. Safety Analysis

Analysis of safety data will be conducted on the Safety Population, which includes enrolled subjects who receive at least 1 dose of ibrutinib/placebo or rituximab. The baseline value is defined as the last value collected on or prior to the first dose date of ibrutinib/placebo or rituximab, whichever comes first.

The safety variables to be analyzed include exposure to ibrutinib/placebo or rituximab, AEs, deaths, clinical laboratory test results (hematology and chemistry), ECOG performance status score, physical examination, and vital sign measurements. In general, continuous variables will be summarized using descriptive statistics (n, mean, median, standard deviation, standard error and range). Categorical variables will be summarized using frequencies and percentages. No formal statistical testing is planned.

10.5.1. Adverse Events

Adverse event parameters to be evaluated are the type, incidence, and intensity of AEs; the relationship of AEs to study treatment; and the action taken with respect to study treatment due to AEs.

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The treatment-emergent period is defined as the period of time from the first dose of study treatment, until the earlier of:

- Thirty days following the last dose of ibrutinib/placebo or 30 days following the last dose of rituximab, whichever occurs later

OR

- The start date of a new anticancer therapy.

The Treatment-emergent adverse events (TEAEs) are those events that:

- Are not present prior to the treatment-emergent period and occur during the treatment-emergent period,
- The onset dates are missing, and end dates are during treatment-emergent period,
- Are considered related to study drug by the investigator regardless of the start dates of the events, or
- Are present prior to the treatment-emergent period but worsen in severity during the treatment-emergent period or are subsequently considered related to study drug by the investigator.

All TEAEs will be included in the analysis. For each AE, the number and percentage of subjects who experience at least one occurrence of the given event will be summarized. The number and percent of subjects with TEAEs will be summarized according to intensity (CTCAE, v4.03) and drug relationship, as well as categorized by system organ class and preferred term. Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe AE or a SAE.

10.5.2. Clinical Laboratory Tests

Laboratory tests will be summarized separately for hematology and serum chemistry. Local laboratory results will be standardized using the International System SI unit. Selected hematologic and chemistry laboratory parameters are detailed in Section 7. All laboratory values will be graded using the NCI CTCAE v4.03. The worst toxicity grade during the study will be tabulated.

A summary of the shifts in selected laboratory hematology and serum chemistry parameters from baseline to the worst toxicity grade during the study will be provided. The worst toxicity grade during the study will be tabulated.

10.6. Analysis Methods for Selected Exploratory Endpoints

10.6.1. Pharmacokinetic Analysis

The plasma concentration data for ibrutinib and PCI-45227 will be summarized using descriptive statistics at each time-point. Population PK analysis of plasma concentration-time data of ibrutinib will be performed using nonlinear mixed-effects modeling. Data may be combined with data from other studies to support a relevant population PK model. Available subject characteristics (e.g., demographics, laboratory variables, genotypes, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

Ibrutinib PK data in this study will be compared to observed/reported concentration data for ibrutinib and/or population PK models to explore the potential for a pharmacokinetic interaction

between ibrutinib in combination use with rituximab. Rituximab concentration data in this study will be compared between two arms with and without ibrutinib to explore the potential for a pharmacokinetic interaction between rituximab in combination use with ibrutinib.

For the drug combination of ibrutinib and rituximab, model-derived exposure parameters (PK parameters) may be used to explore PK/PD correlation between the exposure of ibrutinib and its active metabolites with relevant clinical or biomarker information to assess effectiveness and toxicity.

10.6.2. Biomarker Analyses

As an exploratory objective, subgroups defined by molecular and genetic biomarkers at baseline will be tested for interaction of the treatment effects over strata as a potential predictive marker.

10.6.3. Patient-reported Outcomes (PRO) as Measured by FACT-Lym

Subject compliance on PRO measure by visit, a maximum change from the baseline score, a change from the baseline per visit over time, and the portion of subjects who meet the particular post-baseline improvement/worsening criteria, if applicable, will be summarized by treatment arm. Time to improvement/worsening will be summarized by treatment arm.

Analysis methods for exploratory endpoints not described above will be detailed in the SAP.

10.7. Data Monitoring Committee (DMC)

An independent DMC will be established to review unblinded data at pre-defined time points to ensure the continuing safety of the subjects enrolled/randomized in this study. The DMC will consist of at least two medical experts in relevant therapeutic area and at least one statistician.

At least three safety review meetings are planned that will occur approximately 1 month after 88 subjects have been randomized (20% of expected enrollment), 1 month after 220 subjects have been randomized (50% of expected enrollment), and 1 month after all subjects have been randomized. Additional meetings may be considered as needed by the DMC. The safety review will focus on deaths, treatment discontinuations, serious adverse events, Grade ≥3 events, and events of special interest. Based on the results from these scheduled safety review meetings, the DMC chair may request additional safety interim analyses and more frequent monitoring.

Two interim analyses are planned, and both will be performed by the DMC. The first interim analysis (IA1) is for futility and is to be conducted when approximately 55% of the 200 PFS events have occurred. The second interim analysis (IA2) is for efficacy and is planned after approximately 75% of the 200 events (150 PFS events) are observed and after the last subject has been enrolled.

Details on the DMC responsibilities, authorities, review process, access to unblinded data will be documented in the DMC charter.

11. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

11.1. Definitions

11.1.1. Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study treatment, whether or not considered related to the study treatment (ICH-E2A 1995).

For the purposes of this clinical study, AEs include events which are either new or represent detectable exacerbations of pre-existing conditions.

