PROTOCOL

TITLE:	A Multicenter Open-Label Phase 1b/2 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Combination with Lenalidomide and Rituximab in Subjects with Relapsed or Refractory Diffuse Large B-Cell Lymphoma
PROTOCOL NUMBER:	PCYC-1123-CA
STUDY DRUG:	Ibrutinib (PCI-32765)
IND NUMBER:	102,688
EudraCT NUMBER:	2013-004341-17
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DATE FINAL:	21 October 2013
AMENDMENT 1.0:	13 January 2014
AMENDMENT 2.0:	03 February 2015
AMENDMENT 3.0:	13 July 2015
AMENDMENT 4.0:	10 November 2015
AMENDMENT 5.0:	01 June 2016

PROTOCOL APPROVAL PAGE

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I have carefully read Protocol PCYC-1123-CA entitled "A Multicenter Open-Label Phase 1b/2 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Combination with Lenalidomide and Rituximab in Subjects with Relapsed or Refractory Diffuse Large B-Cell 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 (dd/mmm/yyyy)

Print Name

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

03 Jun 2016

Medical Monitor's Signature Date (dd/mmm/yyyy)
Jutta K. Neuenburg, M.D., Ph.D.
Clinical Science, Pharmacyclics LLC

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SYNOPSIS

Study Title	A Multicenter Open-Label Phase 1b/2 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Combination with Lenalidomide and Rituximab in Subjects with Relapsed or Refractory Diffuse Large B-Cell Lymphoma
Protocol Number	PCYC-1123-CA
Study Phase	1b/2
Population	Phase 1b: Relapsed or refractory diffuse large B-cell lymphoma (DLBCL) Phase 2: Relapsed or refractory de novo DLBCL of non-germinal center B-cell like (non-GCB) subtype
Study Drugs	Ibrutinib will be supplied as 140 mg hard gelatin capsules for oral (PO) administration. Lenalidomide will be supplied as 5 mg hard gelatin capsules for PO administration. Rituximab will be available as 100 mg/10 mL and 500 mg/50 mL solution in a single-use vial for intravenous (IV) administration.

Objectives	**<u>Phase 1b:</u>**
	Primary Objectives:
	• To determine the maximum tolerated doses (MTD) and/or the recommended Phase 2 (RP2) dose of ibrutinib in combination with lenalidomide and rituximab by dose escalation of lenalidomide in subjects with relapsed or refractory DLBCL.
	• To determine the safety and tolerability of ibrutinib in combination with lenalidomide and rituximab in subjects with relapsed or refractory DLBCL by dose escalating lenalidomide.
	Secondary Objective:
	• To evaluate the efficacy of ibrutinib in combination with lenalidomide and rituximab by assessing the overall response rate (ORR) in subjects with relapsed or refractory DLBCL by lenalidomide dose group.
	<u>Phase 2:</u>
	Primary Objective:
	• To evaluate the efficacy of ibrutinib in combination with lenalidomide and rituximab by assessing the overall response rate (ORR) in subjects with relapsed or refractory non-GCB DLBCL.
	Secondary Objectives:
	• To determine the efficacy of ibrutinib in combination with lenalidomide and rituximab in subjects with relapsed or refractory non-GCB DLBCL by assessing the following efficacy parameters:
	  • Complete Response (CR)
	  • Duration of Response (DOR)
	  • Progression Free Survival (PFS)
	  • Overall Survival (OS)

<table>
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To determine the safety and tolerability of ibrutinib in combination with lenalidomide and rituximab in subjects with relapsed or refractory non-GCB DLBCL.
Exploratory Objectives:
Efficacy analysis based on the activated B-cell like (ABC) subtype identified by gene expression profiling (GEP) will be performed.
Effect of ibrutinib on peripheral T/B/natural killer (NK) cell counts.
Effect of ibrutinib on serum immunoglobulin levels (IgG, IgM, and IgA).
Pharmacokinetics:
Plasma pharmacokinetics of ibrutinib and PCI-45227.
Biomarkers:
Identify signaling pathways or biomarkers that predict sensitivity or resistance to ibrutinib.
Frequency of tumor mutations (or other molecular markers).
</td></tr>
<tr><td>Study Design</td><td>
This Phase 1b/2 study is designed to assess the safety and efficacy of ibrutinib in combination with lenalidomide and rituximab in subjects with relapsed/refractory DLBCL not eligible for transplant. Phase 2 will evaluate only subjects with de novo non-GCB subtype DLBCL. Approximately 46 subjects will be enrolled in the Phase 1b portion. Phase 2 will enroll approximately 55 subjects to ensure enrollment of at least 49 response-evaluable subjects at 20 mg lenalidomide; approximately 28 additional subjects may be enrolled at 25 mg lenalidomide.

<u>Phase 1b:</u>

In the dose escalation portion of the study, up to four cohorts may be explored and lenalidomide dose escalation will follow the 3+3+3 principle for MTD determination. Due to the fact that the subject population studied is significantly ill and an inability to complete the DLT observation period may occur due to progression of disease, additional subjects may be screened and enrolled in any cohort. The DLT rules will continue to apply whereas if 1 DLT is observed, the cohort will be expanded to 6, and if 2 DLTs occur, the cohort will be expanded to 9.

Ibrutinib will be administered orally daily at 560 mg and will be initiated on Day 1 of the first cycle. Treatment will be continuous (without interruption) and will continue until disease progression or unacceptable toxicity. Lenalidomide will be administered orally daily at the dose designated by cohort on Days 1-21 of each 28-day cycle and will continue until disease progression or unacceptable toxicity. Rituximab 375 mg/m^2 will be administered intravenously (IV) on Day 1 of each 28-day (4 weeks) cycle for 6 cycles.
<table>
<tr><th></th><th>Ibrutinib (PO)</th><th>Lenalidomide* (PO)</th><th>Rituximab (IV)</th></tr>
<tr><td>Cohort 1 & 1+</td><td>560 mg</td><td>15 mg</td><td>375 mg/m^2</td></tr>
<tr><td>Cohort 2</td><td>560 mg</td><td>20 mg</td><td>375 mg/m^2</td></tr>
<tr><td>Cohort 3</td><td>560 mg</td><td>25 mg</td><td>375 mg/m^2</td></tr>
</table>
*If DLT criteria are met in Cohort 1, an additional cohort will be enrolled with a lenalidomide dose of 10 mg.
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</table>

If 3 subjects in Cohort 1 experience a dose limiting toxicity (DLT), dose level -1 (10 mg lenalidomide) was planned to be enrolled. After completion of Cohort 1, due to 3 DLTs in 7 evaluable subjects, a cohort at Dose Level -1 was opened. After completion of the Dose Level -1 cohort, if <33% of subjects experience a DLT, dose re-escalation to higher dose levels starting with the lenalidomide dose of 15 mg may occur. If the dose level of 20 mg lenalidomide is determined to be safe and tolerated in the Phase 1b, this dose will be considered the recommended Phase 2 dose (RP2D) and a Phase 2 cohort with 20 mg lenalidomide will be initiated. Concurrent with the Phase 2 at 20 mg lenalidomide, a Phase 1b cohort with 25 mg lenalidomide may be initiated. If the interim analysis of the 20 mg lenalidomide cohort is negative, the 25 mg lenalidomide dose may be used in an additional cohort in the Phase 2, if safe and tolerated in the Phase 1b.

Phase 2:

Phase 2 will be conducted as an international, multicenter, open-label study.

Phase 2 will enroll approximately 49 response-evaluable subjects at 20 mg lenalidomide; approximately 28 additional subjects may be enrolled at 25 mg lenalidomide.

Eligible subjects will receive ibrutinib, lenalidomide and rituximab per the treatment schedule as shown below. If determined to be safe and tolerated in the Phase 1b portion of the trial, the proposed dose of lenalidomide for Phase 2 is 20 mg. Subjects will be treated until disease progression or unacceptable toxicity.

Treatment Schedule[a]

	Cycles 1-6	Cycles 7+
Ibrutinib	PO daily	PO daily
Lenalidomide	PO daily Days 1-21	PO daily Days 1-21
Rituximab	IV on Day 1	NA

[a.] Each cycle will be 28-days in length (4 weeks) and subjects will continue until disease progression or unacceptable toxicity. Rituximab will be given for the first 6 cycles.

An interim analysis will be performed including approximately 28 evaluable subjects with adequate tumor response assessment. Details of the interim analysis and decision rules will be described in the statistical analysis plan (SAP). In addition, if there are safety concerns, a cohort with ibrutinib and lenalidomide without rituximab may be considered in the Phase 2.

Immunohistochemistry (IHC) and GEP will be used to assess subject status with respect to subtype of DLBCL. The limitations of IHC allow only a distinction between subjects as either non-GCB or GCB phenotype since within the non-GCB group one may include subjects with a true unclassified (intermediate) subtype. With GEP the subjects can be further categorized into the following subtypes: ABC, GCB, unclassified, and unknown due to tissue limitations. Throughout the protocol description of enrolled subjects as non-GCB is based on IHC testing used at screening; and the use of the term ABC subtype refers to subjects who have been subsequently profiled by GEP and then classified as the true ABC subtype.

Inclusion Criteria	**Inclusion Criteria:** 1. Pathologically confirmed: • Phase 1b: diffuse large B-cell lymphoma • Phase 2: de novo non-GCB DLBCL by IHC (Hans method) Note: Sufficient tissue sample for evaluation by IHC and GEP is required for subjects in Phase 2. 2. Relapsed or refractory disease, such as either: 1) recurrence of disease after a complete response (CR), or 2) partial response (PR), stable disease (SD) or progressive disease (PD) at completion of the treatment regimen preceding entry to the study (residual disease). 3. Subjects must have previously received an appropriate first-line treatment regimen. 4. For subjects having a computed tomography (CT) scan abnormality with uncertain interpretation following completion of the most recent treatment regimen: biopsy confirmation of residual DLBCL is required prior to study entry to confirm residual DLBCL and to rule out a non-lymphomatous process (e.g., fibrosis). 5. Subjects who have not received HDT/SCT must be ineligible for HDT/SCT as defined by meeting any of the following criteria: a. Age ≥70 years. b. Diffuse lung capacity for carbon monoxide <50% by pulmonary function test. c. Left ventricular ejection fraction <50% by multiple gated acquisition/echocardiogram. d. Other organ dysfunction or co-morbidities precluding the use of HDT/SCT on the basis of unacceptable risk of treatment-related morbidity. e. Failure to achieve PR or CR with salvage therapy. f. Subject refusal of HDT/SCT. 6. One or more measurable disease sites on CT scan (>1.5 cm in longest dimension). Lesions in anatomical locations (such as extremities or soft tissue lesions) that are not well visualized by CT may be measured by MRI instead (see Section 7.3.1). 7. Adequate hematologic function with screening laboratory assessment independent of growth factor and transfusion support for at least 7 days, with the exception of pegylated G-CSF (pegfilgrastim) and darbepoetin which require at least 14 days, defined as: a. Absolute neutrophil count >1,500 cells/mm^3 (1.5 x 10^9/L). b. Platelet count >75,000 cells/mm^3 (75 x 10^9/L). c. Hemoglobin >8.0 g/dL. 8. Adequate hepatic and renal function with screening laboratory assessment defined as: a. Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤2.5 x upper limit of normal (ULN). b. Creatinine clearance (Cockcroft-Gault or 24-hour creatinine clearance collection) >60 mL/min.

	c. Bilirubin <1.5 x ULN [unless bilirubin rise is due to Gilbert's syndrome (as defined by >80% unconjugated hyperbilirubinemia) or of non-hepatic origin]. 9. PT/INR <1.5 x ULN and PTT (aPTT) <1.5 x ULN. 10. Men and women ≥18 years of age. 11. Eastern Cooperative Oncology Group performance status of <2. 12. All study participants must be registered into the mandatory Revlimid REMS™ program, and be willing and able to comply with the requirements of the Revlimid REMS™ program (**US sites only**). 13. Female subjects of childbearing potential (FCBP)[a] must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days as required by Revlimid REMS™) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. See Appendix 7 **(US sites only).** 14. Female subjects of childbearing potential (FCBP)[a] must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days and again within 24 hours prior to starting Cycle 1 of lenalidomide. FCBP must also agree to ongoing pregnancy testing. All subjects must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix 8 **(ex-US sites only).** 15. Male subjects must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. See Appendix 7 **(US sites only).** 16. Male subjects must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. All subjects must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix 8 **(ex-US sites only).** 17. Female subjects of childbearing potential (FCBP)[a] and male subjects who are sexually active must use TWO acceptable methods of birth control, one highly effective method of birth control plus one additional effective method of birth control for at least 28 days prior to study treatment and during the study treatment period. For female subjects, these birth control requirements must be adhered to for 12 months after the last dose of rituximab or 30 days after the last dose of ibrutinib and lenalidomide, whichever is later. For male subjects, these birth control requirements must be adhered to for 90 days after the last dose of ibrutinib and lenalidomide, whichever is later. Male subjects must agree to not donate sperm during the study

[a] A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

	treatment period and up to 90 days after the last dose of ibrutinib and lenalidomide. 18. Life expectancy of more than 3 months.
Exclusion Criteria:	**Exclusion Criteria:** **Phase 2 only** 1. Transformed DLBCL, GCB DLBCL or DLBCL with coexistent histologies (eg, follicular or mucosa-associated lymphoid tissue [MALT] lymphoma). 2. Primary mediastinal (thymic) large B-cell lymphoma. **Phase 1b/2** 3. Medically apparent central nervous system lymphoma or leptomeningeal disease. 4. History of allogeneic stem-cell (or other organ) transplantation. 5. Any chemotherapy, external beam radiation therapy, or anticancer antibodies within 2 weeks of the first dose of study drug. 6. Radio- or toxin-immunoconjugates within 10 weeks prior to first dose of study drug. 7. Concurrent enrollment in another therapeutic investigational study or have previously taken ibrutinib and/or lenalidomide. 8. History of other malignancies, except: a. Malignancy treated with curative intent and with no known active disease present for ≥5 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician. b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease. c. Adequately treated carcinoma in situ without evidence of disease. 9. Concurrent systemic immunosuppressant therapy (eg, cyclosporine A, tacrolimus, etc., or chronic administration of >20 mg/day of prednisone) within 28 days of the first dose of study drug. 10. Recent infection requiring intravenous anti-infective treatment that was completed ≤14 days before the first dose of study drug. 11. Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 4.03), ≤ Grade 1 or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia. 12. Known bleeding diathesis (eg, von Willebrand's disease) or hemophilia. 13. Known history of human immunodeficiency virus (HIV), chronic or active hepatitis C virus (HCV) or hepatitis B virus (HBV) infection. 14. Major surgery within 4 weeks prior to first dose of study drug. 15. 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 enrollment. 16. Unable to swallow capsules, malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the

	stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction. 17. Concurrent use of warfarin or other Vitamin K antagonists (eg, phenprocoumon). 18. Requires treatment with a strong cytochrome P (CYP) 450 3A inhibitor. 19. Any life-threatening illness, medical condition including uncontrolled Diabetes Mellitus, or organ system dysfunction that, in the opinion of the investigator, could compromise the subject's safety or put the study outcomes at undue risk 20. Currently active, clinically significant hepatic impairment Child-Pugh class B or C according to the Child-Pugh classification 21. Known hypersensitivity to lenalidomide (or thalidomide) or rituximab. 22. Lactating or pregnant. 23. Unwilling or unable to participate in all required study evaluations and procedures. 24. 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).
Safety Monitoring	This study will be monitored in accordance with the Sponsor's Pharmacovigilance Committee procedures. Adverse events (AEs) and serious adverse events (SAEs) will be reviewed by the Sponsor on an ongoing basis to identify safety concerns. The Sponsor may schedule periodic conference calls with the Investigators to discuss study progress, obtain Investigator feedback and exchange, and discuss study-specific issues including AEs and SAEs. A Dose Level Review Committee will evaluate safety data following the completion of each dose observation period of the Phase 1b portion. Members of this committee will include the Sponsor (at a minimum: the Medical Monitor or designee, a Drug Safety representative and a Biostatistician) as well as participating Investigators/designees.
Study Treatment	One cycle of treatment is 28-days in length and consists of daily administration of ibrutinib, daily administration of lenalidomide Days 1-21 each cycle and rituximab once each cycle on Day 1 for 6 cycles. Ibrutinib and lenalidomide dosing will continue as long as the subject is deriving clinical benefit (CR, PR, or SD) and the subject is not experiencing any unacceptable toxicity. **Phase 1b:** Cohort -1 - Ibrutinib 560 mg, lenalidomide 10 mg and rituximab 375 mg/m^2 Cohort 1 & 1+ - Ibrutinib 560 mg, lenalidomide 15 mg and rituximab 375 mg/m^2 Cohort 2 - Ibrutinib 560 mg, lenalidomide 20 mg and rituximab 375 mg/m^2 Cohort 3 - Ibrutinib 560 mg, lenalidomide 25 mg and rituximab 375 mg/m^2 **Phase 2:**

	Treatment: Ibrutinib, lenalidomide and rituximab Refer to the current rituximab package insert for more details. **Premedication:** Premedication for rituximab should be administered per the package insert. **Dosing/Administration:** The dosage and schedules for the 3 drugs will be administered as follows until disease progression or unacceptable toxicity: • Ibrutinib 560 mg PO once daily (continuous) • Lenalidomide (dose from Phase 1b) mg PO once daily Days 1-21 of a 28-day cycle • Rituximab 375 mg/m^2 IV per package insert on Day 1 of each cycle for 6 cycles
Concomitant Therapy	Refer to Section 6.1.1 for permitted concomitant medications. Refer to Section 6.1.2 for medications to be used with caution. Refer to Section 6.1.3 for prohibited concomitant medications.
Statistical Methods and Data Analysis	**Analysis Methods for Phase 1b** The ORR and its 95% confidence interval (CI) will be calculated using the exact binomial distribution. The CR rate and its corresponding 95% CI will be calculated likewise. **Analysis Methods for Phase 2** The primary analysis for all efficacy endpoints will be conducted based on the response-evaluable population with de novo non-GCB subtype DLBCL. The ORR and its 95% CI will be calculated using the exact binomial distribution. If the lower bound of the CI around the ORR is greater than or equal to 40%, the primary efficacy objective is achieved. Duration of response will be analyzed for responders and is defined as the interval between the date of initial documentation of a response of CR or PR, and the date of first documented evidence of progressive disease, or death. The distribution (median, its 95% CI and Kaplan-Meier curves) of DOR will be provided using Kaplan-Meier estimates for responders in the all-treated population. Progression-free survival will be assessed and defined as the period from the date of first dose of study drug until the date of first documented evidence of progressive disease or death, whichever occurs earlier. Overall survival is measured from the date of first dose of study drug to the date of the subject's death from any cause. Progression-free survival and OS will be analyzed by the same Kaplan-Meier analysis method used for DOR.
Sample Size Determination	The planned sample size for Phase 2 is approximately 55 subjects to ensure enrollment of at least 49 response-evaluable subjects; approximately 28 additional subjects may be enrolled at 25 mg lenalidomide. The main analysis will be the comparison of the response rate to the ORR of a historical control of 40%.

	An interim analysis will be performed including approximately 28 evaluable subjects with adequate tumor response assessment. Enrollment in the 20 mg lenalidomide cohort will continue while the interim analysis is performed. Details of the interim analysis and decision rules will be described in the SAP. At the interim analysis, the review committee could recommend 1. continuation of the study with 20 mg lenalidomide; or 2. increase of the lenalidomide dose to 25 mg, if determined to be safe and tolerated in the Phase 1b, including approximately 28 evaluable subjects with adequate tumor response assessment followed by an interim analysis. The null hypothesis that the true ORR is 40% will be tested against a 1-sided alternative that the ORR is 60%. The null hypothesis will be rejected if 27 or more responses are observed in the 49 subjects. This design yields a 1-sided type I error rate of 0.025 and power of 80% when the true ORR is 60%. This statistical design including the number of subjects and the number of responders follows the statistical framework of Simon's minmax two-stage design (Simon 1989).