The term "disease progression" should not be reported as an AE term. As an example, "worsening of underlying disease" or the clinical diagnosis that is associated with disease progression should be reported.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms provided by the subject and/or observed by the investigator or study staff including laboratory abnormalities of clinical significance.
- Any AEs experienced by the subject through the completion of final study procedures.
- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the underlying disease that were not present before the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies).

The following are NOT considered AEs:

- **Pre-existing condition:** A pre-existing condition (documented on the medical history eCRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Pre-planned or elective hospitalization:** A hospitalization planned before signing the ICF is not considered an SAE, but rather a therapeutic intervention. However, if during

the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.

- **Diagnostic Testing and Procedures:** Testing and procedures should not be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.

11.1.2. Serious Adverse Events

A serious adverse event (SAE) based on International Conference on Harmonisation (ICH) and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death (ie, the AE actually causes or leads to death).
- Is life-threatening. Life-threatening is defined as an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the investigator or the Sponsor believes that an AE meets the definition of life-threatening, it will be considered lifethreatening.
- Requires in-patient hospitalization >24 hours or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.

Is an important medical event that may not result in death, be immediately lifethreatening or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject or subject may require intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsion that does not result in hospitalization; or development of drug dependency or drug abuse.

Given that the investigator's perspective may be informed by having actually observed the event, and the Sponsor is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event, if either the Sponsor or the investigator believes that the event is serious, the event will be considered serious.

11.1.3. Severity Criteria (Grade 1-5)

Definitions found in the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) will be used for grading the severity (intensity) of AEs. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE.

Should a subject experience any AE not listed in the CTCAE v4.03, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death-related to AE) experiences which result in subject death

11.1.4. Causality (Attribution)

The investigator is to assess the causal relation (ie, whether there is a reasonable possibility that the study treatment caused the event) using the following definitions:

Not Related:	Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.
Unlikely:	The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.
Possibly Related:	There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.
Related:	The AE is clearly related to use of the investigational product.

11.1.5. Serious Adverse Reactions and Suspected Unexpected Serious Adverse Reactions

The following definitions will be used for Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

SAR is defined as all noxious and unintended responses to an investigational medicinal product (IMP) related to any dose administered that result in an SAE as defined in Section 11.1.2.

SUSAR refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, and is unexpected (not listed in the applicable Reference Safety Information).

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local requirements, including reporting to the Eudravigilance database in accordance with EU Clinical Trial Regulation.

11.2. Unexpected Adverse Events

An "unexpected" AE is an AE that is not listed in the IB/package insert or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be "unexpected" (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be "unexpected" (by virtue of greater specificity) if the IB/package insert listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

11.3. Special Reporting Situations

Special reporting situation on a Sponsor study may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of any study treatment
- Suspected abuse/misuse of a study treatment
- Inadvertent or accidental exposure to a study treatment
- Medication error involving a product (with or without subject exposure to the study treatment, e.g., name confusion)

Occurrence of any special reporting situations should be recorded in the eCRF. If any special reporting situation meets the criteria of an AE, it should be recorded on the AEs eCRF. If the AE is considered serious, it should be recorded on the AEs eCRF as serious and should be reported on the Serious Adverse Event Report Form. The Serious Adverse Event Report Form should be sent via email or fax to Pharmacyclics Drug Safety or designee within 24 hours of awareness.

11.4. Documenting and Reporting of Adverse Events and Serious Adverse Events by Investigators

11.4.1. Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation time points during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, detected through physical examination, clinically significant

laboratory test, or other means, will be recorded in the subject's medical record and on the AEs CRF and, when applicable, on the Serious Adverse Event Report Form.

Each recorded AE or SAE will be described by its duration (i.e., start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to the investigational product, and any actions taken.

11.4.2. Adverse Event Reporting Period

All AEs whether serious or non-serious, will be documented from the time signed and dated ICF is obtained until 30 days following the last dose of study treatment. SAEs will be reported to the Sponsor Drug Safety via an SAE reporting form and will be recorded in the eCRF from the time of ICF signing. Non-serious AEs will be recorded in the source documents from the time of ICF signing and will be recorded in the eCRF from the first dose of study treatment.

Serious adverse events reported after 30 days following the last dose of study treatment should also be reported if considered related to study treatment. Resolution information after 30 days should be provided.

Progressive disease should NOT be reported as an event term, but instead symptoms/clinical signs of disease progression may be reported (See Section 11.1.1).

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study drug, investigator's evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection”). Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. Autopsy and postmortem reports must be forwarded to the Sponsor, or designee, as outlined above, if allowed per local regulatory guidelines.

If a death occurs within 30 days after the last dose of study treatment, the death must be reported to the Sponsor as a SAE.

11.4.3. Reporting Requirements for Serious Adverse Events

All SAEs (initial and follow-up information) will be reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of the discovery of the event or information. Pharmacyclics may request follow-up and

other additional information from the investigator (e.g., hospital admission/discharge notes and laboratory results). The contact information (phone, email and fax) for Pharmacyclics Drug Safety can be found on the Serious Adverse Event Report Form and instructions.

A single DSUR will be provided for all IMPs used in the clinical trial.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study treatment or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts)

The Sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities and governing bodies according to the local regulations.

The investigator (or Sponsor where required) must report these events to the appropriate Independent Ethics Committee/ Research Ethics Board/Institutional Review Board (IEC/REB/IRB) that approved the protocol unless otherwise required and documented by the IEC/REB/IRB.