ABBREVIATIONS

ABC	activated B-cell like (DLBCL subtype as determined by GEP)
AE	adverse event
ANC	absolute neutrophil count
AUC	area under the curve
BCR	B-cell receptor
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
CEPP	cyclophosphamide/etoposide/cisplatin/prednisone
CFR	Code of Federal Regulations
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
CI	confidence interval
CLL	chronic lymphocytic leukemia
CTCAE	Common Terminology Criteria for Adverse Events
CR	complete response
CSR	Clinical Study Report
CT	computed tomography
CYP	cytochrome P
DLBCL	diffuse large B cell lymphoma
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DVT	deep vein thrombosis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eCRF	electronic case report form
EOT	End-of-Treatment
EMR	electronic medical records
ESMO	European Society for Medical Oncology
FCBP	female of childbearing potential
FDA	Food and Drug Administration
^{18}F-FDG	^{18}F-fluorodeoxyglucose
FFPE	formalin-fixed, paraffin-embedded (FFPE) tissues
GCB	germinal-cell B-cell-like (subtype)
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GDP	gemcitabine/dexamethasone/cisplatin
GEP	gene expression profiling
HBV	hepatitis B virus
HCV	hepatitis C virus
HDT	high dose therapy
HIPAA	Health Insurance Portability and Accountability Act

HIV	human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFNβ	interferon beta
Ig	Immunoglobulin
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IHC	Immunohistochemistry
IκBα	inhibitor of kappa B, alpha
ILD	Interstitial Lung Disease
IPI	International Prognostic Index
IRB	Institutional Review Board
IRC	Independent Review Committee
IRF4	interferon regulatory factor 4
ITT	intent-to-treat
IUD	intra-uterine device
IV	Intravenous
LDH	lactic acid dehydrogenase
MAD	maximum administered dose
MALT	mucosa-associated lymphoid tissue
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MTD	maximum tolerated dose
MRI	magnetic resonance imaging
MYD88	myeloid differentiation factor 88
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCCN	National Comprehensive Cancer Network
NDC	National Drug Code
NF-κB	nuclear factor- κB
NHL	non-Hodgkin's lymphoma
NK	natural killer (cells)
ORR	overall response rate (ORR = CR + PR)
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PE	pulmonary embolism
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PO	per os (oral)

PPP	Pregnancy Prevention Program
PR	partial response
aPTT	activated prothrombin thromboplastin time
PT	prothrombin time
QTcF	corrected QT interval (Fridericia formula)
RBC	red blood cells
R-CHOP	rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone
REB	Research Ethics Board
REMS™	Risk Evaluation and Mitigation Strategies
R-GEMOX	rituximab/gemcitabine/oxaliplatin
RNA	ribonucleic acid
RP2	recommended Phase 2
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCT	stem cell transplantation
SD	stable disease
SEER	Surveillance Epidemiology and End Results
SLL	small lymphocytic lymphoma
SOP	standard operating procedures
SPD	sum of the product of the diameters
TLS	tumor lysis syndrome
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
VTE	venous thromboembolism
WM	Waldenström's macroglobulinemia

1. INTRODUCTION

1.1. Ibrutinib (PCI-32765) Background

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 covering the treatment of patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy, patients with chronic lymphocytic leukemia (CLL), including CLL with a deletion of the short arm of chromosome 17 (del17p) or a *TP53* mutation, and patients with Waldenström's macroglobulinemia. Ibrutinib is currently under investigation in various indications as a single agent and in combinations.

B-cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B-cells express cell surface immunoglobulins comprising the B-cell receptor (BCR), which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways (Bishop 2003).

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

1.2. Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common of the aggressive non-Hodgkin lymphomas (NHL) in the United States, with an annual incidence that has been rising gradually since the 1990s (Fisher 2004). The estimated 2010 prevalence of NHL in the US was approximately 509,000 individuals, with over 200,000 of these cases in individuals over the age of 70 years (SEER 2010). It is estimated that 30-40% of NHL cases are of the DLBCL category (Hans 2004). According to the current SEER data, the median age at diagnosis is 67 years (SEER 2010). While approximately half of the incremental rise in incidence of DLBCL is attributable to identifiable factors, such as the increase in the incidence of human immunodeficiency virus (HIV)-related DLBCL, the evolution of more specific diagnostic techniques, and revisions in lymphoma classification schemes, much of the rising incidence remains unexplained (Holford 1992). A very aggressive malignancy in its untreated natural history, DLBCL is a potentially curable disease, with a significant proportion of patients cured with modern chemoimmunotherapy. Nonetheless, for those patients not cured by standard initial therapy, the prognosis remains generally poor (Gisselbrecht 2010) and DLBCL still accounts for the highest number of deaths per year of all the NHL histologies.

1.2.1. ABC (Non-GCB) Subtype

The major clinical prognostic factors for NHL are well described and have been incorporated into the International Prognostic Index (IPI) scoring system. The specific factors are: age >60 years, stage III or IV disease, performance status ≥2, and elevated lactate dehydrogenase (LDH) levels. These factors are combined in the IPI into 4 categories, with 5-year progression free survival (PFS) ranging from 40% to 70% and 5-year OS ranging from 26% to 73% among patients treated with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) (Ziepert 2010). Regarding applicability of the IPI in the era of modern chemoimmunotherapy (eg, R-CHOP), a recent report of a large series of patients treated with rituximab-based regimens found the IPI remains predictive for disease-free and overall survival (The International Non-Hodgkin's Lymphoma Prognostic Factors Project 1993).

Diffuse large B cell lymphoma is a heterogeneous disease not only clinically, but also morphologically and molecularly. Recent progress has been made in terms of understanding and categorizing the molecular heterogeneity of DLBCL. In a retrospective analysis of a large series of patients with DLBCL, the Leukemia and Lymphoma Molecular Profiling Project used deoxyribonucleic acid (DNA) microarray to identify distinct gene-expression profiles on the basis of hierarchical clustering (Rosenwald 2002). Two principal independent gene-expression subgroups were identified: germinal-center B-cell-like (GCB) and activated B-cell-like (ABC). Following standard chemotherapy, the GCB and ABC subgroups were not only prognostically distinct in direct comparison (with superior outcome in the GCB subgroup), but this prognostic distinction was also independent of the IPI. Therefore, it may be possible to distinguish prognostic subgroups of DLBCL on a molecular as well as clinical basis.

1.3. Standard Treatment and Unmet Medical Need

Even with the approval of new agents for the treatment of DLBCL patients, the prognosis for those not eligible for high dose therapy (HDT) and stem cell transplant after relapse remains poor. The choice of treatment and intensity is dependent upon patient age, co-morbidities, residual treatment related toxicities, and response to previous therapies.

At this time the standard of care for relapsed and refractory patients with chemosensitive disease to second-line therapy is to proceed on to HDT and stem cell transplant (SCT), although no preferred regimen has been identified.

For those patients with relapsed and refractory DLBCL not eligible for HDT/SCT, both the U.S. National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) recommend inclusion in a clinical trial whenever possible. According to the NCCN 2013 guidelines, if no appropriate clinical trials are available multiple immunotherapy and chemotherapy regimens with or without rituximab can be considered. Under the same circumstances the ESMO treatment guidelines state that multiple salvage chemotherapy regimens, including R-GEMOX (rituximab, gemcitabine and oxaliplatin) may be used (Tilly 2012). The reported outcomes for multiple salvage chemotherapy regimens are summarized in Table 1.

Table 1: Efficacy of Therapies in Relapsed/Refractory NHL Patients

Study	Number of Patients	ORR %	CR %	PFS (Months)	OS (Months)
CEPP +/- B (Chao 1990)					
All patients	69	70%	34%	7	12
DLBCL	22	77%	36%	--	--
DA-EPOCH + R (Jermann 2004)					
All patients	50	68%	28%	--	17.9
DLBCL	25	--	--	--	--
GDP +/- R (Crump 2004)					
All patients	51	53%	22%	3.1[a]	8.9[a]
DLBCL	40	--	--	--	--
GemOx +/- R (Lopez 2008)					
All patients	0	--	--	--	--
DLBCL	32	43%	34%	29%[b]	41%[b]
GemOx +/- R (Corazzelli 2009)					
All patients	62	57/78%	30/50%	7/28%	7/37%
DLBCL	--	--	--	FFS at 42m	at 42m
GemOx +/- R (El Gnaoui 2007)					
All patients	46	83%	50%	22	66%
DLBCL	33	82%	73%	24	at 2 years
Bendamustine +/- R (Ohmachi 2013)					
All patients	63	62.7%	37.3%	--	--
DLBCL	0	--	--	--	--
Bendamustine +/- R (Weidmann 2002)					
All patients	18	44%	17%	--	--
DLBCL	0	--	--	--	--

CEPP – cyclophosphamide, etoposide, prednisone, procarbazine; B – bleomycin; DA-EPOCH – dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; R – rituximab; GDP – gemcitabine, dexamethasone, carboplatin; GemOx – gemcitabine, oxaliplatin; FFS – failure-free survival

[a.] Outcomes for DLBCL patients not eligible for transplant, not reported for those that went on to HDT and SCT
[b.] Calculated as percent of patients at 12 months

It should be noted that the efficacy observed with various chemotherapy regimens with or without rituximab is often reported for all B-cell lymphomas, with very few studies reporting long-term outcomes and/or efficacy in patients specifically with DLBCL histologies (Table 1). In addition, we know that the different subtypes of DLBCL can be identified that have significant differences in prognosis translating into poor outcomes.

Although there are currently no approved therapies specifically for the different phenotypic subtypes of DLBCL in clinical practice, there is data available for the different subtypes in studies evaluating lenalidomide, rituximab and ibrutinib (Table 2).

Table 2: Efficacy of Select Studies in Relapsed/Refractory NHL Patients

Study	Number of Patients	ORR %	CR %	PFS (Months)	OS (Months)
Lenalidomide (Wiernik 2008)					
All patients	49	35	4	4	--
DLBCL	26	19	4	--	--
Lenalidomide (Witzig 2011)					
All patients	217	35	13	3.7	NA
DLBCL	108	28	7	2.7	NA
Lenalidomide (Hernandez-Ilizaliturri 2011)					
All patients	40	27.5	15	2.6	--
GCB	23	8.7	4.3	1.7	13.5
Non-GCB	17	52.9	29.4	6.2	14
Lenalidomide + Rituximab (Zinzani 2011)					
DLBCL	23	35	30	DFS at 12 m 34.8%	OS at 18 m 55.1%
Lenalidomide + Rituximab (Wang 2013)					
All patients	45[a]	33.3	22.2	3.7	10.7
DLBCL	32	28	22	2.8	10.2
Ibrutinib : PCYC-1106-CA (De Vos 2013)					
All patients	70	25	9		
GCB	20	5	0		9.8
Non-GCB	29	41	17		3.4

[a.] 41 evaluable for response

In a Phase 2 study of lenalidomide monotherapy in relapsed or refractory aggressive NHL (n=49), the ORR was 35% with a CR rate of 4%. The DLBCL subgroup had an ORR of 19% (5/26) comprised of 1 CR, 2 unconfirmed CRs and 2 PRs. The transformed low-grade lymphoma subgroup had an ORR of 33% (1/3) comprised of 1 PR, with the other 2 having SD as best response. The overall study population had a PFS of 4 months (Wiernik 2008). An additional Phase 2 study of lenalidomide monotherapy in patients with relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma (n=217) reported similar outcomes with an ORR of 35% with a CR rate of 13%. The overall study population had a PFS of 3.7 months. In the subset of patients with DLBCL (n=108) the ORR was 28% (30/108) with a 7% CR rate and median PFS of 2.7 months. In the subset of patients with transformed lymphoma (n=33) the ORR was 45% with a 21% CR rate and a median PFS of 12.8 months (Witzig 2011). A retrospective analysis was performed on three different studies evaluating the use of lenalidomide alone or in combination with rituximab or dexamethasone for the treatment of NHL. The final reported analysis was on 40 patients that received lenalidomide monotherapy for treatment of DLBCL, with an ORR of 27.5%. The outcomes were also reported based upon DLBCL subtype. Of the patients with ABC subtype (n=17), the ORR was 53% with 29.4% CR and 23.5% PR, and a median PFS of 6.2 months. For those patients with the GCB subtype (n=23), the ORR was 9% with 1 CR and 1 PR and a median PFS of 1.7 months. The OS for both groups was similar at 14 months and 13.5 months respectively (Hernandez-Ilizaliturri 2011).

Two Phase 2 trials have evaluated the safety and efficacy of lenalidomide in combination with rituximab in relapsed or refractory NHL. The first study enrolled multiple histologies (n=45) and included patients eligible for SCT. The outcomes for all patients included an ORR of 33% with a CR rate of 22% and a median PFS and OS of 3.7 and 10.7 months respectively. For those patients with DLBCL (n=32) the ORR was 28% with a CR rate of 22% and a median PFS of 2.8 months and OS of 10.2 months. There were no significant differences in clinical responses by DLBCL subtype. For those patients with transformed large cell lymphoma (n=9), the ORR was 56% with a CR rate of 33% and a median PFS of 4.3 and OS of 11.5 months (Wang 2013). The second trial evaluated only patients with DLBCL (n=23), and all were elderly and ineligible for SCT. The ORR was 35% and the CR rate was 30%. Disease free survival at 12 months was 33% with an OS of 55.1% at 18 months (Zinzani 2011).

Ibrutinib has demonstrated single agent activity in the treatment of relapsed or refractory de novo DLBCL in Study PCYC-1106-CA. Study PCYC-1106-CA is an ongoing Phase 2, open-label, non-randomized, multicenter study in patients with relapsed or refractory *de novo* DLBCL receiving 560 mg/day of ibrutinib. Data are currently available on 70 patients from this trial who have relapsed or refractory disease with 29 ABC subtype, 20 GCB subtype, 16 Type 3 subtype and 5 subjects subtype unknown. The ORR in these 70 patients was 25% (17/70) with 9% of patients achieving a complete response (CR) and 16% of patients achieving a partial response (PR). Of the patients with ABC subtype, the ORR was 41% (12/29) with 17% CR and 24% PR. Of the patients with GCB subtype the ORR was 5% (1/20) with the one responder achieving a PR. The median OS was 9.76 months for those with ABC subtype and 3.35 months for those with GCB subtype (De Vos 2013).

1.4. BTK and B cell Lymphoma

BCR signaling is essential for normal B cell differentiation and function. In addition, several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B cell malignancies. First, expression of a functional BCR is maintained throughout lymphoma progression even as the non-expressed immunoglobulin heavy chain is involved in oncogenic translocations and despite prolonged treatment of tumor cells with anti idiotype therapies (Küppers 2005, Meeker 1985). Also, selective knockdown of BCR components by RNA interference results in apoptosis in multiple B cell lymphoma cell lines (Gururajan 2006).

Recent studies indicate that chronic active BCR signaling is a pathogenic mechanism in ABC DLBCL and this chronic activation engages the classic NF-κB pathway; in contrast GCB DLBCL pathogenesis is independent of this pathway (Lenz 2010). This difference in the molecular mechanism of pathogenesis (ie, constitutive activation of NF-κB in ABC DLBCL) may explain why the ABC subtype is less sensitive to chemotherapy and remains less curable than the GCB subtype.

Btk plays an essential role in the chronic active BCR signaling cascade in which engages NF-κB activation in wild-type CARD11 ABC DLBCL. In vitro data targeting this pathway in ABC DLBCL cells was recently reported by Davis and colleagues (Davis 2010). Activated B-cell like

DLBCL cell lines with constitutive BCR signaling undergo cell death when treated with ibrutinib, while these drugs had no effect on ABC and GCB DLBCL cell lines that did not rely on constitutive BCR signaling. Clinical evidence that targeting the nuclear factor- κB (NF-κB) pathway has a favorable response to outcome in ABC versus GCB subtypes was reported by Dunleavy and colleagues (Dunleavy 2009). They showed in a Phase 2 study that bortezomib, which indirectly targets the NF κB pathway by inhibiting proteasome degradation of IκBα, in combination with chemotherapy had a response rate of 85% in ABC subtype versus 13% in GCB subtype (P=0.0004). Thus, inhibition of the BCR-NF-κB pathway by blocking Btk activity may represent a novel therapeutic strategy in ABC DLBCL.

1.5. Summary of Nonclinical Data

1.5.1. 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.

1.5.2. 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.

1.6. Summary of Clinical Data

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

1.6.1. Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging from 420 to 840 mg/day, exposure to ibrutinib increased proportionally to doses increased 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 regarding pharmacokinetics (PK) and product metabolism, please refer to the current version of the ibrutinib IB.

1.7. Summary of Clinical Safety of Ibrutinib

A brief summary of safety data from monotherapy and combination therapy studies is provided below. For more 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, USPI, SmPC).

1.7.1. Monotherapy Studies

Pooled safety data for a total of 1071 subjects treated with ibrutinib monotherapy from 9 studies in B-cell malignancies, which includes subjects from 2 randomized-control studies who crossed over from comparator treatment or placebo to receive ibrutinib monotherapy, are summarized below.

Most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N=1071):

Most frequently reported TEAEs >10%	Most frequently reported Grade 3 or 4 TEAEs >2%	Most frequently reported Serious TEAEs >1%
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	Pyrexia
Anemia	Hypertension	
Pyrexia	Atrial fibrillation	
Neutropenia		

1.7.2. Combination Therapy Studies

Pooled safety data for a total of 423 subjects treated with various therapies in combination with ibrutinib from 4 studies conducted in B-cell malignancies, which included 1 randomized-control study, are summarized below. Therapies used in combination with ibrutinib in these studies, included BR (bendamustine and rituximab), FCR (fludarabine, cyclophosphamide, and rituximab), ofatumumab, and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

Most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib in combination therapy (N=423):

Most frequently reported TEAEs >10%	Most frequently reported Grade 3 or 4 TEAEs >2%	Most frequently reported Serious TEAEs >1%
Neutropenia	Neutropenia	Febrile neutropenia
Diarrhea	Thrombocytopenia	Pneumonia
Nausea	Febrile neutropenia	Atrial fibrillation
Thrombocytopenia	Pneumonia	Pyrexia
Fatigue	Hypertension	

1.8. Risks (Ibrutinib)

1.8.1. Lymphocytosis and Leukostasis

Leukostasis

There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes (>400,000/µL) may confer increased risk. For subject and ibrutinib management guidance, refer to Section 5.4.4.

Lymphocytosis

Upon initiation of treatment, a reversible increase in lymphocyte counts (ie, ≥50% increase from baseline and above absolute count 5,000/µL), often associated with reduction of lymphadenopathy, has been observed in most subjects with CLL/small lymphocytic lymphoma (SLL) treated with ibrutinib. This effect has also been observed in some subjects with MCL treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few weeks of ibrutinib therapy (median time 1.1 weeks) and typically resolves within a median of 8.0 weeks in subjects with MCL and 18.7 weeks in subjects with CLL/SLL.

A large increase in the number of circulating lymphocytes (eg, >400,000/µL) has been observed in some subjects. Lymphocytosis was not observed in subjects with Waldenström's macroglobulinemia treated with ibrutinib. Lymphocytosis appeared to occur in lower incidence and at lesser magnitude in subjects with CLL/SLL receiving ibrutinib in combination with chemoimmunotherapy.

For subject and ibrutinib management guidance, refer to Section 5.4.4.

Available data in subjects with DLBCL that have been treated with ibrutinib in multiple Phase 1 and Phase 2 studies, revealed no evidence of treatment related lymphocytosis.

1.8.2. Bleeding-related Events

There are reports of hemorrhagic events in subjects 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 subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied. See Section 6.1.2.3 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 6.2 for guidance on ibrutinib management with surgeries or procedures.

1.8.3. Rash

Rash has been commonly reported in subjects 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.

1.8.4. Non-melanoma skin cancer

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

1.8.5. 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 5.4.4).

1.8.6. Tumor Lysis Syndrome

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

1.8.7. Infections

Fatal and non-fatal infections have occurred with ibrutinib therapy. At least 25% of subjects with MCL and 35% of subjects with CLL had Grade 3 or greater infections per NCI Common Terminology Criteria for Adverse Events (CTCAE, v4.03). The most commonly reported infections include pneumonia, cellulitis, urinary tract infection and sepsis. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib.