11.4.4. Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur in a female study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

A female subject must immediately inform the investigator if she becomes pregnant from the time of initial dose to 6 months after the last dose of study drug or 12 months after the last dose of rituximab, whichever comes later. A male subject must immediately inform the investigator if his partner becomes pregnant from the time of initial dose to 6 months after the last dose of study drug. Any female subjects receiving study treatment(s) who become pregnant must immediately discontinue study treatment. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an AE, the outcome will need to be documented. Any pregnancy occurring in a female subject or female partners of male subjects during the

period as described above must be reported. Any occurrence of pregnancy must be recorded on the Pregnancy Report Form Part I and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of learning of the event. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. For pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing the Pregnancy Report Form Part II. Any congenital anomaly/birth defect noted in the infant must be reported as a SAE.

11.4.5. Other Malignancies

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol- specified follow-up periods including post-progression follow-up for overall survival. If observed, enter data in the corresponding eCRF.

11.4.6. Eye-Related Adverse Events

New or worsening eye-related symptoms that are Grade 2 or higher, or a symptom that was Grade 2 or higher at baseline worsens, should be evaluated by an ophthalmologist whose findings should be reported on the ophthalmologic eCRF.

11.4.7. Adverse Events of Special Interest (AESI)

Specific AEs, or groups of AEs, will be followed as part of standard safety monitoring activities by the Sponsor. These events (regardless of seriousness) should be reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of awareness.

11.4.8. Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic AEs of Grade 3 or higher*
- Any treatment-emergent serious adverse events of bleeding of any grade
- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade

*All hemorrhagic events requiring transfusion of red blood cells should be reported as Grade 3 or higher AE per CTCAE v4.03.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 11.4.7 above.

11.4.9. COVID-19 Pandemic-Related Provisions for Adverse Event Reporting

Supplemental study case report forms will be completed in the event of COVID-19-related missed/virtual visits, study drug interruptions or discontinuations, vaccines, or adverse events (including capture of specific signs/symptoms of infection and testing results).

SARS-CoV-2 infections will be captured as adverse events if a subject is experiencing symptoms of COVID-19 (please refer to CRF Completion Guidelines). If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the protocol and above. The following COVID-19-related supplemental eCRFs will be completed (for both serious and nonserious events) as applicable:

- COVID-19 Visit Impact
- COVID-19 Lab Test
- COVID-19 Vaccine Details

Reactions known to be associated with the SARS-CoV-2 vaccine should be reported as adverse events. If the event meets the criteria for an SAE, then follow the SAE reporting directions. All adverse events associated with the SARS-CoV-2 vaccine will be linked to the vaccine on the COVID-19 Vaccine eCRF.

12. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

12.1. Regulatory and Ethical Compliance

This clinical study was designed and will be implemented in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practices, with applicable global and local regulations (including US Code of Federal Regulations [CFR] Title 21and EU Clinical Trial Regulation), and with the ethical principles laid down in the Declaration of Helsinki. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

12.2. Institutional Review Board (IRB), Research Ethics Board (REB) and Independent Ethics Committee (IEC) Approval

The investigator will submit this protocol, the ICF, IB, and any other relevant supporting information (e.g., all advertising materials or materials given to the subject during the study) to the appropriate IRB/REB/IEC for review and approval before study initiation. Amendments to the protocol and ICF must also be approved by the IRB/REB/IEC before the implementation of changes in this study.

The investigator is responsible for providing the IRB/REB/IEC with any required information before or during the study, such as SAE expedited reports or study progress reports.

The IRB/REB/IEC must comply with current United States (US) regulations (§21 CFR 56) as well as country-specific national regulations and/or local laws.

The following documents must be provided to Pharmacyclics or its authorized representative before entering subjects in this study: (1) a copy of the IRB/REB/IEC letter that grants formal approval; and (2) a copy of the IRB/REB/IEC-approved ICF.

12.3. Informed Consent

The ICF and process must comply with the US regulations (§ 21 CFR Part 50) as well as country specific national regulations and/or local laws. The ICF will document the study-specific information the investigator or his/her designee provides to the subject and the subject's agreement to participate.

The investigator or designee (designee must be listed on the Delegation of Authority log), **must** explain in terms understandable to the subject the purpose and nature of the study, study procedures, anticipated benefits, potential risks, possible AEs, and any discomfort participation in the study may entail. This process must be documented in the subject's source record. Each subject must provide a signed and dated ICF before any study-related (nonstandard of care) activities are performed. The original and any amended signed and dated consent forms must remain in each subject's study file at the study site and be available for verification by study monitors at any time. A copy of each signed consent form must be given to the subject at the time that it is signed by the subject.

12.4. Quality Control and Quality Assurance

Sponsor shall implement and maintain quality control and quality assurance procedures to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2008) and all revisions thereof, and in accordance with the Food and Drug Administration (FDA) regulations (21 CFR Parts 11, 50, 54, 56, and 312, Subpart D Responsibilities of Sponsors and investigators) and with the ICH guidelines on GCP (ICH E6) and with applicable regulatory requirements, including EU Clinical Trial Regulation.

12.5. Protected Subject Health Information Authorization

Information on maintaining subject confidentiality in accordance to individual local and national subject privacy regulations must be provided to each subject as part of the informed consent process (refer to Section 12.3), either as part of the ICF or as a separate signed document (for example, in the US, a site-specific HIPAA consent may be used). The investigator or designee **must** explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Pharmacyclics and its designees, regulatory agencies, and IRBs/REBs/IECs. As the study Sponsor, Pharmacyclics will

not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each subject. If a subject withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the subject **and** to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

During the review of source documents by the monitors or auditors, the confidentiality of the subject will be respected with strict adherence to professional standards and regulations.