1.8.8. Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Monitor subjects for pulmonary symptoms indicative of ILD. Should symptoms develop follow the protocol dose modification guidelines (see Section 5.4.4).

1.8.9. Cytopenias

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

1.8.10. Atrial Fibrillation

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 5.4.4).

1.9. Summary of Clinical Safety for Lenalidomide in Lymphoma

Lenalidomide is currently approved for the treatment of relapsed or refractory mantle cell lymphoma at a recommended starting dose of 25 mg orally once daily for 21 days every 28 days.

The safety data for 134 patients receiving monotherapy for MCL has been evaluated. The most common treatment-emergent adverse events (>15%) were neutropenia (49%), thrombocytopenia (36%), fatigue (34%), diarrhea (31%), anemia (31%), nausea (30%), cough (28%), pyrexia (23%), rash (22%), dyspnea (18%), pruritis (17%), constipation (16%), and peripheral edema (16%). The most common Grade 3 or 4 adverse events were hematologic in nature: neutropenia (43%), thrombocytopenia (28%), and anemia (11%). Pneumonia (9%) was the most frequent non-hematologic Grade 3/4 adverse event.

The median duration of treatment in this patient population was 95 days (1-1002 days). Seventy-six patients (57%) required at least one dose interruption for an adverse event, while 51 patients (38%) had at least one dose reduction due to toxicity. Twenty-six patients (19%) discontinued treatment due to adverse events.

Lenalidomide has a black box warning for embryo-fetal toxicity, hematologic toxicity and venous thromboembolism.

Complete and updated safety information is available in the current Revlimid® Investigator's Brochure.

1.9.1. Venous Thromboembolism

Venous thromboembolism including deep vein thromobis (DVT) and pulmonary embolism (PE), has been reported in patients during treatment for NHL generally, occurring at incidences from ~7% up to 20% (Zhou 2010; Park 2012; Lyman 2013). In lenalidomide clinical trials, DVT and PE were reported in 7 (2.6%) and 6 (2.2%) of 266 subjects with relapsed or refractory NHL receiving lenalidomide in clinical studies NHL-002 and NHL-003 (Wiernik 2008; Witzig 2011). Anti-thrombotic prophylaxis was not suggested in NHL-002 but was required for subjects considered to be at high risk of developing DVT in NHL-003. In a study evaluating lenalidomide plus rituximab versus lenalidomide alone in relapsed follicular lymphoma subjects, thrombosis was reported in 2 (4%) of the combination arm versus 7 (16%) in the single agent arm (Leonard 2012). In an additional study evaluating lenalidomide plus rituximab in MCL patients 2 (5%) Grade 3 and 1 (5%) Grade 4 thromboembolic events were reported (Wang 2013).

1.9.2. Second New Cancers

According to researchers, patients with cancer have a higher risk of developing a second new cancer when compared to people without cancer. In clinical studies of newly diagnosed multiple myeloma, a higher number of second cancers were reported in patients treated with induction therapy (treatment as a first step to reducing the number of cancer cells) and/or bone marrow transplant and then with lenalidomide for a long period of time compared to patients treated with induction therapy and/or bone marrow transplant and then with placebo (a capsule containing no lenalidomide). Patients should make their doctors aware of their medical history and any concerns they may have regarding their own increased risk of other cancers.

For more complete safety information, refer to the current Revlimid® Investigator's Brochure.

1.10. Summary of Clinical Safety for Rituximab

Rituximab is currently approved for the treatment of diffuse large B-cell NHL at a recommended starting dose of 375 mg/m^2 IV on Day 1 of each cycle for up to 8 infusions.

The safety data for 2,783 patients receiving rituximab monotherapy or in combination with chemotherapy for lymphoid malignancies has been integrated, and of this population 927 patients had DLBCL. The most common treatment-emergent adverse events (≥25%) were infusion reactions, fever, lymphopenia, chills, infection, and asthenia. The incidence of infusion reactions was highest during the first infusion (77%) and could be characterized by fever, chills/rigors, nausea, pruritis, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. The overall incidence of infection was 31%, with serious infections (Grade 3 or 4), including sepsis occurring in <5% in single arm studies. In patients receiving monotherapy, Grade 3 hematologic toxicity was seen in 48% including lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%) and thrombocytopenia (2%). Rituximab-induced B-cell depletion occurred in 70-80% of patients with NHL, with decreased IgM and IgG serum levels in 14% of these patients.

Rituximab has a black box warning for fatal infusion reactions, tumor lysis syndrome, severe mucocutaneous reactions and progressive multifocal encephalopathy.

For more complete safety information, refer to the prescribing information (Rituxan®/MabThera® Prescribing Information and Package Insert).

1.11. Rationale for Combination

Preclinical studies document the potential synergy of ibrutinib and lenalidomide in the treatment of ABC DLBCL based upon their mechanism of action and specificity for the genetic alterations seen in ABC DLBCL (Yang 2012). Activated B-cell like DLBCL tumors depend upon both the BCR and MYD88 signal pathways for survival. Genetic alterations in the BCR subunits CD79A and CD79B promote cell survival by activating NF-κB and inducing IRF4, which decreases the cytotoxic effects of interferon β (IFNβ). MYD88 mutations increase the production of interferon β (IFNβ), which is detrimental to tumor cell survival. Interferon regulatory factor 4 (IRF4)

expression is also a characteristic of the ABC subtype and appears to be at the center of the cells regulatory activities. Ibrutinib plays a role by blocking chronic BCR signaling leading to a decrease in NF-κB activity. Lenalidomide downmodulates IRF4, leading to an increase in IFNβ secretion and a decrease in NF-κB activity. Combining ibrutinib and lenalidomide therefore appears to target key pathways in ABC DLBCL that may lead to synergy in vivo.

It is unclear whether or not the addition of rituximab to the combination of lenalidomide and ibrutinib will confer a significant improvement in outcomes. Although the ORR to lenalidomide is similar to that of lenalidomide + rituximab in patients with DLBCL (Table 2), there may be an improved depth of response with an increased CR rate when rituximab is added which may translate clinically into an improvement in the duration of the response and possible the OS in this patient population. For that reason, the 3 drugs in combination were chosen for the Phase 2 portion of the study. In addition, should safety concerns arise with the 3-drug combination, a 2-drug combination of ibrutinib with lenalidomide may be considered.

With respect to safety, in the studies evaluating lenalidomide in combination with rituximab the overall safety profile is similar to that reported in monotherapy studies with the most common Grade 3 and 4 AEs being hematologic in nature. Based upon the safety profile of ibrutinib monotherapy and the lack of significant myelosuppression, the combination of lenalidomide, ibrutinib, and rituximab may be well tolerated with the potential to exploit synergistic effects for improvement in outcomes in a frail population with minimal therapeutic options and poor prognosis.

1.12. Rationale for Dose

The rationale for the current dose and schedule of each agent is based not only upon the approved dose for these treatments, but also based upon the safety data known regarding the use of these therapies for the treatment of NHL in the relapsed and refractory setting. The established dose in monotherapy studies of lenalidomide is 25 mg administered orally once daily for 21 days of a 28 day cycle (Witzig 2011). Rituximab alone or in combination is approved at a dose of 375 mg/m^2 IV on Day 1 of each cycle for up to 8 doses in patients with DLBCL. Studies combining both lenalidomide and rituximab have followed various dosing schedules for rituximab, but the dosing schedule for lenalidomide has remained the same. For the combination, rituximab has been given at a dose of 375 mg/m^2 and lenalidomide has been administered at 20 mg once daily on the 21/28 day schedule. The 20 mg dose of lenalidomide has been used in studies where rituximab was given weekly for four doses in the first cycle (Wang 2013), as well as on days 1 and 21 every 28 days for four cycles (Zinzani 2011). In this trial dose escalation of lenalidomide will proceed above 20 mg to 25 mg since rituximab will be administered on a 28 day schedule.

The first escalation cohort will begin lenalidomide at one dose level below that used in the lenalidomide and rituximab combination studies with a dose level-1 built in to allow for further evaluation of the three drug combination if a lower lenalidomide dose is needed. Since ibrutinib has been studied at the 560 mg dose in several types of NHL on a continuous daily dosing

schedule and is well tolerated, it will be administered daily until disease progression or unacceptable toxicity.

1.13. Rationale for Implementation of Dose Re-Escalation

1.13.1. Cohort 1 Findings at Dose Level 1 (15 mg lenalidomide)

In Cohort 1 at Dose Level 1 (560 mg ibrutinib, 15 mg lenalidomide and 375 mg/m^2 rituximab), a total of 13 subjects were enrolled. Seven of 13 subjects were evaluable for DLT observation per protocol and 6 subjects were non-evaluable due to >4 missed doses during the DLT observation period due to AEs or study drug non-compliance. In 7 evaluable subjects, 3 DLTs were observed, 2 DLTs were Grade 3 rash and 1 DLT was Grade 3 neutropenia lasting longer than 7 days.

As of the data cut of 29 Dec 2014, other AEs of interest that occurred during the study were 2 rashes with onset during Cycle 1: a Grade 2 rash in 1 subject, and a Grade 1 rash on the face only in another subject. Another subject developed a Grade 2 rash related to Augmentin in Cycle 3.

Of the 13 subjects in Cohort 1 that were dosed at Dose Level 1, 4 subjects (31%, and in 2 of 7 evaluable subjects, 29%) experienced an AE of rash with onset during Cycle 1, and 2 of these rashes were Grade 3 and considered DLTs; the other 2 rashes were Grade 1 in 1 subject and Grade 2 in the other subject. None of the subjects who experienced rash were taking allopurinol. One subject with a DLT developed a Grade 3 pruritic rash on Day 10 with a bilateral hand edema, all study drugs were permanently withdrawn and the subject was treated with prednisone PO for 6 days (60-60-40-40-20-20 mg/day). The subject responded to the drug hold and corticosteroid therapy and is in follow-up observation. The other subject with a DLT developed a Grade 1 maculopapular rash on Day 11, which on Day 12 became a Grade 3 rash on chest, back and extremities with pruritus, the subject was treated with a permanent hold of all study drugs and 40 mg of prednisone PO daily (Days 12-18), benadryl (Days 12-21) and cortisone cream. The subject responded to the drug hold and concomitant therapy and is in follow-up observation.

1.13.2. Findings in Study CTEP/A051103

In the ongoing investigator (NCI)-sponsored clinical trial CTEP/A051103 (clinicaltrials.gov # NCT01829568/since 4/2013, ibrutinib, lenalidomide and rituximab are being administered in combination; 22 subjects with follicular lymphoma were enrolled at different dose levels.

Dose Level	Ibrutinib(mg)	Lenalidomide (mg)	Rituximab (mg/m^2)
0	420	15	375
1	560	15	375
2	560	20	375

Of 22 subjects, 8 developed a Grade 1 or 2 rash, and 8 subjects developed a Grade 3 rash; rash was not considered a DLT in this study unless the rash did not resolve to < Grade 2 within 10 days with corticosteroid treatment. In addition, rash was associated with allopurinol in several cases and with Bactrim (sulfamethoxazole and trimethoprim) in 1 case. No cytokine storm reactions were seen. As a result of this approach, in the CTEP/A051103 study, no DLTs were seen and no MTD was identified. The rashes were manageable with temporary holding of ibrutinib and lenalidomide, concomitant therapy with corticosteroids and/or antihistamines, and discontinuation of potential contributors such as allopurinol if applicable. The maximum dose of lenalidomide given was the highest planned dose of 20 mg. Similar DLT rules are implemented in the PCYC-1123-CA Protocol Amendment 2.0 with the objective to escalate to 25 mg of lenalidomide since DLBCL is a more aggressive lymphoma (than follicular lymphoma) and may require higher doses. A de-escalation cohort (Cohort -1) will be completed prior to re-escalation to higher lenalidomide dose cohorts (Cohort 1+, 2 and 3).

1.13.3. Rationale for Changes in Amendment 2.0

Potential re-escalation to higher doses of lenalidomide after confirmation of safety in Cohort -1 (de-escalation cohort) was included in Protocol Amendment 2.0 to enable a higher and potentially more efficacious dose of lenalidomide for the Phase 2 portion of the study.

Based on the findings in the CTEP/A051103 study and the findings in Cohort 1 at Dose Level 1, the DLT rules for rash were modified in this amendment. In both studies, rash was being reported frequently mostly early in the treatment period (during the DLT observation period [Cycle 1]), the cases were clinically manageable, no cytokine storm reactions were seen, and re-treatment after a drug hold was clinically permissible if allowed. Thus, higher and potentially more efficacious doses of lenalidomide will be explored in this study.

1.14. Rationale for Changes in Amendment 3.0

1.14.1. Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a known possible side effect of antineoplastic treatment and usually indicates benefit from treatment. Thus, it was determined between the study Investigators and the sponsor that if a TLS occurs during study treatment, only severe forms of TLS which require dialysis should result in an event considered a DLT. This would also be consistent with other studies testing the ibrutinib and lenalidomide combination (Christian ASH 2014). Since CTCAE grading specifies that if TLS is present, it represents a Grade 3 event, the DLT definition has been updated to specify that only a TLS requiring dialysis will be considered a DLT.

Patients with bulky tumors have an increased risk of TLS, and sufficient hydration and close monitoring of laboratory parameters (eg, a chemistry panel) is recommended for this patient population (see Section 5.2).

1.14.2. Neutropenia

Neutropenia is an expected side effect for both lenalidomide and ibrutinib and has also been described with rituximab.

In the lenalidomide label (Revlimid® USPI, February 2015) for the indications of multiple myeloma and myelosysplastic syndrome, there is a black box warning for hematological toxicity. Lenalidomide can cause significant neutropenia and thrombocytopenia and patients may require dose interruption and/or dose reduction per label.

In the pooled multiple myeloma studies, Grade 3 and 4 hematologic toxicities were more frequent in patients treated with the combination of lenalidomide and dexamethasone than in patients treated with dexamethasone alone. Grade 3 or 4 neutropenia was seen in 33.4% (118/353) of patients with the combination compared to 3.4% (12/350) of patients with dexamethasone alone.

In the myelodysplastic syndrome study (N=148), 58.8% (87/148) of patients developed neutropenia overall, and 48% developed Grade 3 or 4 neutropenia. In the 48% of patients who developed Grade 3 or 4 neutropenia, the median time to onset was 42 days (range, 14-411 days), and the median time to documented recovery was 17 days (range, 2-170 days). In the 54% of patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was 28 days (range, 8-290 days), and the median time to documented recovery was 22 days (range, 5-224 days).

In the ibrutinib label (Imbruvica® USPI, January 2015), neutropenia is among the most common adverse reactions (≥25%) in patients with B-cell malignancies (MCL, CLL, Waldenström's macroglobulinemia [WM]). Grade 3 or 4 neutropenia occurred in patients treated with ibrutinib with a range of 19-29% in clinical studies. Further, an adverse event of "neutrophils decreased" as a laboratory finding was noted in 47% of patients for all grades and in 29% of patients with Grade 3 or 4 in the MCL study (N=111). In the CLL Study 1 (N=48), 54% of patients had an adverse event of "neutrophils decreased" (all grades) as a laboratory finding and 23% of patients had a Grade 3 or 4 finding. In the CLL Study 2 (N=195), 51% of patients had an adverse event of "neutrophils decreased" (all grades) as a laboratory finding and 27% of patients had a Grade 3 or 4 finding. In the WM study (N=63), 44% of patients had an adverse event of "neutrophils decreased" (all grades) as a laboratory finding and 19% of patients had a Grade 3 or 4 finding.

In the rituximab label (Rituxan® USPI, August 2014) for lymphoid malignancies, neutropenia is described as a common adverse reaction (≥25%) in clinical trials. Neutropenia of all grades was found in 14% of patients and Grade 3 or 4 neutropenia in 6% of patients with relapsed/refractory NHL (N=356) and has been described in other studies with rituximab.

In summary, neutropenia is a common finding in patients treated with lenalidomide, with ibrutinib, and with rituximab, and thus the combination of the 3 agents in this study is expected to result in adverse events of neutropenia. Unless life-threatening, neutropenia is generally

easily managed in an oncology setting and the risk-benefit ratio for this study population would still be in favor of continued treatment to achieve an anti-tumor response despite episodes of neutropenia. In addition, in subsequent treatment cycles beyond the DLT window, dose modifications for neutropenia are permitted per Table 6 of the protocol. For these reasons, the DLT criteria for neutropenia were updated in this amendment.

1.14.3. Deep Venous Thrombosis

In the lenalidomide label (Revlimid® USPI, February 2015) for the indication of multiple myeloma, there is a black box warning for deep venous thrombosis and pulmonary embolism. In patients with multiple myeloma receiving lenalidomide with dexamethasone, there is a significantly increased risk of deep venous thrombosis and pulmonary embolism.

As per the FDA label, venous thromboembolic events (predominantly deep venous thrombosis and pulmonary embolism) have occurred in patients with multiple myeloma treated with lenalidomide combination therapy and patients with myelodysplastic syndrome treated with lenalidomide monotherapy. A significantly increased risk of deep venous thrombosis and pulmonary embolism was observed in patients with multiple myeloma who were treated with lenalidomide and dexamethasone therapy (see label). It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with lenalidomide may lessen the potential for venous thromboembolic events, however thromboprophylaxis is recommended (see label). The decision to administer prophylactic measures should be done carefully after an assessment of an individual patient's underlying risk factors.

Since deep venous thrombosis can be clinically managed with anticoagulation, and the risk-benefit ratio for this study population would still be in favor of continued treatment to achieve an anti-tumor response, only deep venous thrombosis that is unresponsive to anticoagulation will be considered a DLT. This would also be consistent with other studies testing the ibrutinib and lenalidomide combination (Christian ASH 2014).

1.14.4. Treatment of Subjects with DLTs

In the original protocol subjects who experienced a DLT were required to discontinue study treatment. The experience thus far in this study has shown that subjects with a toxicity qualifying for a DLT (including 2 subjects with Grade 3 rash, 1 subject each with Grade 3 neutropenia >7 days, 1 subject with TLS, and 1 subject with Grade 4 neutropenia) have manageable toxicity despite fitting the criteria for DLT and could benefit from further treatment with study drugs. Based on this experience and with input from Investigators, the Sponsor has updated the language in the protocol amendment. If clinically warranted and agreed upon by Investigator and Sponsor, subjects experiencing a DLT may continue with study treatment if the treating physician is of the opinion that the subject would benefit from continued therapy and the toxicity experienced was manageable.

1.15. Rationale for Changes in Amendment 4.0

1.15.1. Removal of Arm without Rituximab

The use of rituximab in the DLBCL salvage setting is considered standard. To maximize potential efficacy in a population with relapsed/refractory and aggressive DLBCL, the arm with the 2-drug combination of ibrutinib and lenalidomide has been removed. Only should safety concerns arise with the 3-drug combination, a 2-drug combination of ibrutinib with lenalidomide may be considered in this study.

Removing one arm from the study will lead to a smaller overall sample size of the trial. The statistical assumptions remain, i.e. to test the null hypothesis (H_0) of 60% versus the alternative hypothesis (H_a) of 40% for ORR in the remaining arm with the 3-drug combination.

1.15.2. Proposed Lenalidomide Dose for Phase 2

If the dose level of 20 mg lenalidomide is determined to be safe and tolerated in the Phase 1b, this dose will be considered the recommended Phase 2 dose (RP2D) and a Phase 2 cohort with 20 mg lenalidomide will be initiated. Concurrent with the Phase 2 at 20 mg lenalidomide, a Phase 1b cohort with 25 mg lenalidomide may be initiated. If the interim analysis of the 20 mg lenalidomide cohort is negative, the 25 mg lenalidomide dose may be used in an additional cohort in the Phase 2, if safe and tolerated in the Phase 1b.