Before subject data are shared with AbbVie, the study investigator and staff will replace the subject's name, address, and contact information with a generic code which AbbVie cannot link to that subject's identity to protect the confidentiality of the data.

For the personal data that AbbVie acting as sponsor of the submitted study controls and maintains, AbbVie has developed a robust security program focused on due diligence in design, managed change, and information security governance. Information Security policies govern the Information Security functions including identity and access management, operations, infrastructure, application, and third-party security requirements. The risk-based AbbVie Data Classification Tool dictates the level of scrutiny and control required for the relevant activities per AbbVie Information Security policies taking into account the sensitivity of the data.

AbbVie has a data protection impact assessment (DPIA) program to ensure and document the appropriate controls and safeguards stated above are in place for clinical trial data that it controls and maintains, and these processing activities respect privacy of clinical trial subjects. AbbVie also maintains robust security incident response policies and procedures, including requirements for the containment of any data-related incidents, the mitigation measures where needed, and notification to authorities or affected individuals where required.

AbbVie as the sponsor shall document any personal data breaches for which it is a controller and notify where required the competent national supervisory authority without undue delay and at the latest within 72 hours after becoming aware of such an incident. AbbVie shall create and maintain appropriate records of such an incident.

12.6. Study Files and Record Retention

The investigator **must** keep a record of **all** subjects who have consented to enroll in the study. For those subjects subsequently excluded from enrollment, the reason(s) for exclusion is to be recorded.

The investigator/study staff must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Essential documentation includes, but is not limited to, the IB, signed protocols and amendments,

IRB/REB/IEC approval letters (dated), signed Form FDA 1572/IIA and Financial Disclosures, signed ICFs (including subject confidentiality information), drug dispensing and accountability records, shipping records of investigational product and study-related materials, signed (electronically), dated and completed case report forms (CRFs), and documentation of CRF corrections, SAE forms transmitted to Pharmacyclics and notification of SAEs and related reports, source documentation, normal laboratory values, decoding procedures for blinded studies, curricula vitae for study staff, and all relevant correspondence and other documents pertaining to the conduct of the study.

All essential documentation will be retained by the investigator for at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated and until there are no pending or contemplated marketing applications; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after formal discontinuation of clinical development of the drug.

The investigator must notify Pharmacyclics and obtain written approval from Pharmacyclics before destroying any clinical study documents or images (e.g., scan, radiograph, ECG tracing) at any time. Should an investigator wish to assign the study records to another party or move them to another location, advance written notice will be given to Pharmacyclics. Pharmacyclics will inform the investigator of the date that study records may be destroyed or returned to Pharmacyclics.

Pharmacyclics must be notified in advance of, and Pharmacyclics must provide express written approval of, any change in the maintenance of the foregoing documents if the investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the investigator and Pharmacyclics to store such documents in sealed containers away from the study site so that they can be returned sealed to the investigator for audit purposes.

12.7. Case Report Forms and Record Maintenance

The case report forms will be used to collect the clinical study data and must be completed for each enrolled subject with all required study data accurately recorded such that the information matches the data contained in medical records (e.g., physicians' notes, nurses' notes, clinic charts and other study-specific source documents). Authorized study site personnel (i.e., listed on the Delegation of Authority log) will complete CRFs designed for this study according to the completion guidelines that will be provided. The investigator will ensure that the CRFs are accurate, complete, legible, and completed within a reasonable period of time. At all times, the investigator has final responsibility for the accuracy and authenticity of all clinical data.

The eCRFs exists within an electronic data capture (EDC) system with controlled access managed by Pharmacyclics or its authorized representative for this study. Study staff will be appropriately trained in the use of eCRFs and application of electronic signatures before the start

of the study and before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The investigator attests that the information contained in the eCRFs is true by providing electronic signature within the EDC system. After database lock, the investigator will receive a copy of the subject data (e.g., paper, CD, or other appropriate media) for archiving at the study site.

12.8. Investigational Study Treatment Accountability

Ibrutinib and any comparator used must be kept in a locked limited access room. The study treatment must not be used outside the context of the protocol. Under no circumstances should the investigator or other site personnel supply ibrutinib or comparator to other investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol without prior authorization from Pharmacyclics.

Accountability records for ibrutinib and any comparator must be maintained and readily available for inspection by representatives of Pharmacyclics and are open to inspections by regulatory authorities at any time.

An Investigational Treatment Accountability Log must be used for drug accountability. For additional details on investigational product management, please refer to the Pharmacy Manual.

12.9. Study Monitoring/Audit Requirements

Representatives of Pharmacyclics or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the investigator and site staff, remote monitoring, as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the study is conducted in compliance with the protocol, standard operating procedures (SOPs), and other written instructions and regulatory guidelines, and to ensure the quality and integrity of the data. This study is also subject to reviews or audits.

To assure the accuracy of data collected in the eCRFs, it is mandatory that the monitor/auditor have access to all original source documents, including all electronic medical records (EMR) at reasonable times and upon reasonable notice. If access to the EMR cannot be granted to the monitor, the site must ensure that all certified copies of documents are available during monitoring visits for all screened and enrolled subjects. During the COVID-19 pandemic and geo-political conflict in Ukraine and surrounding impacted regions, remote data review/verification may be employed if allowed by the local regulatory authority, IRB/REB/IEC, and the study site. During the review of source documents, every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the investigator agrees to allow the IRB/REB/IEC, representatives of Pharmacyclics, its designated agents and authorized employees of the appropriate Regulatory Authority to inspect the facilities used in this study and, for purposes of

verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

Pharmacyclics or its authorized representative may perform an audit at any time during or after completion of this study. All study-related documentation must be made available to the designated auditor. In addition, a representative of the FDA or other Regulatory Agencies may choose to inspect a study site at any time before, during, or after completion of the clinical study. In the event of such an inspection, Pharmacyclics will be available to assist in the preparation. All pertinent study data should be made available as requested to the Regulatory Authority for verification, audit, or inspection purposes.