The rationale for initiating the Phase 2 with the lenalidomide dose of 20 mg is based on efficacy/toxicity considerations. In the initial cohort with 15 mg lenalidomide (Cohort 1), 3 responses (2 CR and 1 PR) including 2 long-term responses (2 CR subjects with more than 12 months of response) were observed among 8 subjects who received study drug for more than 1 cycle and were evaluable for response. Importantly, in the lower dose cohort with 10 mg lenalidomide (Cohort -1), there were no responses, implying that higher doses may be more efficacious. In addition, the lower dose cohort appeared better tolerated with fewer DLTs reported. Several other studies have used a maximum dose of 10 mg, 15 mg and 20 mg of lenalidomide when combined with ibrutinib due to apparent increased toxicity with increasing doses of lenalidomide (eg, CTEP/A051103 [20 mg]; CTEP/9540 [15 mg]; CTEP/9254 [10 mg]). Thus, the dose of 20 mg lenalidomide was chosen for the Phase 2, representing the best balance of safety and efficacy for this study. However, since higher doses may be more efficacious and justified in a population with relapsed/refractory and aggressive DLBCL, if determined to be safe and tolerated in the Phase 1b, the 25 mg lenalidomide dose may be explored in the Phase 2.

1.16. Rationale for Changes in Amendment 5.0

The purpose of Amendment 5 is inclusion of preliminary safety data from the Phase 1b into the protocol to support initiation of the Phase 2 portion of the trial.

1.17. PCYC-1123-CA Phase 1b Data Summary

As of 25 April 2016, a total of 38 subjects were enrolled (37 treated) in Cohort 1 (13 subjects enrolled, 12 treated), Cohort -1 (7 subjects enrolled), Cohort 1+ (9 subjects enrolled) and Cohort 2 (9 subjects enrolled).

1.17.1. Preliminary Summary of Safety Data

Cohort 1 (15 mg lenalidomide)

In Cohort 1 (15mg lenalidomide), 13 subjects were enrolled and 12 subjects treated (1 subject did not meet dosing criteria on Day 1 and could not be dosed). Seven subjects were evaluable for dose-limiting toxicity (DLT) observation purposes. Three DLTs were observed: One subject with Grade 3 neutropenia lasting longer than 7 days, and 2 subjects with a Grade 3 rash. Three subjects in this cohort experienced SAEs. All SAEs experienced in this cohort were unrelated to study drug. One subject experienced 1 SAE of myocardial infarction (unrelated to study drug), 1 subject experienced 1 SAE of chest pain which was musculoskeletal per exclusion of other causes (unrelated to study drug), and 1 subject following disease progression and subsequent anticancer therapy experienced 1 SAE of neutropenic sepsis (unrelated to study drug) and 1 SAE of cardiac arrest (unrelated to study drug). Two subjects are receiving study treatment as of 28 Apr 2016, and 10 subjects discontinued treatment (2 subjects are in follow-up, 3 subjects withdrew full consent, and 5 subjects expired [1 due to cardiac arrest, 1 due to unknown cause, 3 due to progressive disease]). Due to the 3 DLTs of neutropenia and two events of rash observed in this cohort, a de-escalation cohort with 10 mg lenalidomide was opened. In addition, the DLT criteria were modified in regards to rash.

Cohort -1 (10 mg lenalidomide)

In Cohort -1 (10mg lenalidomide), 7 subjects were enrolled. Six subjects were evaluable for DLT observation purposes. There was 1 DLT of a Grade 4 salmonella sepsis. Two subjects experienced SAEs during the DLT observation period. One subject experienced 1 SAE of pleural effusion, which was unrelated to study drugs and related to DLBCL, another subject experienced 1 SAE of salmonella sepsis, and later experienced pancytopenia and pneumonia, all possibly related to study drug. Three additional subjects experienced SAEs after the DLT observation period. One subject experienced cellulitis and folliculitis (possibly related to study drug); dehydration, thrombocytopenia, pseudomonas sepsis and Grade 5 pneumonia (all unrelated to study drug). Two other subjects experienced Grade 5 SAEs of worsening of DLBCL (not related to study drug). As of 28 Apr 2016, all 7 subjects discontinued treatment (2 subjects are in follow-up and 5 subjects expired [1 due to pneumonia, 4 due to progressive disease]). Due to the fact that only one DLT was identified during the DLT observation period in this cohort, a dose re-escalation cohort with 15 mg lenalidomide was opened.

Cohort 1+ (15 mg lenalidomide)

In Cohort 1+ (15mg lenalidomide), 9 subjects were enrolled. Seven subjects were evaluable for DLT observation purposes, 1 subject was non-evaluable for DLT observation purposes due to

death/sepsis while on vacation during and after the DLT observation period (died before completion of C2D1) and 1 subject was non-evaluable due to receiving 10 mg lenalidomide instead of 15 mg (in error) during the DLT observation period. There was 1 DLT of Grade 4 neutropenia. Two subjects experienced SAEs during the DLT period, the subject with a DLT of neutropenia experienced tumor lysis syndrome (TLS) (possibly related to study drug), as well as dehydration (unrelated to study drug), and worsening of DLBCL (unrelated to study drug). The subject that was non-evaluable who died during the DLT observation period experienced an SAE of sepsis (possibly related to study drug). Three subjects experienced SAEs after the DLT observation period, 1 subject experienced a transient ischemic attack (TIA) (possibly related to study drug), 1 subject experienced cellulitis (unrelated to study drug) and pneumonia (possibly related to study drug), and 1 subject experienced 1 SAE of malignant neoplasm progression/lymphoma in the right eye (unrelated to study drug). As of 28 Apr 2016, 4 subjects were on study treatment, and 5 subjects discontinued treatment (2 subjects are in follow-up, 1 subject withdrew consent and 2 subjects expired [1 due to sepsis and 1 due to progressive disease]). Due to the fact that with 1 DLT there were less than 33% of subjects experiencing DLTs during the re-escalation cohort, dose escalation to 20 mg lenalidomide was pursued.

Cohort 2 (20 mg lenalidomide)

In Cohort 2 (20 mg lenalidomide), 9 subjects were enrolled. Eight subjects were evaluable for DLT observation purposes. One subject was non-evaluable due to disease progression and death during the DLT observation period. There were no DLTs identified in this dose cohort. Three subjects experienced SAEs. During the DLT observation period, one subject with a history of vaginal bleeding experienced Grade 3 vaginal bleeding which was related to tumors surrounding the vaginal area, unrelated to study drug and therefore not considered a DLT. The same subject experienced 3 SAEs that were also unrelated to study drug after the DLT observation period, a Grade 3 urinary tract infection, a Grade 3 partial bowel obstruction and a Grade 3 hydronephrosis; 1 subject experienced Grade 2 fever (possibly related to study drug); 1 subject that was non-evaluable experienced Grade 4 hypercalcemia, Grade 4 hypoxic respiratory failure and Grade 5 disease progression. Per Investigator, the respiratory failure was thought to be related to lymphoma; the CT showed worsening lymphadenopathy, suggesting disease progression of DLBCL along with diffuse infiltrates in the lung. As of 28 Apr 2016, 6 subjects were on study treatment, 3 subjects discontinued treatment (2 subjects are in follow-up and 1 subject progressed and died during the DLT observation period).

1.17.2. DLRC Meeting Outcome

Safety and preliminary efficacy data for all enrolled cohorts were reviewed by the DLRC on 25 April 2016. The voting members (e.g. medical monitors, participating Investigators, safety officer, and biostatistician) present during the call and 4 Investigators who voted per e-mail unanimously voted to continue the study in Phase 1b with Cohort 3 (dose level of 25 mg of lenalidomide in combination with ibrutinib and rituximab) and to repeat safety assessments. In addition, the voting members unanimously voted to proceed to Phase 2 with the dose of 20 mg of

lenalidomide in parallel with Cohort 3 (25 mg lenalidomide) in the Phase 1b.Based on the DLRC recommendation, the Sponsor (Pharmacyclics LLC) is planning to proceed with the 25 mg lenalidomide dose level in the Phase 1b of the study. In parallel, the Sponsor is planning to proceed with the Phase 2 portion of the study with the recommended Phase 2 dose of 20 mg lenalidomide, which is the same or similar recommended Phase 2 dose level tested in other trials using ibrutinib, lenalidomide and rituximab (Ujjani et al ASH 2015, NCT02160015 [15 and 20 mg lenalidomide]; NCT02532257 [15 and 20 mg lenalidomide], NCT02446236 [10-25 mg lenalidomide], NCT02636322 [25 mg lenalidomide]; Wilson et al ASH 2015, NCT02142049 [15, 20 and 25 mg lenalidomide].

2. STUDY OBJECTIVE

2.1. Primary Objectives

Phase 1b:

- To determine the maximum tolerated doses (MTD) and/or the recommended Phase 2 (RP2) dose of ibrutinib in combination with lenalidomide and rituximab by dose escalation of lenalidomide in subjects with relapsed or refractory DLBCL
- To determine the safety and tolerability of ibrutinib in combination with lenalidomide and rituximab in subjects with relapsed or refractory DLBCL by dose escalating lenalidomide

Phase 2:

- To evaluate the efficacy of ibrutinib in combination with lenalidomide and rituximab by assessing the overall response rate (ORR) in subjects with relapsed or refractory non-GCB DLBCL

2.2. Secondary Objectives

Phase 1b:

- To evaluate the efficacy of ibrutinib in combination with lenalidomide and rituximab by assessing the overall response rate (ORR) in subjects with relapsed or refractory DLBCL by lenalidomide dose group

Phase 2:

- To determine the efficacy of ibrutinib in combination with lenalidomide and rituximab in subjects with relapsed or refractory non-GCB DLBCL by assessing the following efficacy parameters:
  - Complete Response (CR)
  - Duration of Response (DOR)
  - Progression Free Survival (PFS)
  - Overall Survival (OS)

- To determine the safety and tolerability of ibrutinib in combination with lenalidomide and rituximab in subjects with relapsed or refractory non-GCB DLBCL

2.3. Exploratory Objectives

Phase 2:

- Efficacy analysis based on the activated B-cell like (ABC) subtype identified by gene expression profiling (GEP) will be performed
- Effect of ibrutinib on peripheral T/B/NK cell counts
- Effect of ibrutinib on serum immunoglobulin levels (IgG, IgM and IgA)

Pharmacokinetics:

- Plasma pharmacokinetics of ibrutinib and PCI-45227

Biomarkers:

- To identify signaling pathways or biomarkers that predict sensitivity or resistance to ibrutinib
- To determine the frequency of tumor mutations (or other molecular markers) between pre and post treatment tissue that predict acquired resistance

3. STUDY DESIGN

3.1. Overview of Study Design

The study will be conducted in two Phases.

Phase 1b will be an open-label study. The dose escalation portion of the study is designed to establish the MTD of the ibrutinib, lenalidomide, and rituximab combination. The dose levels outlined in (Table 4) may be explored and dose escalation of lenalidomide will follow the 3+3+3 dose escalation schema. After completion of Cohort 1 at Dose Level 1, due to 3 DLTs in 7 evaluable subjects, a cohort at Dose Level -1 was opened. After completion of the Dose Level -1 cohort, if <33% of subjects experience a DLT, dose re-escalation to higher dose levels starting with the lenalidomide dose of 15 mg may occur. Approximately 46 subjects will be enrolled in the Phase 1b portion.

Phase 2 will be an open-label study designed to evaluate the overall response rate of ibrutinib in combination with lenalidomide and rituximab, in relapsed or refractory non-GCB DLBCL subjects ineligible for transplant. If the dose level of 20 mg lenalidomide is determined to be safe and tolerated in the Phase 1b, this dose will be considered the recommended Phase 2 dose (RP2D) and a Phase 2 cohort initiated with 20 mg lenalidomide. Concurrent with the Phase 2 at 20 mg lenalidomide, a Phase 1b cohort with 25 mg lenalidomide may be initiated.

An interim analysis will be performed including approximately 28 evaluable subjects with adequate tumor response assessment. Details of the interim analysis and decision rules will be

described in the statistical analysis plan (SAP). At the interim analysis, the review committee could recommend:

1. continuation of the study with 20 mg lenalidomide; or
2. increase of the lenalidomide dose to 25 mg, if determined to be safe and tolerated in the Phase 1b, including approximately 28 evaluable subjects with adequate tumor response assessment followed by an interim analysis.

In addition, if there are safety concerns, a cohort with ibrutinib and lenalidomide without rituximab may be considered.

Phase 2 may enroll approximately 55 subjects to ensure enrollment of at least 49 response-evaluable subjects. Approximately 129 subjects, inclusive of Phase 1b and Phase 2, will be enrolled. Both Phases will include a Screening Phase, Treatment Phase and a Follow-Up Phase.

The Screening Phase assessments will be performed within 28 days prior to study treatment. Eligible subjects will have pathologically confirmed DLBCL, having received at least 1 prior therapy, with documented disease that is relapsed or refractory in subjects ineligible for HDT and transplant. For Phase 2, subjects must have pathologically confirmed de novo non-GCB DLBCL by Hans method testing using immunohistochemistry (IHC).

The Treatment Phase will extend from the first dose of study treatment until criteria for permanent discontinuation of ibrutinib or study treatment are met (Section 9.2), such as disease progression, unacceptable toxicity or 2 years after the last subject has been enrolled, whichever occurs first. During the Treatment Phase, efficacy evaluations will be performed every 3 cycles (28-day cycle) as specified in Section 7.3.

The Follow-up Phase will begin once a subject discontinues ibrutinib treatment and will continue until death, lost to follow up, consent withdrawal, or study end, whichever occurs first.

- Subjects who discontinue for reasons other than disease progression (ie, for adverse event or Investigator decision) will complete an End-of-Treatment Visit (30 ± 3 days from the last dose of ibrutinib, lenalidomide or rituximab, whichever is later), and must continue to have disease evaluations (12 weeks ±7 days). (See Figure 1)
- Subjects who discontinue due to disease progression will complete an End-of-Treatment Visit and be followed for survival and subsequent anticancer therapy (12 weeks ±7 days) until study ends. (See Figure 1)

It is imperative that survival status be assessed and that the date of death is documented for each subject who has died. The study completion is defined as 3 years from the last study treatment, the time point that all subjects have exited the study for any reason, or study termination at the Sponsor's discretion, whichever occurs first.

A Dose Level Review Committee will evaluate safety data following the completion of each dose observation period of the Phase 1b portion. Members of this committee will include the

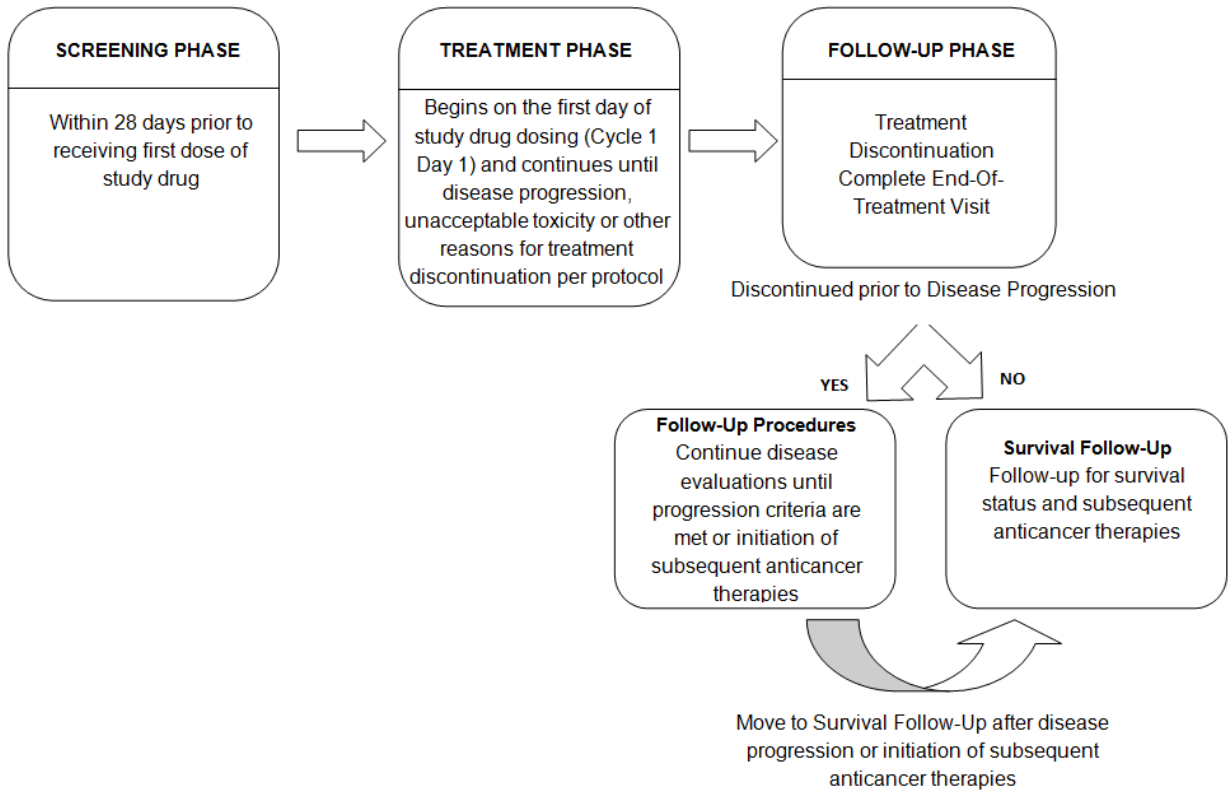
Sponsor (at a minimum: the Medical Monitor or designee, a Drug Safety representative and a Biostatistician) as well as participating Investigators/designee.

Table 3: Dosing Schedule

Agent	Phase 1b		Phase 2	
	Cycles 1-6	Cycles 7+	Cycles 1-6	Cycles 7+
Ibrutinib	560 mg PO daily		560 mg PO daily	
Lenalidomide	15-25 mg PO Days 1-21		RP2 dose = 20 mg PO Days 1-21, if determined to be safe and tolerated in the Phase 1b portion of the study*	
Rituximab	375 mg/m^2 IV Day 1	NA	375 mg/m^2 IVDay 1	NA

*25 mg may be explored as outlined in the protocol

Figure 1: Study Design Schematic



3.2. Phase 1b Dose Escalation and Expansion Overview

Phase 1b will be conducted in the United States (US), with approximately 46 subjects enrolled. Additional subjects may be screened and enrolled in any cohort as outlined. In the dose escalation portion, up to four dose levels of lenalidomide will be explored and the dose escalation will follow the 3+3+3 principles. The decision to expand any individual cohort up to

9 subjects for the purpose of safety evaluation will be made after review of the dose escalation safety data.

During Phase 1b the doses of both ibrutinib and rituximab will remain fixed with up to 4 dose levels of lenalidomide to be explored according to cohort (Table 4). After completion of Cohort 1 at Dose Level 1, due to 3 DLTs in 7 evaluable subjects, a cohort at Dose Level -1 was opened. After completion of the Dose Level -1 cohort, if <33% of subjects experience a DLT, dose re-escalation to higher dose levels starting with the lenalidomide dose of 15 mg may occur. Both ibrutinib and lenalidomide will continue until disease progression or unacceptable toxicity, while rituximab will be discontinued after 6 cycles. See Section 5 for study treatment details.

After completion of Phase 1b Cohort 2 at Dose Level 2 (20 mg lenalidomide), enrollment into Phase 2 will commence with 20 mg lenalidomide, if determined to be safe and tolerated in the Phase 1b portion of the study. Concurrent with the Phase 2 at 20 mg lenalidomide, Phase 1b Cohort 3 at Dose Level 3 (25 mg lenalidomide) may be enrolled.

3.3. Phase 2 Efficacy Evaluation Overview

Phase 2 will be an open-label, international, multi-center study. This portion of the study will be conducted at up to 70 international clinical centers, with approximately 55 subjects enrolled. Subjects will be treated with the 20 mg lenalidomide dose, if determined to be safe and tolerated in the Phase 1b portion of the trial.

An interim analysis will be performed as outlined in Section 10.

4. SUBJECT SELECTION

The inclusion and exclusion criteria for enrolling subjects on this study are described below. If there are any questions about the entry criteria, the Investigator should consult with the Medical Monitor before enrolling a subject in the study. Selected eligibility criteria must be confirmed in writing by the Medical Monitor prior to enrollment.