12.10. Investigator Responsibilities

A complete list of investigator responsibilities are outlined in the clinical trial research agreement and the Statement of Investigator Form FDA 1572/IIA, both of which are signed by the investigator before commencement of the study. In summary, the investigator will conduct the study according to the current protocol; will read and understand the IB; will obtain IRB/REB/IEC approval to conduct the study; will obtain informed consent from each study participant; will maintain and supply to the Sponsor or designee, auditors and regulatory agencies adequate and accurate records of study activity and drug accountability for study-related monitoring, audits, IRB/REB/IEC reviews and regulatory inspections; will report SAEs to the Sponsor or designee and IRB/ REB/IEC according to the specifics outlined in this protocol; will personally conduct or supervise the study; and will ensure that colleagues participating in the study are informed about their obligations in meeting the above commitments.

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP), as well as and applicable laws, regulations, and guidelines. Certain laws, regulations, or guidelines may apply to conduct of the study at investigator's site even if such laws, regulations or guidelines originate in a foreign jurisdiction. The investigator agrees and acknowledges that applicable law or regulation may require AbbVie to submit inspection reports, instances of significant non-compliance with the study protocol, or other documents regarding conduct of the study at the investigator's site to regulatory authorities, and such documents may be publicly disclosed by such authorities. In signing the Investigator Agreement, the investigator also agrees to the following.

Report the following to AbbVie within 1 calendar day of becoming aware:

- Any departure from relevant clinical trial regulation, GCP, or the trial protocol that has affected or is likely to affect to a significant degree the following:
    - Rights, safety, physical or mental integrity of the subjects of the clinical trial

  - Scientific value of the clinical trial, reliability or robustness of data generated
- Any unanticipated problems involving risks to human subjects

Where required by local regulation, inform relevant Ethics Committees / Institutional Review Boards and other appropriate individuals (e.g. Co-ordinating Investigator, Institution Director).

12.11. Sponsor Responsibilities

A complete list of the Sponsor responsibilities is outlined in the clinical trial research agreement and in the laws and regulation of the country in which the research is conducted. In summary, the Sponsor will select qualified investigators, provide them with the information they need to properly conduct the study, ensure adequate monitoring of the study, conduct the study in accordance with the general investigational plan and protocols and promptly inform investigators, health and regulatory agencies/authorities as appropriate of significant new adverse effects or risks with respect to the drug.

12.12. Financial Disclosure

A separate financial agreement will be made between each principal investigator and Pharmacyclics or its authorized representative before the study treatment is delivered.

For this study, each investigator and Sub-Investigator (as designated on the Form FDA 1572/IIA) will provide a personally signed Financial Disclosure Form in accordance with § 21 CFR 54. Each investigator will notify Pharmacyclics or its authorized representative of any relevant changes in financial disclosure information during the conduct of the study and for 1 year after the study has been completed.

12.13. Liability and Clinical Trial Insurance

In the event of a side effect or injury, appropriate medical care as determined by the investigator/designee will be provided.

The ICF will include a description of treatment in the event of a study related injury and handling of the costs associated therewith, incorporating country-specific national regulations and/or local laws. Financial compensation for lost wages, disability or discomfort due to the study is not available.

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

12.14. Protocol Amendments

Pharmacyclics will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the regulatory authorities and IRB/REB/IEC together with,

if applicable, a revised model ICF. Written documentation of regulatory authorities, IRB/REB/IEC and required site approval must be received by Pharmacyclics before the amendment may take effect at each site. Additionally, under this circumstance, information on any change in risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand and sign each revised ICF confirming their willingness to remain in the trial.

No other significant or consistent change in the study procedures, except to eliminate an immediate hazard, shall be effected without the mutual agreement of the investigator and Pharmacyclics.

12.15. Publication of Study Results

Pharmacyclics may use the results of this clinical study in registration documents for Regulatory Authorities in the US or abroad. The results may also be used for papers, abstracts, posters, or other material presented at scientific meetings or published in professional journals or as part of an academic thesis by an investigator. In all cases, to avoid disclosures that could jeopardize proprietary rights and to ensure accuracy of the data, Pharmacyclics reserves the right to preview all manuscripts and abstracts related to this study, allowing Pharmacyclics sufficient time to make appropriate comments before submission for publication.

AbbVie is committed to fostering the highest standard of conduct related to Scientific Publications and transparency, while at the same time, protecting its confidential information. Authorship related to scientific publications shall be determined in accordance with and governed by the criteria defined by the International Committee of Medical Journal Editors ("ICMJE") "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals." AbbVie's role in support of the Study should be appropriately disclosed in any scientific publications.

12.16. Study Discontinuation

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, both the Sponsor and the investigator will arrange discontinuation procedures. In terminating the study, the Sponsor and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

12.17. Start-of-Study, End-of-Study, and Study Completion

The start-of-study is defined as the date of the first site activated.

The end-of-study is defined as the date of end-of-study participation by the last subject in the last country where the study was conducted [e.g., last post treatment safety follow-up or last survival follow-up, whichever comes last].