4.1. Inclusion Criteria

To be enrolled in the study, each potential subject must satisfy all of the following inclusion criteria.

Disease Related

1. Pathologically confirmed:
   a. Phase 1b: diffuse large B-cell lymphoma.
   b. Phase 2: de novo non-GCB DLBCL by Hans method testing using immunohistochemistry

   Note: Sufficient tissue sample for evaluation by IHC and GEP is required for subjects in Phase 2 (refer to Laboratory Manual for requirements).

2. Relapsed or refractory disease, such as either: 1) recurrence of disease after a complete response (CR), or 2) partial response (PR), stable disease (SD) or progressive disease (PD) at completion of the treatment regimen preceding entry to the study (residual disease).
3. Subjects must have previously received an appropriate first-line treatment regimen.
4. For subjects having a computed tomography (CT) scan abnormality with uncertain interpretation following completion of the most recent treatment regimen: biopsy confirmation of residual DLBCL is required prior to study entry to confirm residual DLBCL and to rule out a non-lymphomatous process (eg, fibrosis).
5. Subjects who have not received HDT/SCT must be ineligible for HDT/SCT as defined by meeting any of the following criteria:
    a. Age ≥70 years.
    b. Diffuse lung capacity for carbon monoxide <50% by pulmonary function test.
    c. Left ventricular ejection fraction <50% by multiple gated acquisition/echocardiogram.
    d. Other organ dysfunction or co-morbidities precluding the use of HDT/SCT on the basis of unacceptable risk of treatment-related morbidity.
    e. Failure to achieve PR or CR with salvage therapy.
    f. Subject refusal of HDT/SCT.
6. One or more measurable disease sites on CT scan (>1.5 cm in longest dimension). Lesions in anatomical locations (such as extremities or soft tissue lesions) that are not well visualized by CT may be measured by MRI instead (see Section 7.3.1).

Laboratory

7. Adequate hematologic function with screening laboratory assessment independent of growth factor and transfusion support for at least 7 days, with the exception of pegylated G-CSF (pegfilgrastim) and darbepoetin which require at least 14 days, defined as:
    a. Absolute neutrophil count (ANC) >1,500 cells/mm^3 (1.5 x 10^9/L).
    b. Platelet count >75,000 cells/mm^3 (75 x 10^9/L).
    c. Hemoglobin >8.0 g/dL.
8. Adequate hepatic and renal function with screening laboratory assessment defined as:
    a. Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤2.5 x upper limit of normal (ULN).
    b. Creatinine clearance (Cockcroft-Gault or 24-hour creatinine clearance collection) >60 mL/min.
    c. Bilirubin <1.5 x ULN [unless bilirubin rise is due to Gilbert's syndrome (as defined by >80% unconjugated hyperbilirubinemia) or of non-hepatic origin].
9. PT/INR <1.5 x ULN and aPTT <1.5 x ULN.

Demographic

10. Men and women ≥18 years of age.
11. Eastern Cooperative Oncology Group (ECOG) performance status of <2.

Ethical/Other

12. All study participants must be registered into the mandatory Revlimid REMS™ program, and be willing and able to comply with the requirements of the Revlimid REMS™ program **(for US sites only).**
13. Female subjects of childbearing potential (FCBP)[a] must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days as required by Revlimid REMS™) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. Female subjects of childbearing potential (FCBP) must also agree to ongoing pregnancy testing. See Appendix 7 **(for US sites only).**
14. Female subjects of childbearing potential (FCBP)[a] must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days and again within 24 hours prior to starting Cycle 1 of lenalidomide. FCBP must also agree to ongoing pregnancy testing. All subjects must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix 8 (**for ex-US sites only**).
15. Male subjects must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. See (**for US sites only**).
16. Male subjects must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. All subjects must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix 8 (**for ex-US sites only**).
17. Female subjects of child bearing potential (FCBP)[b] and male subjects who are sexually active must use TWO acceptable methods of birth control, one highly effective method of birth control plus one additional effective method of birth control for at least 28 days prior to study treatment and during the study treatment period. For female subjects, these birth control requirements must be adhered to for 12 months after the last dose of rituximab or 30 days after the last dose of ibrutinib and lenalidomide, whichever is later. For male subjects, these birth control requirements must be adhered to for 90 days after the last dose of ibrutinib and lenalidomide, whichever is later. Male subjects must agree to not donate sperm during the study treatment period and up to 90 days after the last dose of ibrutinib and lenalidomide.
18. Life expectancy of more than 3 months.

[b] A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

4.2. Exclusion Criteria

To be enrolled in the study, potential subjects must not have any of the following exclusion criteria:

Disease-Related

Phase 2 Only

1. Transformed DLBCL, germinal center B-cell (GCB) DLBCL or DLBCL with coexistent histologies (eg, follicular or mucosa-associated lymphoid tissue [MALT] lymphoma).
2. Primary mediastinal (thymic) large B-cell lymphoma.

Phase 1b/2

3. Medically apparent central nervous system lymphoma or leptomeningeal disease.
4. History of allogeneic stem-cell (or other organ) transplantation.
5. Any chemotherapy, external beam radiation therapy, or anticancer antibodies within 2 weeks of the first dose of study drug.
6. Radio- or toxin-immunoconjugates within 10 weeks of the first dose of study drug.
7. Concurrent enrollment in another therapeutic investigational study or have previously taken ibrutinib and/or lenalidomide.

Concurrent Conditions

8. History of other malignancies, except:
    a. Malignancy treated with curative intent and with no known active disease present for ≥5 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician.
    b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
    c. Adequately treated carcinoma in situ without evidence of disease.
9. Concurrent systemic immunosuppressant therapy (eg, cyclosporine A, tacrolimus, etc., or chronic administration of >20 mg/day of prednisone) within 28 days of the first dose of study drug.
10. Recent infection requiring intravenous anti-infective treatment that was completed ≤14 days before the first dose of study drug.
11. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 4.03), Grade ≤ 1 or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia.
12. Known bleeding diathesis (eg, von Willebrand's disease) or hemophilia.
13. Known history of human immunodeficiency virus (HIV) or chronic or active hepatitis C virus (HCV) or hepatitis B virus (HBV) infection.

14. Major surgery within 4 weeks of first dose of study drug.
15. 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 enrollment.
16. Unable to swallow capsules, malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.
17. Concurrent use of warfarin or other Vitamin K antagonists (eg, phenprocoumon).
18. Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor (see Appendix 4).
19. Any life-threatening illness, medical condition including uncontrolled Diabetes Mellitus, or organ system dysfunction that, in the opinion of the Investigator, could compromise the subject's safety or put the study outcomes at undue risk.
20. Currently active, clinically significant hepatic impairment Child-Pugh class B or C according to the Child-Pugh classification
21. Known hypersensitivity to lenalidomide (or thalidomide) or rituximab.
22. Lactating or pregnant.
23. Unwilling or unable to participate in all required study evaluations and procedures.
24. 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. Phase 1b Dose Escalation and Stopping Rules

This is an open-label dose escalation study using a 3+3+3 design. Before applying the dose escalation rules, 3 subjects in any given cohort must have completed the DLT observation period which is defined as 28 days (1 cycle of therapy followed by laboratory evaluation for toxicity on Cycle 2 Day 1, Study Day 29). The modified 3+3+3 design defines the MTD to have been exceeded when ≥3 out of 9 subjects in a cohort experience a DLT. If there are 3 DLTs in Dose Level 1, Dose Level -1 will be enrolled.

After completion of Cohort 1 at Dose Level 1, due to 3 DLTs in 7 evaluable subjects, a cohort at Dose Level -1 was opened. After completion of the Dose Level -1 cohort, if <33% of subjects experience a DLT, dose re-escalation to higher dose levels starting with the lenalidomide dose of 15 mg may occur. Due to the fact that the subject population studied is significantly ill and an inability to complete the DLT observation period may occur due to progression of disease, additional subjects may be screened and enrolled in each cohort. The DLT rules will continue to apply whereas if 1 DLT is observed, the cohort will be expanded to 6, and if 2 DLTs occur, the cohort will be expanded to 9.

Enrollment in a cohort will proceed as follows:

- If no dose limiting toxicity (DLT) is observed during the DLT observation period in the initial 3 subjects of a cohort, dose escalation to the next higher dose level cohort will occur.
- If 1 DLT is observed, 3 additional subjects will be enrolled at the same dose level for a total of at least 6 subjects. If no further DLT(s) are observed, escalation to the next higher dose level cohort will occur.
- If a second DLT is observed, 3 additional subjects may be enrolled at the same dose level for a total of at least 9 subjects. If no further DLTs are observed, dose escalation to the next higher dose level will occur. Note: If appropriate, no further expansion of this cohort will occur if significant safety concerns are recognized after the first 6 subjects are enrolled.
- If ≥3 DLTs are observed in the 9 subjects, then enrollment will stop at the third DLT observation and enrollment into a cohort at a lower dose level (with the exception of Cohort -1) will be considered.
- After enrollment of a cohort at Dose Level -1 (10mg lenalidomide) and if <33% of subjects experience a DLT, dose re-escalation to higher dose levels starting with the lenalidomide dose of 15 mg may occur.

If a subject experiences a DLT during the DLT observation window, the subject may continue study treatment, if continued clinical benefit from study treatment is expected per the treating physician and the toxicity observed is manageable; the Sponsor should be notified in this case.

The decision to proceed to the next dose level will be made in a Dose Level Review Committee Meeting by the Sponsor in conjunction with the Investigators after careful consideration of all available safety and laboratory information. Safety data from subjects on preceding cohorts that remain on continuous dosing will also be considered.

Dose escalation will occur at the planned dose levels until the MTD is determined or until the highest dose level is tested. The MTD is defined as the highest dose at which <33% of the subjects enrolled in a cohort experience a DLT. If all evaluated dose levels demonstrate an observed incidence of DLT in <33% of subjects, the MTD of lenalidomide in the combination has not been reached. At least 6 subjects will be treated at the MTD or in any cohort that supports the Phase 2. The assessment of DLT will follow the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE, version 4.03).

5.2. Dose Limiting Toxicity (DLT) Definition

A DLT is defined as one of the following events that is possibly related to study drug:

Hematologic:

- Grade 4 neutropenia (ANC <500/mm^3) lasting for >7 days
- Life-threatening Grade ≥3 neutropenia (ANC <1,000/mm^3) with fever ≥38.3ºC

- Grade 4 thrombocytopenia (<25,000/ mm^3) that persists for ≥7 days, despite holding treatment
- Grade 3 thrombocytopenia associated with Grade ≥2 bleeding or requiring RBC or platelet transfusions

Non-Hematologic:

Any Grade 3 or higher non-hematologic adverse event with the clarifications noted below:

(Note: excludes rituximab infusion reactions)

- Grade 3 tumor lysis syndrome would be considered a DLT only if it requires dialysis.
- Grade 3 deep venous thrombosis would be considered a DLT only if it is unresponsive to anticoagulation
- Grade 3 rash that has not improved within 10 days to at least Grade 1 using a temporary drug hold of all study drugs and administration of up to 100 mg of prednisone PO or equivalent (with or without taper) and/or antihistamines PO daily
- Grade 3 infection is not a DLT, however an infection with life-threatening consequences or requiring urgent intervention (grade 4) will be considered a DLT
- Grade ≥3 nausea, vomiting, or diarrhea uncontrolled by maximal supportive care and persisting greater than 7 days
- Grade 3 fatigue persisting for greater than 7 days
- Treatment delay of any drug greater than 7 days for toxicity

In the Dose Escalation Phase, if a subject is non-compliant with the prescribed therapy or ends treatment within the first cycle for reasons other than study drug(s) related toxicity, ie, withdraws consent, they will be replaced. In addition, any subject that misses >7 doses of ibrutinib and/or lenalidomide for reasons other than AEs of rash will be replaced; subjects with AEs of rash that miss >10 doses of ibrutinib and/or lenalidomide will be replaced unless considered a DLT. Any subject that requires rituximab discontinuation during the first cycle per the guidance in Section 5.6.4 will be replaced. Subjects with bulky tumors have an increased risk of TLS, and sufficient hydration and close monitoring of laboratory parameters (eg, a chemistry panel every 3 days) is recommended for this patient population. Investigators are encouraged to monitor subjects at high risk for TLS closely.

Table 4: Phase 1b Dosing Levels

28-Day Dosing Cycle	Ibrutinib[a]	Lenalidomide[b]	Rituximab[c]
Dose Level -1[d]	560 mg once daily	10 mg	375 mg/m^2
Dose Level 1 = starting dose (Cohort 1 & 1+)	560 mg once daily	15 mg	375 mg/m^2
Dose Level 2 (Cohort 2)	560 mg once daily	20 mg	375 mg/m^2
Dose Level 3 (Cohort 3)	560 mg once daily	25 mg	375 mg/m^2

[a] Ibrutinib will be administered orally daily beginning Cycle 1 Day 1
[a] Lenalidomide will be administered orally daily on Days 1-21 of each 28-day cycle
[c] Rituximab will be administered IV on Day 1 of each 28-day cycle for 6 cycles
[d] If <33% of subjects experience a DLT at Dose Level -1, dose re-escalation to a higher dose level may occur.

5.3. Treatment Regimens

All eligible subjects will be treated with rituximab, ibrutinib and lenalidomide.

5.3.1. Phase 1b

Ibrutinib and rituximab will be administered at set doses and lenalidomide will be administered according to the assigned dose level (Table 4).

5.3.2. Phase 2

Subjects will be treated with ibrutinib in combination with lenalidomide and rituximab per the table below. If determined to be safe and tolerated in the Phase 1b portion of the trial, the proposed dose of lenalidomide is 20 mg. Additional subjects may receive 25 mg lenalidomide as outlined.

Each cycle is 28 days in length. Missed doses of ibrutinib, lenalidomide, and rituximab will not be made up. Treatment will continue until disease progression or unacceptable toxicity.

5.3.2.1. Treatment

Ibrutinib: 560 mg (4 capsules) orally administered daily

Lenalidomide: Recommended Phase 2 dose = 20 mg* orally administered Days 1-21 in each cycle, if determined to be safe and tolerated in the Phase 1b portion of the trial

*25 mg may be explored as outlined in the protocol

Rituximab: 375 mg/m^2 IV per package insert on Day 1 of cycles 1 – 6 only

5.4. Ibrutinib

All subjects in both phases of this study will receive ibrutinib and will follow guidelines for ibrutinib dosing and toxicity management.

5.4.1. Formulation, Packaging, and Storage of Ibrutinib

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 Investigator's Brochure for a list of excipients.

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

Refer to the Pharmacy Manual for additional guidance on study drug storage, preparation and handling.

5.4.2. Dose and Administration of Ibrutinib

The first dose of ibrutinib will be administered orally on Cycle 1 Day 1, of the Treatment Phase, after which ibrutinib will be self-administered daily by the subjects on an outpatient basis.

Ibrutinib will be dosed 0−30 minutes before the rituximab infusion and at the same time as lenalidomide.

Ibrutinib 560 mg (4 x 140-mg capsules) is administered orally once daily with 8 ounces (approximately 240 mL) of water at approximately the same time each day. The capsules should be swallowed intact and patients 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 6.1.2.1).

If a dose is missed, 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.

Ibrutinib dosing is continuous (without interruption) throughout the Treatment Phase. Treatment will continue until disease progression or other reason for treatment discontinuation as outlined in Section 9.

Dose modifications for toxicity are outlined in Section 5.4.4.

Unused ibrutinib capsules dispensed during previous visits must be returned and drug accountability records updated at the beginning of the next cycle. Returned capsules must not be re-dispensed to the same subject or to another subject.

5.4.3. Dose Hold, Reduction or Discontinuation of Ibrutinib

In order to continue ibrutinib at the start of a new cycle, the subject must not meet any of the criteria for ibrutinib dose modification (see Section 5.4.4).

Treatment with ibrutinib should be withheld for any unmanageable, potentially study drug-related non-hematological toxicity that is Grade 3 or higher in severity and any hematologic toxicity meeting the criteria in Section 5.4.4.

For Grade ≥3 rash, hold ibrutinib until rash improves to Grade ≤1, then resume at original dose (for the first episode) or lower dose as clinically indicated. Treatment with 20 mg prednisone PO or equivalent daily for 10 days (with or without taper) and/or antihistamines PO daily is recommended; discontinue allopurinol if rash is thought to be at least possibly related to allopurinol.

During the DLT observation period: If Grade 3 rash has not improved to at least Grade 1 using a temporary drug hold and administration of up to 100 mg of prednisone or equivalent (with or without taper) and/or antihistamines daily for 10 days, rash is considered a DLT.

Outside of the DLT observation period: see recommendations for Grade ≥3 rash above.

For lenalidomide dose modifications due to rash: see Table 6.

Subjects who require full-dose of anticoagulant treatment (eg, heparin) should have ibrutinib held until stable on anticoagulant therapy (Section 6.1.2.3). Subjects that require an invasive procedure or surgery must have ibrutinib withheld according to the guidance in Section 6.2. Any other clinically important events where dose delays may be considered appropriate by the Investigator must be discussed with the Medical Monitor.

Ibrutinib may be withheld for a maximum of 28 consecutive days for toxicity. Ibrutinib should be discontinued in the event of an ibrutinib toxicity lasting more than 28 days, unless reviewed and approved by the Medical Monitor.

5.4.4. Dose Modification of Ibrutinib

Recommendations for dose modification of ibrutinib are provided in Table 5 if any of the following toxicities occur:

- Grade 3 neutropenia (ANC <1,000/µL) with an associated temperature ≥38.5°C
- Grade 4 neutropenia (ANC <500/µL) for more than 7 days. Refer to Section 6 for instruction regarding the use of growth factor support
- Grade 3 thrombocytopenia (platelets <50,000/µL) in the presence of Grade ≥2 bleeding events
- Grade 4 thrombocytopenia (platelets <25,000/µL)
- Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy
- Any other Grade 4 or unmanageable Grade 3 toxicity attributed to ibrutinib

For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, consider the risks and benefits of ibrutinib treatment. If clinically indicated, the use of anti-coagulants or anti-platelet agents may be considered for the thromboprophylaxis of atrial fibrillation (Section 6.1.2.3).

If tumor lysis syndrome is diagnosed, follow institutional guidelines for management.

Table 5: Ibrutinib Dose Modifications

Hematologic Adverse Events	
Occurrence	**Action to be Taken**
First	Withhold ibrutinib until recovery to an ANC ≥750/µL or platelets >25,000/µL with no evidence of Grade ≥2 bleeding; may restart at original dose level
Second	Withhold ibrutinib until recovery to an ANC ≥750/µL or platelets >25,000/µL with no evidence of Grade ≥2 bleeding; may restart at 1 dose level lower (ie, 420 mg/day)
Third	Withhold ibrutinib until recovery to an ANC ≥750/µL or platelets >25,000/µL with no evidence of Grade ≥2 bleeding; may restart at 1 dose level lower (ie, 280 mg/day)
Fourth	Discontinue ibrutinib[a]
Non-Hematologic Adverse Events	
First	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level
Second	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (ie, 420 mg/day)
Third	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (ie, 280 mg/day)
Fourth	Discontinue ibrutinib[a]

[a] If ibrutinib is discontinued for toxicity, subject will end the Treatment Phase of the study.

Dose changes must be recorded in the Dose Administration eCRF. At the Investigator's discretion, the dose of ibrutinib may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction.

5.4.5. Ibrutinib 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 develop mild liver impairment while on study (Child-Pugh class A), the recommended dose reduction for ibrutinib 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 9).

5.5. Lenalidomide

All subjects in both phases of this study will receive lenalidomide and will follow guidelines for lenalidomide dosing and toxicity management.

5.5.1. Formulation, Packaging, and Storage of Lenalidomide

Lenalidomide (Revlimid®) will be supplied as capsules for oral administration by Celgene Corporation.

Lenalidomide will be shipped to the pharmacy at the study site in individual bottles or blister packs. Bottles or blister packs will contain a sufficient number of capsules to last for one cycle of dosing. Lenalidomide must be dispensed in the original packaging with the label clearly visible. **Only enough lenalidomide for 1 cycle of therapy may be provided to the subject each cycle.**

The Investigator or designee is responsible for taking an inventory of each shipment of lenalidomide received on the drug accountability form.

Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

5.5.2. Lenalidomide Prescribing Information (applies to US sites only)

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this study at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with Celgene Corporation's Revlimid REMS™ program. Per standard Revlimid REMS™ program requirements, all physicians who prescribe lenalidomide, and all research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS™ program. All lenalidomide prescribers must be certified to prescribe lenalidomide and included on the Form FDA 1572. Study drug will be shipped on a per subject basis by the contract pharmacy (ie, Biologics, Inc.) to the clinical site. All subjects will be counseled through the Revlimid REMS™ program with all pregnancy requirements, including the use of birth control and pregnancy testing before lenalidomide can be shipped to the site investigational pharmacy to dispense to the subjects. Only enough lenalidomide for one cycle of therapy will be supplied to the subject each cycle.

Pregnancy Testing

Refer to Appendix 7.

5.5.3. Lenalidomide Drug Dispensing Requirements (applies to ex-US sites only)

In investigational studies, lenalidomide will be dispensed through a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians) and lenalidomide prescribers must be included on the Form FDA 1572. These healthcare professionals will be trained by Celgene or designee in requirements specific to counseling of subjects. Each site is

required to have two trained counselors at all times. Once trained, these healthcare staff will counsel the subjects prior to medication being dispensed to ensure that the subject has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the subject understands the risks associated with lenalidomide. This step will be documented with a completed Education and Counseling Guidance Document (Appendix 8), and no drug will be dispensed until this step occurs. Counseling includes verification with the subject that required pregnancy testing was preformed and results were negative. A Lenalidomide Information Sheet (Appendix 8) will be supplied with each medication dispense.

Pregnancy Testing

Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

Pregnancy tests must occur within 10–14 days and again within 24 hours prior to initiation of Cycle 1 of lenalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on lenalidomide therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. A FCBP with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on lenalidomide therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix 8).

Counseling

All subjects must be counseled about pregnancy precautions, risks of fetal exposure and other risks. The counseling must be done on Day 1 of each cycle (or at a minimum of every 28 days) throughout the entire duration of lenalidomide treatment, including dose interruptions, and at lenalidomide discontinuation. The Appendix 8 (Section 3): Education and Counseling Guidance Document must be completed by a trained counselor.

5.5.4. Dosage, Preparation and Administration of Lenalidomide

The first dose of lenalidomide will be administered orally on Cycle 1 Day 1, of the Treatment Phase, after which lenalidomide will be self-administered daily by the subjects on Days 1-21 of each cycle.

Lenalidomide will be dosed 0-30 minutes before the rituximab infusion and at the same time as ibrutinib.

Lenalidomide should be administered with water at approximately the same time each day. The capsule should be swallowed intact and subjects should not attempt to chew capsules, open

capsules or dissolve them in water. Females of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves.

If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If a dose is missed for the entire day, it should not be made up.

Lenalidomide dosing during the Treatment Phase occurs on Days 1-21 each cycle followed by a mandatory 7-day drug-free interval. If a Day 1 (of any Cycle) is delayed due to scheduling, instruct the subject that lenalidomide dosing should not be initiated until Day 1 assessments can occur.

Treatment will continue until disease progression or other reason for treatment discontinuation as outlined in Section 9.

Dose modifications for toxicity are outlined in Section 5.5, Table 6 and Table 7.

For instructions regarding drug accountability and disposal/return of unused lenalidomide refer to the Pharmacy Manual.

5.5.5. Dose Delay, Reduction or Discontinuation of Lenalidomide

In order to initiate a new cycle of therapy with lenalidomide, the subject must have an ANC ≥1,000/µL and a platelet count ≥50,000/µL and no lenalidomide related Grade ≥3 toxicity on Day 1. If these two criteria are not met, the entire cycle with all drugs is to be delayed and a repeat assessment is to be performed per the Investigator's decision. The initiation of lenalidomide should be delayed until the subject meets the above criteria at which time the subject will initiate drug without dose modification. The initiation of lenalidomide may occur on any day of the cycle, but missed doses must be omitted. Omitted doses should not be made up, and lenalidomide dosing must end no later than Day 21 of any given cycle. Once a cycle has initiated, if lenalidomide must be held for toxicity during dosing, except for an AE of rash, lenalidomide will not resume until Day 1 of the subsequent cycle, provided the subject meets the cycle initiation criteria above, with dose adjustments as per Table 6.

Treatment with lenalidomide should be withheld for any unmanageable, potentially study drug-related non-hematological toxicity that is Grade 3 or higher in severity and any hematologic toxicity as described in Table 6. In the event the subject is diagnosed with a thyroid condition or experiences a drop in creatinine clearance to ≤60 mL/min, refer to Table 6 for further instructions.

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

Lenalidomide may be withheld for a maximum of 28 consecutive days for toxicity. Lenalidomide treatment should be discontinued in the event of a lenalidomide related toxicity lasting more than 28 days, unless approved by the Medical Monitor.

5.5.6. Dose Modification of Lenalidomide during a Cycle (applies to Days 1-21)

The dose of lenalidomide should be modified according to the dose modification guidelines in Table 6 if any of the following toxicities occur:

Table 6: Dose Modification or Interruption for Lenalidomide Toxicity during a Cycle

Toxicity	Intervention
Thrombocytopenia: • Grade 3 (decrease to <50,000/µL) associated with Grade ≥2 bleeding, OR • Grade 4 (decrease to <25,000/µL)	• Interrupt lenalidomide treatment for the remainder of the cycle • Reduce the dose of lenalidomide by one dose level (5 mg) at the start of the next cycle. Do not initiate a new cycle until the subject meets cycle initiation criteria (see Section 5.5.5). Do not dose below 5 mg daily.
Neutropenia: • ANC <1,000/µL for > 7 days, OR • ANC <1,000/µL with an associated temperature ≥38.5°C, OR • ANC <500/µL	• Interrupt lenalidomide treatment for the remainder of the cycle • Reduce the dose of lenalidomide by one dose level (5 mg) at the start of the next cycle. Do not initiate a new cycle until the subject meets cycle initiation criteria (see Section 5.5.5). Do not dose below 5 mg daily.
Rash: • Any Grade desquamating (blistering) • Grade 4 non-blistering • Grade ≥ 3	• For any Grade desquamating or Grade 4, discontinue lenalidomide permanently • For Grade ≥3 rash, hold lenalidomide until rash improves to ≤ Grade 1, then resume at original dose (for first episode) or lower dose as clinically indicated. Treatment with 20 mg prednisone PO or equivalent daily for 10 days (with or without taper) and/or antihistamines PO daily is recommended; discontinue allopurinol if rash is thought to be at least possibly related to allopurinol. • **During DLT observation period:** If ≥ Grade 3 rash has not improved to at least Grade 1 within 10 days using a temporary hold of study drugs and administration of up to 100 mg of prednisone or equivalent (with or without taper) and/or antihistamines daily, rash is considered a DLT. • **Outside of DLT observation period:** see recommendations for Grade ≥3 rash above
Venous thromboembolism Grade ≥3	• Interrupt lenalidomide treatment for the remainder of the cycle • Initiate therapeutic anticoagulation – see Section 6.1.2.3. • Resume lenalidomide without dose modification at the start of the next cycle if the benefit of therapy on this study outweighs the risk for bleeding.
Hyperthyroidism or hypothyroidism	• Interrupt lenalidomide treatment for the remainder of the cycle

Toxicity	Intervention
	• Evaluate etiology and initiate appropriate therapy • Reduce the dose of lenalidomide by one dose level (5 mg) at the start of the next cycle. Do not initiate a new cycle until the subject meets cycle initiation criteria (see Section 5.5.5). Do not dose below 5 mg daily.
Creatinine Clearance ≤60 mL/min (Cockcroft-Gault or 24-hour creatinine clearance collection)	• Interrupt lenalidomide treatment for the remainder of the cycle • Reduce the dose of lenalidomide according to the recommendations below based upon creatinine clearance at the start of the next cycle. Do not initiate a new cycle until the patient meets cycle initiation criteria (see Section 5.5.5). Do not dose below 5 mg daily. o CrCl 30-60 mL/min: – If the dose for subjects with CrCl >60 mL/min is 25 or 20 mg of lenalidomide, the starting dose is 10 mg every 24 hours. – If the dose for subjects with CrCl >60 mL/min is 15 or 10 mg of lenalidomide, the starting dose is 5 mg. o CrCl <30 mL/min (not requiring dialysis): 15 mg every 48 hours • At Investigator discretion, subjects started with a reduced lenalidomide dose due to baseline CrCl ≥30mL/min but <60mL/min may have the lenalidomide dose gradually increased in a step-wise manner at the start of Cycle 2 or at the start of subsequent treatment cycles, if they tolerated the prior treatment cycle without requiring dose modifications, dose interruptions or delays due to toxicity. Lenalidomide dose titrations are permitted in 5 mg increments on the same dosing schedule up to the maximum allowable target dose. • The lenalidomide dose may only be increased once every 28 days (or less frequently), and may only be increased if the prior treatment cycle was completed without requiring dose modifications, interruptions or delays due to toxicity. • If creatinine clearance becomes >60mL/min for a minimum of 2 cycles then one may re-escalate to the dose prior to reduction for renal dysfunction at the discretion of theInvestigator.
Any other Grade 3/4 non-hematologic toxicities attributed to lenalidomide	• Interrupt lenalidomide treatment for the remainder of the cycle. • Reduce the dose of lenalidomide by one dose level (5 mg) at the start of the next cycle. Do not initiate a new cycle until the patient meets cycle initiation criteria (see Section 5.5.5). Do not dose below 5 mg daily.

Table 7: Dose Reduction of Lenalidomide

Current Dose Level	10 mg	15 mg	20 mg	25 mg
Dose Reduction 1	5 mg	10 mg	15 mg	20 mg
Dose Reduction 2	Discontinue	5 mg	10 mg	15 mg
Dose Reduction 3	NA	Discontinue	5 mg	10 mg
Dose Reduction 4	NA	NA	Discontinue	5 mg
Dose Reduction 5	NA	NA	NA	Discontinue

5.6. Rituximab

All subjects will receive rituximab and will follow guidelines for rituximab dosing and toxicity management.

5.6.1. Formulation, Packaging, and Storage of Rituximab

Rituximab will be available in either 100 mg/10 mL single-use vials or 500 mg/50 mL single-use vials. The active ingredient is rituximab and the inactive ingredients are sodium chloride, sodium citrate dihydrate, polysorbate 80, and water for injection.

Rituximab vials are stable at 2°C to 8°C (36°F to 46°F) and should not be used beyond expiration date stamped on carton. Rituximab vials should be protected from direct sunlight. Do not freeze or shake.

For more information regarding stability and storage refer to the Pharmacy Manual.

5.6.2. Dosage, Preparation and Administration of Rituximab

The first dose of rituximab will be administered IV on Cycle 1 Day 1, of the Treatment Phase, and will continue to be administered at the clinical site on Day 1 of each cycle through Cycle 6.

Rituximab will be administered IV by clinic staff according to the prescribing information. Both ibrutinib and lenalidomide will be administered 0-30 minutes prior to rituximab infusion.

Rituximab will be administered as an IV infusion. Premedication will be given prior to each administration.

Premedication: Prior to each infusion administer acetaminophen (or equivalent) and an antihistamine.

- First Infusion: Initiate infusion at a rate of 50 mg/hr. In the absence of infusion toxicity, increase infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
- Subsequent Infusions: If no infusion reactions occur during the first infusion, initiate infusion at a rate of 100 mg/hr. In the absence of infusion toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr.

In the event of an infusion reaction, institute medical management (eg, glucocorticoids, epinephrine, bronchodilators, or oxygen) as appropriate. Depending on the severity of the infusion reaction and the required interventions, temporarily or permanently discontinue. See Section 5.6.3 for further instructions.

If a dose is missed in Cycle 2 or beyond due to scheduling conflicts, it can be delayed up to 2 days after the scheduled time. If dosing must be delayed for more than 2 days for reasons other than toxicity, contact the Medical Monitor.

Rituximab dosing during the Treatment Phase occurs on Day 1 of each cycle. Treatment will continue for 6 cycles unless disease progression or other reason for treatment discontinuation as outlined in Section 9.2 occurs before the completion of Cycle 6.

Dose modifications for toxicity are outlined in Section 5.6.5.

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

5.6.3. Dose Delay of Rituximab

In order to initiate a new cycle of therapy with rituximab, the subject must not have any unmanageable, potentially rituximab-related non-hematological toxicity that is Grade 3 or higher in severity.

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

Rituximab may be withheld for a maximum of 28 consecutive days for toxicity. Rituximab should be discontinued in the event of a rituximab toxicity lasting more than 28 days, unless reviewed and approved by the Medical Monitor.

5.6.4. Dose Interruption of Rituximab

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

- 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 complete the infusion at the decreased rate. If symptoms do not improve, or worsen, discontinue the infusion. May resume at next scheduled dose per Table 8 guidelines.

- 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.

Note: A Grade 4 infusion reaction on Cycle 1 Day 1 of Phase 1b will not be considered a DLT and the subject will be replaced.

5.6.5. Dose Modification of Rituximab

The dose of rituximab should be modified according to the dose modification guidelines in Table 8 if any of the following toxicities occur:

- Any Grade 4 or unmanageable Grade 3 non-hematologic toxicity attributed to rituximab.

Note: For guidance on management of rituximab in relation to infusion reactions see Section 5.6.4.

Table 8: Dose Modification for Rituximab Toxicity

Occurrence	Action to be Taken
1st-3rd	Withhold rituximab until recovery to Grade ≤1 or baseline; may restart at original dose level
Fourth	Discontinue rituximab

5.7. Study Drug Compliance

5.7.1. Ibrutinib and Lenalidomide Compliance

The study drugs (ibrutinib and lenalidomide) are to be prescribed only by the principal Investigator or a qualified physician listed as a Sub-Investigator on the Form FDA 1572. The study site personnel must maintain all study drug records in the study file, and record all study drugs dispensing and returning on the drug accountability form and in the subject's source documents. The study drugs 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 Interactive Web Response System (IWRS) 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 drugs to each study visit. The site personnel must reconcile and document the returned capsules from the study subjects at each study visit to ensure ibrutinib and lenalidomide dosing compliance. Instructions for self-administration and storage conditions of ibrutinib and lenalidomide will be provided to the subjects by the site personnel. Precautions associated with the use of study drugs 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.

5.7.2. 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.

5.8. Overdose Instructions

Any dose of study drug administered in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose of any of the study drugs that meet any Serious Adverse Event (SAE) criterion must be reported as an SAE in the appropriate time frame and documented as clinical sequelae to an overdose.

5.8.1. Ibrutinib

There is no specific experience in the management of ibrutinib overdose in patients. 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.

Refer to Section 11 for further information regarding AE reporting.

5.8.2. Lenalidomide

There is no specific experience in the management of lenalidomide overdose in patients; although in dose-ranging studies, some patients were exposed to up to 150 mg and in single-dose studies, some patients were exposed to up to 400 mg.

Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

5.8.3. Rituximab

There has been no experience with overdose in human clinical trials. Single doses of up to 500 mg/m^2 have been administered in clinical trials.

5.9. 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 Visit (Section 8.3.19) is required for all subjects except for those subjects who have withdrawn full consent (see Section 9.3).

6. CONCOMITANT MEDICATIONS/PROCEDURES

6.1. Concomitant Medications

6.1.1. Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted.

Erythropoietic growth factors (eg, erythropoietin) and hematopoietic growth factors are allowed per institutional policy and in accordance with the ASCO guidelines (Smith 2006). Transfusional support (packed red blood cells and platelets) may be given in accordance with institutional policy.

Short courses (≤14 days) of corticosteroid treatment for non-cancer-related medical reasons (eg, joint inflammation, asthma exacerbation, rash, antiemetic use, autoimmune cytopenias and infusion reactions) at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted. For purposes of premedication or management of rituximab infusion reactions only, 100 mg of corticosteroid treatment per day may be exceeded.

For rash management, please see Sections 5.4.3 and 5.5.6 (Table 6).

Prophylaxis for hepatitis is permitted as per local guidelines provided no contraindicated antiviral medications are used.

6.1.2. Medications to be Used with Caution

6.1.2.1. CYP3A Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A4. Avoid co-administration with strong CYP3A4 or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.

- If a strong CYP3A inhibitor (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone, or cobicistat) must be used, reduce the ibrutinib dose to 140 mg or withhold treatment for the duration of the inhibitor use. Subjects should be monitored for signs of ibrutinib toxicity.
- If a moderate CYP3A inhibitor (eg, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, or dronedarone) must be used, reduce ibrutinib to 140 mg for the duration of the inhibitor use. Avoid grapefruit and Seville

oranges during ibrutinib/placebo treatment, as these contain moderate inhibitors of CYP3A (see Section 5.4.2).

- No dose adjustment is required in combination with mild inhibitors.

Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A (see Appendix 4).

Avoid use of strong CYP3A inducers (eg, 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 4. For further information, please refer to the current version of the ibrutinib IB and examples of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

6.1.2.2. 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 ibrutinib.

6.1.2.3. Concomitant Use of Antiplatelet Agents and Anticoagulants

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. For guidance on ibrutinib and the use of anticoagulants during procedures/surgeries see Section 6.2.

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 should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

6.1.3. Prohibited Concomitant Medications

Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy is prohibited while the subject is receiving study treatment.

Corticosteroids for the treatment of the underlying disease is prohibited. Corticosteroids for the treatment of non-cancer related reasons for longer than 14 days and/or at doses >100 mg of

prednisone or equivalent are prohibited except when given for an AE of rash, where the corticosteroid treatment may exceed 14 days. See Section 6.1.1 for permitted uses.

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

6.2. Guidelines for Ibrutinib Management with Surgeries or Procedures

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

6.2.1. Minor Procedures

For minor procedures (such as a central line placement, needle biopsy, lumbar puncture [other than shunt reservoir access], thoracentesis, or paracentesis) ibrutinib 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 ibrutinib, it is not necessary to hold ibrutinib.

6.2.2. Major Procedures

For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib 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.

6.3. Emergency Procedures

For emergency procedures, ibrutinib should be held as soon as possible and 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. Screening / Administrative

All clinical screening assessments and routine laboratory must be performed within 28 days of the first administration of study drug.

7.1.1. Informed Consent

The subject must read, understand, and sign the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) approved informed consent form (ICF) confirming his or her willingness to participate in this study before any study-specific screening procedures are performed. In addition, subjects must sign all approved ICF amendments per the site IRB/REB/IEC guidelines during the course of the study.

7.1.2. 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 (Section 4) including prior to the first dose on Day 1. Measurable disease documented by radiographic imaging is required at the time of study entry. Confirmation of non-GCB phenotype by IHC according to the central laboratory is required prior to enrollment to confirm eligibility for Phase 2 only.

7.1.3. Medical History and Demographics

The subject's complete 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 and list of all prior anticancer treatments, dates administered, and responses and DOR to these treatments, also will be recorded.

7.1.4. Venous Thromboembolism Risk Assessment

The subject's risk for development of venous thromboembolism (VTE) will be assessed. General risk factors for subjects with cancer include, but are not limited to: underlying disease, family history, age, obesity, immobilization, hormonal therapy, central venous catheter, recent DVT, gender, renal dysfunction and certain chemotherapy-based regimens. It is not known whether prophylactic anticoagulation or anti-platelet therapy prescribed in conjunction with lenalidomide may lessen the potential for venous thromboembolism. It is up to the discretion of the Investigator after consideration of the subject's individual risk/benefit profile whether to institute VTE prophylaxis using a permitted concomitant medication (see Section 6.1.2.3). It is recommended that protocol-appropriate VTE prophylaxis be used in subjects considered at high-risk for thrombosis. This assessment must be performed at the Screening Visit and may be performed anytime thereafter as appropriate. Refer to Table 6 for dose modification in the event a VTE occurs while on treatment.

7.1.5. Prior and Concomitant Medications

All medications from 14 days before Cycle 1, Day 1 through 30 days after the last dose of study treatment will be documented. After a subject discontinues study treatment, subsequent anticancer therapies will be collected.

7.1.6. Adverse Events

The accepted regulatory definition for an adverse event is provided in Section 11.1. The occurrence of adverse events from the time the ICF is signed until the first dose should be recorded under medical history in the eCRF form. All medical occurrences after the first dose with study drug until 30 days after the last dose of study drug that meet the adverse event definition must be recorded as AEs in the eCRF. Laboratory abnormalities designated clinically significant by the Investigator will also be documented as adverse events. Additional important requirements for adverse event and serious adverse event reporting are explained in Section 11.2.2.

7.2. Assessments

7.2.1. Physical Examination, Height, and Weight

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

A limited symptom-directed physical examination is performed at all other time points. A limited physical examination will include all organ systems previously abnormal or involved with disease and documentation of any clinically relevant organ abnormalities. Lymphoma symptoms reported at Screening should be reviewed and noted in the subject source documents during the limited physical examination. Refer to Schedule of Assessments (Appendix 1).

7.2.2. Eastern Cooperative Oncology Group (ECOG) Performance Status

The ECOG performance index is found in Appendix 2. The ECOG performance status will be assessed at time points specified in the Schedule of Assessments (Appendix 1).

7.2.3. Vital Signs

Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature and will be assessed at time points specified in the Schedule of Assessments (Appendix 1). Blood pressure should be obtained after the subject has been resting in the sitting position for at least 3 minutes.

7.2.4. Electrocardiogram (ECG)

A 12-lead ECG will be taken at Screening and at the End-of-Treatment Visit. Subjects should be in a supine position and resting for at least 10 minutes prior to the ECG. The ECG is recommended to be performed prior to any blood samples being collected. Any clinically significant abnormality noted at Screening should be included in the medical history or noted post-Screening should be recorded as an adverse event as appropriate.

An ECG should be performed at any time during the study at the Investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness, atrial fibrillation) or new onset dyspnea.

7.3. Efficacy Assessments

Efficacy assessments (response evaluations) will be performed every 3 cycles up to Cycle 25 and then every 6 cycles thereafter. For Phase 1b, refer to Appendix 5 for the Revised International Working Group Response Criteria (Cheson 2007). For Phase 2, refer to Appendix 6 for the Revised International Working Group Response Criteria or Lugano Classification (Cheson 2014).

7.3.1. Radiographic Imaging

Pretreatment tumor assessment will be performed within 28 days before the first dose of study drug. Lesions that have been irradiated cannot be included in the tumor assessment unless unequivocal tumor progression has been documented in these lesions after radiation therapy. A CT scan (with contrast unless contraindicated) of the neck, chest, abdomen, and pelvis and any other disease sites and a positron emission tomography (PET) scan are required for the pretreatment tumor assessment. Thereafter, a PET scan is to be performed to confirm CR if the PET result was positive at Screening or may be performed at any time if clinically indicated. Information on extranodal involvement (eg, gastric or ocular disease) will also be obtained. Lesions in anatomical locations that are not well visualized by CT may be measured at baseline by MRI instead and should continue to be measured by MRI until disease progression.

In the case where CT with contrast is contraindicated, an alternative would be MRI of the abdomen and pelvis with contrast and CT of the chest and neck without contrast. In this case, neck nodes cannot be used as target lesions.

During treatment, CT/MRI scans will be done for tumor assessments within 7 days of Day 1 of Cycle 4 and Cycle 7 and then every 3 cycles up to Cycle 25, and then every 6 cycles thereafter, until PD or use of alternative anticancer therapy.

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, 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 (eg – central imaging vendor). At the Sponsor's discretion, the Sponsor or designee may conduct an independent review of the Investigator responses.

7.3.2. Physical Examination

Physical examination findings should be used at the time of response evaluation to assess both response and/or progression. Abdominal examination to assess for enlarged liver and/or spleen should be performed and documented, with verification of findings by radiographic imaging preferred. Non-palpable liver and spleen is required for CR response category.

Any new or enlarged palpable masses suspected to be disease progression should be verified by radiographic imaging when possible.

7.3.3. Bone Marrow Aspirate and Biopsy

A unilateral bone marrow aspirate and biopsy will be done at Screening or up to 28 days before the first dose of study drug.

For Phase 1b: Follow-up bone marrow aspirate and biopsy will only be required to confirm CR if result was positive at Screening.

For Phase 2: If the baseline PET result is positive for bone marrow involvement, a baseline bone marrow aspirate and biopsy is no longer required (Cheson 2014). [For clinical trial purposes and to ensure eligibility, baseline bone marrow samples/results will be collected.]

For CR in Phase 2:

If the PET result is positive for bone marrow involvement at baseline and confirmed negative at CR, a follow-up bone marrow aspirate and biopsy is not required to confirm CR; if the PET result is negative at baseline and the bone marrow aspirate and biopsy (which is then required at baseline) is positive at baseline, a confirmatory follow-up bone marrow aspirate and biopsy to confirm CR is required (Cheson 2014).

Subjects who have a bone marrow aspirate and biopsy result since completion of their last therapy for DLBCL may use those bone marrow results in lieu of the baseline bone marrow aspirate and biopsy required for this study provided the biopsy and aspirate were done within 28 days of first dose of study drug.

Additional samples may be collected for biomarkers and other exploratory evaluations.

7.4. Survival and Subsequent Anticancer Therapies

7.4.1. Survival

After disease progression or study treatment discontinuation, subjects will be contacted to assess survival status every 12 weeks (±14 days) from End-of-Treatment Visit until death, subject withdrawal of full consent, lost to follow-up, or study completion, whichever comes first. At the time of the analysis and at study completion, a survival sweep will be conducted. All subjects who are not known to have died or withdrawn consent prior to survival sweep will be contacted at that time.

7.4.2. Subsequent Anticancer Therapies

After study treatment is complete, the following information on subsequent anticancer therapies will be collected every 12 weeks (±14 days) from End-of-Treatment Visit to death, subject withdrawal of full consent, loss to follow-up, or study completion, whichever comes first:

- Receipt of subsequent anticancer therapies
- Indication for subsequent anticancer therapies

7.5. Clinical Laboratory Assessments

7.5.1. Hematology

Hematology parameters will include a complete blood count: white blood cells, red blood cells, hemoglobin, hematocrit, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils and bands (if reported). See time points specified in the Schedule of Assessments (Appendix 1).

7.5.2. Serum Chemistry

Serum chemistry parameters will include sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), phosphate, uric acid, magnesium and bicarbonate. See time points specified in the Schedule of Assessments (Appendix 1).

7.5.3. Creatinine Clearance

Creatinine clearance will be calculated using the Cockcroft-Gault method (Appendix 3) or 24-hour creatinine clearance collection. See time points specified in the Schedule of Assessments (Appendix 1).

7.5.4. Coagulation Studies

Measurement of prothrombin time (PT)/INR, and activated partial thromboplastin time (aPTT) will be performed at Screening and End-of-Treatment Visit.

7.5.5. Hepatitis Serologies

Hepatitis serologies include hepatitis C antibody, hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody. PCR must be confirmed negative prior to enrollment for subjects who are hepatitis B core antibody positive, hepatitis B surface antigen positive or hepatitis C antibody positive.

7.5.5.1. Thyroid Function

Thyroid stimulating hormone (TSH) will be used to evaluate thyroid function. If abnormal, further testing should be performed as clinically appropriate. Testing will be performed at Screening, pre-dose Day 1 of every 3 cycles for the first year, then every 6 cycles thereafter, and at the End-of-Treatment Visit. Testing at additional time points may be performed at the Investigator's discretion.

7.5.5.2. Urinalysis

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. Testing will be performed at Screening and the End-of-Treatment Visit.

7.5.5.3. Pregnancy Test

A pregnancy test (urine or serum) with a sensitivity of 25 mIU/mL must be done in accordance with Celgene Corporation's Revlimid REMS™ or global Pregnancy Prevention Program (PPP) guidelines for females of childbearing potential (FCBP) only. If the pregnancy test is positive at Screening, the subject is not eligible.

A FCBP is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

Pregnancy tests must occur within 10–14 days and again within 24 hours prior to initiation of Cycle 1 of lenalidomide. A FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on lenalidomide therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. A FCBP with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on lenalidomide therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 following lenalidomide discontinuation.

In order to allow for drug delivery in the US, pregnancy testing can be performed on Days 22-28 of each cycle. A pregnancy test may be performed more frequently if required by local and national requirements.

7.6. Biomarker, Correlative and Special Studies

7.6.1. Pharmacokinetics

Plasma concentrations of ibrutinib and its metabolite PCI-45227 will be determined using a validated analytical method in Phase 2 in up to 25 subjects on 20 mg lenalidomide and up to 25 subjects on 25 mg lenalidomide. Other potential metabolites of ibrutinib may be explored. Refer to the Schedule of Assessments (Appendix 1) and the Pharmacokinetic Sample Schedule (Table 9).

Table 9: Pharmacokinetic Sample Schedule

Cycle	Day	Predose	Time Point Postdose[a]			
			1h ± 15 min	2 h ± 15 min	4 h ± 30 min	6 h ± 1 h
1	22	X	X	X	X	X
2	1	X	X	X	X	X

[a.] Record actual time of sample collection

Refer to the Laboratory Manual/Flow Chart for instructions on collecting and processing PK samples. On the day of the sampling visit, the clinical staff will instruct the subject to not take either ibrutinib or lenalidomide before arrival at the clinic. Study drug intake will be observed by clinic staff. The actual time (versus requested time) that each PK sample is drawn must be recorded in the using a 24 hour format.

7.6.1.1. Pharmacokinetics Sample Collection for Subjects who Received Ibrutinib and Concomitant CYP3A Inhibitors

For subjects in Phase 2 who must take strong or moderate CYP3A inhibitors while on treatment with ibrutinib, the PK blood samples for evaluation of ibrutinib exposure should be collected at the next scheduled visit (preferably after the CYP3A inhibitor has started and when it is in use). Pharmacokinetic samples will be collected at the following time points:

- Predose: If possible, the sample should be obtained 22-24 hours post the previous day's dose of ibrutinib and before dosing on the day of the scheduled visit)
- 1 hour postdose ± 15 min
- 2 hours postdose ± 15 min
- 4 hours postdose ± 30 min

Refer to the Laboratory Manual/Flow Chart for instructions on collecting and processing PK samples. On the day of the sampling visit, the clinical staff will instruct the subject to not take either ibrutinib or lenalidomide (if applicable) before arrival at the clinic. Study drug intake will be observed by clinic staff. The actual time (versus requested time) that each sample is drawn must be entered in the eCRF using a 24-hour format.

7.6.2. Biomarkers

Identification of signaling pathways or biomarkers that predict sensitivity or resistance to ibrutinib will be explored in this study.

A pre-dose blood sample will be collected at the following visits: Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1; at response evaluation visits (eg, Cycle 4, 7, 10, etc.); and End-of-Treatment (EOT) Visit. These samples will be sent to a central laboratory for testing.

If a subject progresses and returns to clinic within 24 hours after his or her last dose of ibrutinib, then an additional post-progression blood sample will be collected. If this post-progression blood sample is collected, then the biomarker blood sample collection at the EOT Visit is not required.

Samples collected may be used for pharmacodynamic and biomarker assessments including BTK and other kinase activity and signaling, expression analysis, sequencing, flow cytometry and secreted protein analyses. Fluids including blood collected during the course of the study may be used for, but not limited to, pharmacodynamics and biomarker assessments as noted above.

7.6.3. Gene Expression Profiling and Immunohistochemistry

Immunohistochemistry testing for determination of DLBCL subtype (GCB/non-GCB) will be performed at a central laboratory. DNA and RNA extracted from the tumor samples will be used for GEP and sequencing assays. An adequate amount of tissue must be available for both IHC and GEP to be eligible for the Phase 2 portion. Tumor tissue will also be required for the Phase 1b study to determine the DLBCL subtype. (Local laboratory results for DLBCL subtype for subjects in the Phase 1b may be collected). The sample can be archival tissue from original diagnosis, from relapsed or refractory disease or fresh in order to meet the requirement (see Laboratory Manual/Flow Chart for more details). These samples will be used for ABC/GCB/Type 3 DLBCL subtyping by GEP and may be used to identify biomarkers that may predict response or resistance to ibrutinib. Proteomic analyses to examine BCR-related signaling pathways or activation of BTK or related kinases may also be performed on remaining material from these samples.

The concordance of the central GEP and central IHC classifiers may be assessed with estimates of sensitivity and specificity of the IHC classifier given the central GEP subtype classification. The SAP will provide additional analysis details.

Tissue samples collected during the course of the study may be used for, but not limited to, biomarker assessments as noted above. In addition, samples collected from non-eligible subjects may be retained for purposes of validation of a diagnostic assay.

Refer to the Laboratory Manual/Flow Chart for detailed information on the required amount and acceptable preparations of sample and sample handling specifications and shipment to the central laboratory.

7.6.4. T/B/NK Cell Count

The blood sample(s) for T/B/NK cell count ($CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD16/56^+$) must be collected predose at the time points specified in the Schedule of Assessments (Appendix 1).

These samples will be sent to a central laboratory for testing.

7.6.5. Serum Immunoglobulins (Phase 2 only)

Blood samples will be collected for analysis of serum immunoglobulins in the Phase 2 portion of the study. The blood sample(s) for serum immunoglobulins (IgG, IgM and IgA) must be collected predose at the time points specified in the Schedule of Assessments (Appendix 1).

These samples will be sent to a central laboratory for testing.

7.6.6. Tumor Tissue Sample

Material from either of the optional biopsy samples may be used for exploratory analysis including gene expression profiling, sequencing to identify mutations in BTK, related kinases or other critical genes, and determination of Btk active-site occupancy. Molecular characterization

of this sample may identify altered signaling patterns that associate with response or resistance to ibrutinib treatment.

For a subject who consents to participate in the optional pre-treatment lymph node biopsy, the sample must be collected since the completion of the most recent treatment regimen. For a subject who consents to participate in the optional post-progression lymph node biopsy, the sample must be collected within 30 (±7) days after the last dose of ibrutinib or prior to the start of a new anticancer treatment and as early as possible on or before the End-of-Treatment Visit. All samples must be sent to the central laboratory for processing. Refer to the Study Manual for more information regarding sample submission.

7.7. 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 1) for the timing and frequency of all sample collections.

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

8. STUDY PROCEDURES

8.1. Overview

The study is divided into a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Schedule of Assessments (Appendix 1) summarizes the frequency and timing of efficacy, PK, biomarker, and safety measurements applicable to this study.

8.2. Screening Phase

Screening procedures will be performed up to 28 days before Cycle 1, Day 1. All subjects must first read, understand, and sign the IRB/IEC-approved ICF before any study-specific screening procedures are performed. A subject may be re-screened up to 2 times if the subject does not meet eligibility criteria within the 28-Day Screening Phase and has not been enrolled nor received any study drug treatment.

8.2.1. Screening Visit

The following procedures will be performed at the Screening Visit within 28 days prior to treatment unless otherwise noted:

- Obtain signed, written informed consent
- Medical history including demographic information
- Perform a complete physical examination, including height and weight
- Evaluation of ECOG performance status

- Obtain vital signs (including blood pressure, heart rate, respiratory rate, and body temperature) after the subject has rested in the sitting position for ≥3 minutes
- Obtain a 12-lead ECG after the subject has been in a supine position and resting for at least 10 minutes.
- Record concomitant medication history including over-the-counter drugs, vitamins and herbs
- Imaging by CT/MRI and positron emission tomography (PET) (if not performed within 28 days prior to first dose of study drug)
- Obtain a bone marrow aspirate and biopsy (if not performed within 28 days prior to first dose of study drug)
- Venous thromboembolism assessment
- Obtain blood specimens for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Coagulation studies (PT/INR, aPTT)
  - Hepatitis serologies
  - Thyroid function (TSH)
- Obtain urinalysis
- Obtain urine or serum pregnancy test for women of childbearing potential within 10–14 days prior to initiation of Cycle 1 of lenalidomide according to Section 7.5.5.3.
- Collection of archival or fresh tumor tissue from a lymph node biopsy for determination of DLBCL subtype by IHC using the Hans method
  - Note: Sufficient tissue sample for evaluation by IHC and GEP is required for subjects in Phase 2 (refer to Laboratory Manual/Flow Chart for requirements).
- Calculate creatinine clearance
- Review AEs
- Review inclusion and exclusion criteria to confirm subject eligibility
- Lenalidomide counseling

8.3. Treatment Phase

Subjects must continue to meet eligibility criteria pre-dose on Day 1 Cycle 1 in order to enroll into the study. Safety laboratory assessments performed within 48 hours prior to Day 1 of any cycle of study drug may be used for dosing.

8.3.1. Cycle 1, Day 1

Pre-dose

- Complete physical exam including weight
- ECOG performance status
- Vitals signs including blood pressure, heart rate, respiratory rate, and body temperature
- Collect blood samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - T/B/NK
  - Biomarkers
  - Serum immunoglobulins **(Phase 2 only)**
- Calculate creatinine clearance
- Review of AEs and concomitant medications
- Obtain urine or serum pregnancy test for women of childbearing potential within 24 hours prior to initiation of Cycle 1 of lenalidomide according to Section 7.5.5.3.
- Review inclusion and exclusion criteria to confirm subject eligibility prior to dosing
- Lenalidomide counseling

Dosing and Postdose

- Dispense ibrutinib and lenalidomide
- Review study drug compliance instructions
- Administration of ibrutinib, lenalidomide and rituximab
- Review of AEs and concomitant medications

8.3.2. Cycle 1, Day 8

Predose

- Symptom directed physical exam including weight
- ECOG performance status
- Vitals signs (including blood pressure, heart rate, respiratory rate, and body temperature)
- Collect blood samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
- Review study drug compliance
- Review of AEs and concomitant medications

- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.5.5.3.

Dosing and Postdose

- Administration of ibrutinib and lenalidomide

8.3.3. Cycle 1, Day 15

Predose

- Symptom directed physical exam including weight
- ECOG performance status
- Vitals signs (including blood pressure, heart rate, respiratory rate, and body temperature)
- Collect blood samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
- Review study drug compliance
- Review of AEs and concomitant medications
- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.5.5.3.

Dosing and Postdose

- Administration of ibrutinib and lenalidomide

8.3.4. Cycle 1, Day 22

Predose

- Symptom directed physical exam including weight
- ECOG performance status
- Vitals signs (including blood pressure, heart rate, respiratory rate, and body temperature)
- Collect blood samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
- Review study drug compliance
- Review of AEs and concomitant medications
- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.5.5.3.
- Collect predose PK sample (**Phase 2 only**)

Dosing and Postdose

- Administration of ibrutinib
- Collect PK samples (**Phase 2 only**) at 1 hour (± 15 minutes), 2 hours (± 15 minutes), 4 hours (±30 minutes), and 6 hours (± 1 hour) postdose

8.3.5. Cycle 2, Day 1

Predose

- Complete physical exam including weight
- ECOG performance status
- Vitals signs (including blood pressure, heart rate, respiratory rate, and body temperature)
- Collect blood samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - T/B/NK
  - Biomarkers
- Collect pre-dose PK sample (**Phase 2 only**)
- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.5.5.3
  - FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on lenalidomide therapy (including breaks in therapy).
  - FCBP with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on lenalidomide therapy (including breaks in therapy).
- Calculate creatinine clearance
- Review study drug compliance
- Review of AEs and concomitant medications
- Lenalidomide counseling

Dosing and Postdose

- Administration of ibrutinib, lenalidomide and rituximab
- Collect PK samples (**Phase 2 only**) at 1 hour (±15 minutes), 2 hours (±15 minutes), 4 hours (±30 minutes), and 6 hours (±1 hour) post-dose

8.3.6. Cycle 2, Day 15

Predose

- Symptom directed physical exam including weight
- ECOG performance status
- Vitals signs (including blood pressure, heart rate, respiratory rate, and body temperature)
- Collect a blood sample for the following laboratory test:
  - Hematology
  - Serum Chemistry
- Review study drug compliance
- Review of AEs and concomitant medications
- Females with irregular menstruation must have a pregnancy test every 14 days while on lenalidomide therapy (including breaks in therapy).