The study is expected to be completed after the final analysis for OS, or five years after enrollment of the last subject, or the time point all subjects have exited the study for any reason, or upon study termination at the Sponsor's discretion, whichever occurs first.

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14. APPENDICES

Appendix A. Schedule of Assessments

Study Visits	Screening Phase	Treatment Phase (1 cycle = 28 days)									Suspected PD and/or Treatment Termination	End of Treatment Safety Follow Up	Post-Treatment Survival Follow-up (Post End of Treatment)[q]
		Rituximab Induction				Cycle 2	Rituximab Maintenance		Cycles 27 until Treatment Termination	Response Evaluation q16 weeks from Cycle 5 through Cycle 37, q24 weeks thereafter[l]			
		Cycle 1					Cycle 3	Cycles 5-25 (odd cycles only)	(odd cycles only)				
		D1 (baseline)[a]	D8	D15	D22	D1	D1	D1	D1		At any time	within 30 days[m]	Q24 weeks
Study Visit Windows	28 days	± 3 days						± 7 days		± 7 days	At any time	± 7 days	± 7 days
Screening/Administrative													
Informed consent	X												
Medical history/FLIPI 1	X												
Tumor tissue	X										X (Optional)		
Confirm eligibility and randomize		X[n]											
Study Assessments													
Physical exam/weight (height at Screening)[b]	X	X		X		X	X	X	X	X	X	X	
Eye related symptom assessment[b]	X	X		X		X	X	X	X	X	X	X	
Vital signs	X	X		X		X	X	X	X	X	X	X	
ECOG performance status score	X	X		X		X	X	X	X	X	X	X	
Triplicate 12 lead ECGs[c]	X											X	
Prior and concomitant medications	X	Continuous from ICF to 30 days after last dose of study treatment											
Adverse events[d]	X	Continuous from ICF to 30 days after last dose of study treatment											
Survival status, subsequent therapy and best response, and other malignancies													X
Clinical Laboratory Assessments													
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry	X	X	X	X	X	X	X	X	X	X	X	X	

		Treatment Phase (1 cycle = 28 days)											
		Rituximab Induction					Rituximab Maintenance						
		Cycle 1				Cycle 2	Cycle 3	Cycles 5-25 (odd cycles only)	Cycles 27 until Treatment Termination (odd cycles only)	Response Evaluation q16 weeks from Cycle 5 through Cycle 37, q24 weeks thereafter[l]	Suspected PD and/or Treatment Termination	End of Treatment Safety Follow Up	Post-Treatment Survival Follow-up (Post End of Treatment)[q]
Study Visits	**Screening Phase**	**D1 (baseline)[a]**	**D8**	**D15**	**D22**	**D1**	**D1**	**D1**	**D1**		**At any time**	**within 30 days[m]**	**Q24 weeks**
Study Visit Windows	28 days	± 3 days						± 7 days		± 7 days	At any time	± 7 days	± 7 days
Coagulation panel (PT,PTT,INR)	X										X	X	
Creatinine clearance (Cockcroft Gault)	X												
Hepatitis serologies[e]	X												
Pregnancy test[f]	X	X					X	X	X	X		X	
Urinalysis	X	As clinically indicated										X	
Efficacy Assessments													
B symptoms assessment	X									X			
PRO[g]		X					X			X	X		
CT/MRI scan, also as clinically indicated[h]	X									X	X		
PET scan[h]	X									X (for CR)			
Bone marrow core biopsy/aspirate for bone marrow involvement [i]	X									X (for CR)			
Bone marrow aspirate for MRD[i]	X									X (for CR)			
MRD assessment in peripheral blood[i]	X									X (for CR)	X (for CR)[p]		
Overall Response Assessment										X	X		
Research Laboratory Assessments													
Buccal Swab		X											
PK sampling for study drug[j]					X Pre dose, 1, 2, 4h		X Pre dose						
PK sampling for rituximab[j]		X	X	X	X		X	X Cycles 5 11					

		Treatment Phase (1 cycle = 28 days)											
		Rituximab Induction					Rituximab Maintenance						
		Cycle 1				Cycle 2	Cycle 3	Cycles 5-25 (odd cycles only)	Cycles 27 until Treatment Termination (odd cycles only)	Response Evaluation q16 weeks from Cycle 5 through Cycle 37, q24 weeks thereafter[l]	Suspected PD and/or Treatment Termination	End of Treatment Safety Follow Up	Post-Treatment Survival Follow-up (Post End of Treatment)[q]
Study Visits	**Screening Phase**	**D1 (baseline)[a]**	**D8**	**D15**	**D22**	**D1**	**D1**	**D1**	**D1**		**At any time**	**within 30 days[m]**	**Q24 weeks**
Study Visit Windows	28 days	± 3 days						± 7 days		± 7 days	At any time	± 7 days	± 7 days
Study treatment Administration													
Drug accountability[k]						X	X	X	X	X	X		
Dispense study drug (ibrutinib/placebo)		X				X	X	X	X	X			
In clinic administration of study drug (ibrutinib/placebo)		X			X		X						
In clinic administration of rituximab		X	X	X	X		X	X					
Study drug PO QD[o] (4 capsules)		Continuous daily dosing Dispensed on D1 of Cycle 1 and 2 as a 1 month supply, then every odd cycle (Cycles 3 to 25), continuing every odd cycle (Cycle 27 and beyond) for a maximum of 2 month supply											
Rituximab 375 mg/m^2 IV		Administered on D1, 8, 15 and 22 of Cycle 1. Then Q2 months on odd cycle numbers (every 8 weeks) for up to 12 maintenance doses for 2 years.											

Footnotes:

a. Baseline: To be collected pre dose, unless otherwise specified. Screening evaluations and laboratory values that were obtained prior to Day 1 of Cycle 1 may be used as baseline assessments if they were collected within 7 days of the start of study treatment. Screening window starts with first screening procedure and ICF signature may occur before the window.

b. Physical exam and eye related symptom assessment: Height will only be taken during the Screening Phase. Review of symptoms should include inquiry of ocular symptoms; subjects should be referred to an ophthalmologist for a formal examination if any Grade ≥2 symptoms are reported. The Screening and End of Treatment Safety Follow up visit physical examination will include, at a minimum, the general appearance of the subject, height (Screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen and extremities, musculoskeletal system, nervous system, and lymphatic system. A limited symptom directed physical examination is required at Day 1 of Cycle 1 and 2, Day 15 of Cycle 1, as well as Day 1 of each odd cycle starting at Cycle 3, Response Evaluation Visits and Treatment Termination and includes weight, eye related symptom assessment and evaluation of lymphatic system, liver and spleen.

c. Triplicate 12 lead ECGs will be done (≥1 minute apart). Abnormalities noted at Screening should be documented in the medical history. ECGs may be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset of dyspnea.

d. Adverse events: AEs are reported from the time the subject signs the ICF until 30 days following last dose of study treatment. In addition to all routine AE reporting, all other malignant tumors including solid tumors, skin malignancies and hematologic malignancies are to be reported as AEs for the duration of the study treatment.

e. Hepatitis serologies will be evaluated. If hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody is positive, then PCR to quantitate hepatitis B DNA or hepatitis C RNA must be performed and must be negative prior to randomization.

f. A serum or urine pregnancy test is required at Screening and Cycle 1, Day 1; a urine pregnancy test may be performed at the other time points indicated. Additional pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation to establish the absence of pregnancy at any time during a subject's participation in the study.

g. PRO: To be completed prior to any assessments and before being clinically evaluated by the study nurse or physician (after informed consent).

h. CT/MRI and PET scan: Baseline CT/MRI and PET scan can be performed up to 60 days before randomization.

i. Bone marrow aspirate and biopsy: 1) At Screening, a unilateral bone marrow core biopsy must be obtained for assessment of bone morrow involvement by local laboratory. In cases if the bone marrow biopsy cannot be obtained due to access related or patient condition related issues the bone marrow aspirate sample should be obtained instead. Alternatively results of bone marrow involvement from a bone marrow aspirate and core biopsy performed up to 60 days before randomization will be acceptable. Bone marrow core biopsy and aspirate samples should be submitted to the central laboratory for potential confirmation of bone marrow involvement when available. 2) To confirm complete response if bone marrow involvement positive at baseline, bone marrow biopsy, or aspirate if core biopsy not possible, assessments should be performed in a local laboratory and bone marrow core biopsy / aspirate samples should be sent to central lab for potential confirmation if available. All pathology reports for bone marrow involvement should be sent to central lab. 3) For MRD assessments, aliquot of aspirate should be submitted to the central laboratory at Screening as well as at CR, if bone marrow positive at Screening. 4) For all subjects, a peripheral blood sample for minimal residual disease evaluation should be collected at Screening or latest at C1D1 Pre dose. For subjects who achieve a CR, a peripheral blood sample for minimal residual disease evaluation should be collected at every disease assessment visit (every 16 weeks starting from Cycle 5 through Cycle 37, then every 24 weeks thereafter) starting with the first CR visit. (see Section 7.1.3.5 and Section 7.1.3.6).

j. Sparse pharmacokinetic (PK) sampling: PK samples for study drug (ibrutinib/placebo) will be collected at pre dose and 1, 2, and 4 hours post dose on Cycle 1, Day 22. PK samples will be collected at pre dose only on Cycle 3, Day 1. PK samples for rituximab will be collected at pre dose only on Cycle 1, Days 1, 8, 15, and 22 and pre dose on Cycle 3, 5, 7, 9, and 11 on Day 1.

k. Study drug compliance review: Includes subject instruction and routine review of study drug diary and evaluation of contents of study drug containers from home administration.

l. Response Evaluation Visits: If study drug (ibrutinib/placebo) is held before a scheduled response assessment, then the response assessment can be delayed up to 2 weeks to allow re initiation of study drug prior to the scheduled response assessment. Subjects who discontinue study treatment for reasons other than progressive disease will participate in ongoing response evaluation assessments as detailed in Section 8.3.1.

m. End of Treatment Safety Follow Up: 30 ±7 days after last dose of study treatment or prior to subsequent therapy. May occur sooner if subject is scheduled to start a new anticancer treatment.

n. Randomization should occur as close to the time of the expected first dose as possible and not more than 72 hours prior to the expected first dose of study treatment.

o. Subjects will be randomized to a study treatment assignment and will continue on this study treatment assignment until study treatment discontinuation as described in the protocol Section 8.

p. Peripheral blood MRD assessment for subjects terminating study treatment who have not experienced progressive disease.

q. Once a subject progresses, he/she will be contacted approximately every 24 weeks from the last dose by clinic visit or telephone to assess survival for up to the end of the study. Subsequent anticancer therapies, best response to therapy, and information about other malignancies will be collected.

Appendix B. ECOG Performance Status Scores

Status	Eastern Cooperative Oncology Group (ECOG) Performance Status**
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, 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.

** Oken MM, Creech RH, Tormey DC, et al: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 5:649 655, 1982.

Available at: http://www.ecog.org/general/perf stat.html. Accessed January 4, 2008.

Appendix C. Inhibitors and Inducers of CYP3A

Inhibitors and inducers of CYP3A enzymes are defined as follows. Refer to Section 6.2.1 on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib. Further information can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/main-table/.

Inhibitors of CYP3A	**Inducers of CYP3A**
Strong inhibitors:	carbamazepine
indinavir	efavirenz
nelfinavir	nevirapine
ritonavir	barbiturates
clarithromycin	glucocorticoids
itraconazole	modafinil
ketoconazole	oxcarbarzepine
nefazodone	phenobarbital
saquinavir	phenytoin
suboxone	pioglitazone
telithromycin	rifabutin
cobicistat	rifampin
boceprevir	St. John's Wort
mibefradil	troglitazone
telaprevir	
troleandomycin	
posaconazole	
voriconazole	
Moderate inhibitors:	
aprepitant	
amprenavir	
amiodarone	
atazanavir	
ciprofloxacin	
crizotinib	
darunavir/ritonavir	
dronedarone	
erythromycin	
diltiazem	
fluconazole	
fosamprenavir	
grapefruit juice	
Seville orange juice	
verapamil	
imatinib	
Weak inhibitors:	
cimetidine	
fluvoxamine	
All other inhibitors:	
chloramphenicol	
delaviridine	
gestodene	
mifepristone	
norfloxacin	
star fruit	

Appendix D. Follicular Lymphoma International Prognostic Index-1

The Follicular Lymphoma International Prognostic Index-1 (FLIPI-1) is a prognostic scoring system developed as a result of a large international cooperative effort in which clinical data was collected from 4167 patients with FL diagnosed between 1985 and 1992 (Solal-Céligny 2004). From this database, a prognostic index with five adverse factors was derived and validated. The parameters include age, Ann Arbor stage, and number of nodal areas involved, hemoglobin levels and serum LDH levels (Table 10). Each of these adverse factors is assigned one point if positive, the points are totaled to give the final FLIPI-1 score and lymphoma prognoses are based on this score.

The index is able to separate patients with FL into three distinct prognostic groups with unique survival outcomes. If the score is 0 to 1, the patient is considered "low risk" according to the FLIPI-1. Overall survival at 10 years is estimated to be 70%. If the score is 2, the patient is considered "intermediate risk" according to the FLIPI-1. Overall survival at 10 years is estimated to be 50%. If the score is ≥3, the patient is considered "high risk" according to the FLIPI-1. Overall survival at 10 years is estimated to be 35%.

Table 10. FLIPI-1 Criteria

Parameter	Adverse factor
Age	≥60 years
Ann Arbor stage	III-IV
Hemoglobin level	<12 g/dL
Serum LDH level	>ULN (upper limit of normal)
Number of involved nodal areas	>4
Risk group according to FLIPI-1 score	**Number of factors**
Low	0-1
Intermediate	2
High	≥3

(Solal-Céligny 2004)

Appendix E. New York Heart Association (NYHA) Functional Classification

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

Source:

The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253 256.

Appendix F. Child-Pugh Score for Subjects with Liver Impairment

Measure	1 point	2 points	3 points
Total bilirubin, μmol/L (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/L (g/dL)	>35 (>3.5)	28-35 (2.8-3.5)	<28 (<2.8)
PT/INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	Class
5-6	A
7-9	B
10-15	C

Source:

1. Child CG, Turcotte JG. "Surgery and portal hypertension". In Child CG. The liver and portal hypertension. Philadelphia:Saunders. 1964. pp. 50 64.
2. Pugh RN, Murray Lyon IM, Dawson L, et al . "Transection of the oesophagus for bleeding oesophageal varices". The British journal of surgery, 1973;60: 646 9.

Appendix G. Revised Criteria for Response Assessment of Malignant Lymphoma (Cheson 2014)

The following Table provides a summary of response criteria for malignant lymphoma according to Cheson (Cheson 2014). Please refer to published international guidelines for the most recent and complete details.

Table 11. Criteria for Response Assessment of Non-Hodgkin's Lymphoma

Response	Site	PET-CT-Based Response	CT-Based Response
Complete Response (CR)	Lymph nodes and extralymphatic sites	Complete metabolic response	Complete radiologic response (all of the following)
		Score 1, 2, or 3[a, b] with or without a residual mass on 5PS[b] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, 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
	Non measured 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 Response (PR)	Lymph nodes and extralymphatic sites	Partial metabolic response	Partial remission (all of the following)
		Score 4 or 5[b] 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 lesion	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal

Response	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 (SD)	Lymph nodes and extralymphatic sites	No metabolic response	Stable disease
		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
	Non measured lesion	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 (PD)	Individual target nodes/nodal masses	Progressive metabolic disease	Progressive disease requires **at least 1** of the following. PPD progression: 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 (eg, 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
		Score 4 or 5 with an increase in intensity of uptake from baseline and/or meets criteria below for new FDG-avid foci	
	Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or End of Treatment assessment	
	Non measured lesions	None	New or clear progression of preexisting nonmeasured lesions

Response	Site	PET-CT-Based Response	CT-Based Response
	New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, 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; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

Footnotes:

a. 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 two 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 (eg, 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 (eg, 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 (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

b. 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.

Appendix H. FACT-Lym (Version 4)

FACT-Lym (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Lym (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Lym (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LYM1	I am bothered by itching	0	1	2	3	4
LYM2	I have trouble sleeping at night	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
Gs1	I have a loss of appetite	0	1	2	3	4
HI8	I have trouble concentrating	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4