Dosing and Postdose

- Administration of ibrutinib and lenalidomide.

8.3.7. Cycle 2, Days 22-28

- Review study drug compliance
- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.5.5.3
  - FCBP with regular or no menstruation must have a pregnancy test every 28 days while on lenalidomide therapy (including breaks in therapy).
  - FCBP with irregular menstruation must have a pregnancy test weekly every 14 days while on lenalidomide therapy (including breaks in therapy).
  - In order to allow for drug delivery in the US, pregnancy testing can be done on Days 22-28 of each cycle.

8.3.8. Cycles 3 and 5, Day 1

Predose

- Complete physical exam including weight
- ECOG performance status
- Vitals signs (including blood pressure, heart rate, respiratory rate, and body temperature)
- Collect blood samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Thyroid function (TSH) (Cycle 3, Day 1 only)

  - T/B/NK (Cycle 3, Day 1 only)
  - Biomarkers (Cycle 3, Day 1 only)
- Calculate creatinine clearance
- Review study drug compliance
- Review of AEs and concomitant medications
- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.5.5.3
  - FCBP with regular or no menstruation must have a pregnancy test every 28 days while on lenalidomide therapy (including breaks in therapy).
  - FCBP with irregular menstruation must have a pregnancy test weekly every 14 days while on lenalidomide therapy (including breaks in therapy).
  - In order to allow for drug delivery in the US, pregnancy testing can be done on Days 22-28 of each cycle.
- Lenalidomide counseling

Dosing and Postdose

- Administration of ibrutinib, lenalidomide and rituximab

8.3.9. Cycle 3, Day 15

Predose

- Collect a blood sample for the following laboratory test:
  - Hematology
  - Serum Chemistry
- Review study drug compliance
- Review of AEs and concomitant medications
- FCBP with irregular menstruation must have a pregnancy test weekly every 14 days while on lenalidomide therapy (including breaks in therapy).

Dosing and Postdose

- Administration of ibrutinib and lenalidomide.

8.3.10. Cycle 3, Days 22-28

- Review study drug compliance
- Imaging by CT/MRI and PET if applicable within 7 days of Cycle 4 Day 1
- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.5.5.3

- FCBP with regular or no menstruation must have a pregnancy test every 28 days while on lenalidomide therapy (including breaks in therapy).
- FCBP with irregular menstruation must have a pregnancy test weekly every 14 days while on lenalidomide therapy (including breaks in therapy).
- In order to allow for drug delivery in the US, pregnancy testing can be done on Days 22-28 of each cycle.

- Administration of ibrutinib

8.3.11. Cycle 4, Day 1

The following procedures will be performed on Cycle 4, Day 1:

Predose

- Complete physical exam including weight
- ECOG performance status
- Vitals signs (including blood pressure, heart rate, respiratory rate, and body temperature)
- Collect blood samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Serum immunoglobulins **(Phase 2 only)**
  - T/B/NK
  - Biomarkers
- Calculate creatinine clearance
- Review study drug compliance
- Review of AEs and concomitant medications
- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.5.5.3
  - FCBP with regular or no menstruation must have a pregnancy test every 28 days while on lenalidomide therapy (including breaks in therapy).
  - FCBP with irregular menstruation must have a pregnancy test weekly every 14 days while on lenalidomide therapy (including breaks in therapy).
  - In order to allow for drug delivery in the US, pregnancy testing can be done on Days 22-28 of each cycle.
- Lenalidomide counseling

Dosing and Postdose

- Administration of ibrutinib, lenalidomide and rituximab

8.3.12. Cycle 4, Days 22-28

- Review study drug compliance
- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.5.5.3
  - FCBP with regular or no menstruation must have a pregnancy test every 28 days while on lenalidomide therapy (including breaks in therapy).
  - FCBP with irregular menstruation must have a pregnancy test weekly every 14 days while on lenalidomide therapy (including breaks in therapy).
  - In order to allow for drug delivery in the US, pregnancy testing can be done on Days 22-28 of each cycle.
- Administration of ibrutinib

8.3.13. Cycle 6, Day 1

Predose

- Complete physical exam including weight
- ECOG performance status
- Vitals signs (including blood pressure, heart rate, respiratory rate, and body temperature)
- Collect blood samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Thyroid function (TSH will be tested pre-dose Day 1 every 3 cycles for the first year and every 6 cycles thereafter)
- Calculate creatinine clearance
- Review study drug compliance
- Review of AEs and concomitant medications
- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.5.5.3
  - FCBP with regular or no menstruation must have a pregnancy test every 28 days while on lenalidomide therapy (including breaks in therapy).
  - FCBP with irregular menstruation must have a pregnancy test weekly every 14 days while on lenalidomide therapy (including breaks in therapy).
  - In order to allow for drug delivery in the US, pregnancy testing can be done on Days 22-28 of each cycle.
- Lenalidomide counseling

Dosing and Postdose

- Administration of ibrutinib, lenalidomide and rituximab

8.3.14. Cycle 6, Days 22-28

- Imaging by CT/MRI and PET if applicable within 7 days of Cycle 7, Day 1, then every 3 cycles up to Cycle 25, and every 6 cycles thereafter, until PD or use of alternative anticancer therapy.
- Administration of ibrutinib

8.3.15. Cycle 7, Day 1 and Beyond

Predose

- Complete physical exam including weight
- ECOG performance status
- Vitals signs (including blood pressure, heart rate, respiratory rate, and body temperature)
- Collect blood samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Serum immunoglobulins **(Phase 2 only)**
  - T/B/NK (i.e, every 3 cycles up to Cycle 25, and then every 6 cycles thereafter)
  - Biomarkers (i.e, every 3 cycles up to Cycle 25, and then every 6 cycles thereafter)
- Calculate creatinine clearance
- Review study drug compliance
- Review of AEs and concomitant medications
- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.5.5.3
  - FCBP with regular or no menstruation must have a pregnancy test every 28 days while on lenalidomide therapy (including breaks in therapy).
  - FCBP with irregular menstruation must have a pregnancy test weekly every 14 days while on lenalidomide therapy (including breaks in therapy).
  - In order to allow for drug delivery in the US, pregnancy testing can be done on Days 22-28 of each cycle.
- Lenalidomide counseling

Dosing and Postdose

- Administration of ibrutinib and lenalidomide.

8.3.16. Cycle 7 and 8, Days 22-28

- Review study drug compliance
- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.5.5.3
  - FCBP with regular or no menstruation must have a pregnancy test every 28 days while on lenalidomide therapy (including breaks in therapy).
  - FCBP with irregular menstruation must have a pregnancy test weekly every 14 days while on lenalidomide therapy (including breaks in therapy).
  - In order to allow for drug delivery in the US, pregnancy testing can be done on Days 22-28 of each cycle.
- Administration of ibrutinib

8.3.17. Cycle 9 and Beyond, Days 22-28

- Review study drug compliance
- Imaging by CT/MRI and PET if applicable within 7 days of Cycle 10, Day 1
- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.5.5.3.
  - FCBP with regular or no menstruation must have a pregnancy test every 28 days while on lenalidomide therapy (including breaks in therapy).
  - FCBP with irregular menstruation must have a pregnancy test weekly every 14 days while on lenalidomide therapy (including breaks in therapy).
  - In order to allow for drug delivery in the US, pregnancy testing can be done on Days 22-28 of each cycle.
- Administration of ibrutinib

8.3.18. Response Evaluation

The Response Evaluation should be performed in alignment with the CT/MRI and/or PET scans schedules. The Response Evaluation is to be performed within 7 days of Day 1 of Cycle 4 and Cycle 7, then every 3 cycles up to Cycle 25, and every 6 cycles thereafter, or at any time during the study if indicated per the Investigator. If possible, the visit should be performed within 4 to 24 hours after the subject's most recent dose. The following procedures are required to assess response:

- Imaging by CT/MRI; and PET if applicable
- Bone marrow aspirate and biopsy if applicable

  For Phase 1b (Cheson 2007):

  - If bone marrow biopsy result is positive at Screening, a follow-up bone marrow biopsy is required to confirm CR.

For Phase 2 (Cheson 2014):

- If the baseline PET result is positive for bone marrow involvement, the follow-up PET has to be negative to confirm CR.
- If the baseline PET result is negative for bone marrow involvement, a bone marrow biopsy should be performed:
  - If the bone marrow biopsy result is negative at baseline, a follow-up bone marrow biopsy is not required to confirm CR.
  - If the bone marrow biopsy result is positive at baseline, a follow-up bone marrow biopsy is required to confirm CR, unless a follow-up PET result is available and positive for bone marrow involvement.

- Complete physical exam including weight
- Vitals signs (including blood pressure, heart rate, respiratory rate, and body temperature)
- Collect blood samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - T/B/NK
  - Biomarkers
  - Serum immunoglobulins **(Phase 2 only)**
- Review study drug compliance
- Review of AEs and concomitant medications
- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.5.5.3.
  - FCBP with regular or no menstruation must have a pregnancy test every 28 days while on lenalidomide therapy (including breaks in therapy).
  - FCBP with irregular menstruation must have a pregnancy test weekly every 14 days while on lenalidomide therapy (including breaks in therapy).
  - In order to allow for drug delivery in the US, pregnancy testing can be done on Days 22-28 of each cycle.

8.3.19. End-of-Treatment Visit

An End-of-Treatment Visit should occur 30 days (±7 days) from the last dose of study drug or prior to the start of a new anticancer treatment. If a subject starts a new anticancer treatment less than 7 days after the last visit with a response assessment, only those procedures not conducted at the last visit should be performed at the End-of-Treatment Visit.

The following procedures will be performed at the End-of-Treatment Visit:

- Complete physical exam including weight
- ECOG performance status
- Vitals signs (including blood pressure, heart rate, respiratory rate, and body temperature)
- 12-lead ECG
- Collect blood samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Coagulation studies (PT/INR, aPTT)
  - Thyroid function (TSH)
  - T/B/NK
  - Biomarkers
  - Serum immunoglobulins **(Phase 2 only)**
- Obtain urinalysis
- Obtain urine or serum pregnancy test for women of childbearing potential according to Section 7.5.5.3

  FCBP with regular or no menstruation must have a pregnancy test weekly at discontinuation of lenalidomide (EOT Visit) and at Day 28 post the last dose of lenalidomide

  FCBP with irregular menstruation must have a pregnancy test at discontinuation of lenalidomide (EOT visit) and at Day 14 and Day 28 after last dose of lenalidomide
- Optional tumor tissue biopsy
- Review of AEs and concomitant medications

8.4. Follow-up Phase

Once a subject has completed the End-of-Treatment Visit, he/she will enter the Follow-Up Phase. Subjects that withdraw from treatment for reasons other than PD will participate in ongoing Response Follow-Up.

8.4.1. Response Follow-Up

Subjects who discontinue the study treatment for reasons other than PD will be followed every 3 months (±14 days) until PD or use of alternative anticancer therapies. During this period, CT/MRI and PET scans will be done per the Investigator's discretion.

8.4.2. Long-Term Follow-Up

Once subjects progress (for subjects who have not withdrawn consent), they will be contacted approximately every 3 months (±14 days) by clinic visit or telephone to assess survival.

Subsequent anticancer therapies and information about second malignancies will be collected. Subjects will be contacted until death, subject withdrawal, lost to follow-up, or study completion, whichever occurs first.

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 an AE that prevents further ibrutinib administration
- Dose limiting toxicity (DLT)
- 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 survival.

The Investigator should notify the Sponsor within 24 hours if a subject discontinues ibrutinib treatment due to disease progression. If a subject shows signs of disease progression on physical examination or laboratory assessment, the subject may continue study treatment until disease progression is confirmed. These subjects should stay in the study to be followed for survival.

9.3. Withdrawal from Study (Study Exit)

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 (ie, withdraws consent to treatment and all further contact) or partial consent (ie, withdraws consent to treatment but agrees to participate in follow-up visits)

10. STATISTICAL METHODS AND ANALYSIS

Statistical analysis will be performed by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods for the analysis of the efficacy and safety data is outlined below. Specific details will be provided in the SAP.

10.1. General Considerations

The Phase 1b part of this study is a dose escalation study. All safety and efficacy assessments will be summarized by dose group.

The Phase 2 part of this study is designed to assess the efficacy and safety of ibrutinib in combination with lenalidomide and rituximab in subjects with relapsed or refractory de novo non-GCB DLBCL.

An analysis will occur approximately 12 months after the last subject initiates study treatment or when all subjects have discontinued from the study treatment, whichever occurs first, and will be reported in the Clinical Study Report (CSR). A final follow-up analysis will occur 2 years after the last subject has been enrolled and will be reported in the CSR addendum. The study completion is defined as 3 years from the last study treatment, the time point all subjects have exited the study due to any reason, or study termination at the Sponsor's discretion, whichever occurs first.

10.1.1. Response Assessment

Response assessments will be made by the Investigator. Tumor response will be assessed by the Investigator using the revised International Working Group Response Criteria for NHL (Cheson 2007) for Phase 1b and the revised International Working Group Response Criteria for NHL or Lugano Classification (Cheson 2014) for Phase 2.

Confirmation of Investigator-assessed responses by an independent review committee (IRC) may be done as a supportive assessment. The method of independent review will be governed by an IRC charter.

10.1.2. Safety Monitoring

This study will be monitored in accordance with the Sponsor's Pharmacovigilance Committee procedures. Adverse events (AEs) and Serious Adverse Events (SAEs) will be reviewed by the Sponsor on an ongoing basis to identify safety concerns.

The Sponsor may schedule periodic conference calls with the Investigators to discuss study progress, obtain Investigator feedback and exchange, and discuss study-specific topics including AEs and SAEs.

10.2. Definition of Analysis Populations

The following definitions will be used for the efficacy and safety analysis sets.

- **All-treated analysis population (Phase 1b/2):** will include subjects who have enrolled in the study and received any dose of study drug(s) in each study phase respectively. This is the primary analysis population for all efficacy endpoints (ie, PFS, OS) except ORR and CR rate for the Phase 1b and Phase 2. This is also the sensitivity analysis population for ORR and CR rate.
- **Response-evaluable population (Phase 1b/2):** is defined as subjects in the all-treated population who have measurable disease at baseline and have at least 1 adequate post-treatment disease assessment by the Investigator before the start of a subsequent anti-cancer therapy. This is the primary analysis population for ORR and CR rate.
- **Safety analysis population (Phase 1b/2):** consists of all enrolled subjects who have received any dose of study drug(s). All safety and dose administration analyses will be performed using the safety population.

10.3. Endpoint Data Analysis

10.3.1. Demographic/Baseline Characteristics and Study Conduct

Subject demographics (including age, sex, and race/ethnicity) and other baseline characteristics (including ECOG performance status, disease status, and number of prior therapies) will be summarized. Summary statistics will include means, standard deviations, and medians for continuous variables and proportions for categorical variables.

Further, compliance parameters (including number of doses taken compared with number of doses that should have been taken), the reason for discontinuation, and concurrent treatments will also be similarly summarized.

10.3.2. Efficacy Endpoints for Phase 1b

The efficacy endpoints for the Phase 1b of this study are ORR and CR rate. The ORR of Phase 1b and its 95% 2-sided exact confidence interval will be calculated for the response-evaluable population and the all-treated population of Phase 1b. The CR rate of Phase 1b will be analyzed likewise.

10.3.3. Primary Efficacy Endpoint for Phase 2

The primary efficacy endpoint for Phase 2 is the overall response rate (ORR). The ORR is defined as the rate of subjects who achieve either a PR or CR, according to the revised International Working Group Response Criteria for NHL, as assessed by the Investigator (Cheson 2014). The ORR will be calculated for the response-evaluable population of Phase 2. The corresponding 95% 2-sided exact CI will be derived. If the lower bound of the CI around the ORR is greater than or equal to 40%, then the hypothesis that the ORR of the ibrutinib combination treatment is equal to or lower than 40% will be rejected. The ORR will also be calculated for the all-treated population of Phase 2.

10.3.4. Secondary Efficacy Endpoints for Phase 2

The secondary efficacy endpoints for Phase 2 of this study are CR, DOR, PFS and OS.

10.3.4.1. Complete Response

Complete response rate will be analyzed by the same method used for the analysis of ORR.

10.3.4.2. Duration of Response

For subjects achieving an overall response as assessed by the Investigator, their DOR as assessed by the Investigator will be calculated to determine durability. Duration of response will be measured from the time by which the measurement criteria are met for CR or PR, whichever is recorded first, until death or the first date by which recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). For subjects without disease progression or death, DOR will be censored at the date of the last tumor assessment.

The distribution (median, its 95% CI and Kaplan-Meier curves) of DOR will be provided using Kaplan-Meier estimates for responders in the all-treated analysis population.

10.3.4.3. Progression-Free Survival

Progression-free survival will be measured as time from first study drug administration to lymphoma progression or death from any cause. Data for subjects without disease progression or death will be censored at the date of the last tumor assessment.

Progression-free survival will be calculated using assessments by the Investigator. Kaplan-Meier methodology will be used to estimate event-free curves and corresponding quartiles (including the median). The distribution (median, its 95% CI and Kaplan-Meier curves) of PFS will be provided using Kaplan-Meier estimates in the all-treated analysis population.

10.3.4.4. Overall Survival

The duration of OS will be measured from the time of first study drug administration until the date of death. Kaplan-Meier methodology will be used to estimate overall survival curves and corresponding quartiles (including the median). Data for subjects who have not died will be

censored at the date last known to be alive (on site or phone contact) or study completion whichever comes first.

The distribution (median, its 95% CI and Kaplan-Meier curves) of OS will be provided using Kaplan-Meier estimates in the all-treated analysis population.

10.3.5. Exploratory Analysis (Phase 2 only)

The ORR will be analyzed by ABC vs. non-ABC subtype identified by gene expression profiling (GEP).

The absolute cell counts on peripheral T/B/NK will be summarized by scheduled visits.

The serum immunoglobulin levels (IgG, IgM, and IgA) will be summarized by scheduled visits.

10.3.6. Safety Endpoint

Safety summaries will include tabulations in the form of tables and listings. The frequency (number and percentage) of treatment-emergent AEs will be reported by MedDRA® System Organ Class and Preferred Term. Additional AE summaries will include AE frequency by AE severity and by relationship to study drug.

Adverse events requiring discontinuation of study drug will be summarized separately, both overall and by AE severity and by relationship to study drug.

Clinically significant abnormal laboratory values will be summarized. Laboratory shift tables containing counts and percentages will be prepared by laboratory parameter and time. Summary tables will be prepared for each laboratory parameter. Figures of changes in laboratory parameters over time will be generated.

Safety: Missing or partial start and end dates for AEs and concomitant medications will be imputed according to pre-specified, conservative imputation rules. No other imputation of values for missing data will be performed.

10.3.7. Pharmacokinetics

The PK evaluation in the Phase 2 of the study is to obtain the PK parameters of ibrutinib in subjects with relapsed or refractory DLBCL after administration of ibrutinib in combination with lenalidomide and rituximab. The PK samples will be collected and analyzed in a subset of subjects in Phase 2 (approximately 25 subjects). Although not based on statistical considerations, the number of subjects for PK collections in this study is consistent with the number of subjects collected in other Phase 1 and Phase 2 studies with various histologies and represent approximately 45% of the total number of subjects in the Phase 2 portion of the study.

Plasma concentrations of ibrutinib and a major metabolite (PCI-45227) will be determined using a validated analytical method. Other potential metabolites of ibrutinib may be explored.

Bioanalytical data from this study will be used in noncompartmental PK analysis and also may be combined with data from other studies performed with ibrutinib in subjects with hematologic malignancies as part of a population PK analysis using nonlinear mixed effects models. For the population PK analysis, covariates that could potentially correlate with plasma PK parameters will be evaluated. Pharmacokinetic relationships to pharmacodynamic measures of efficacy or toxicity may also be explored. The results of the population PK analyses will be presented in a separate report. For subjects who received CYP3A inhibitors, as data permits, a comparison of ibrutinib and PCI-45227 plasma concentrations after ibrutinib administration alone and in combination with CYP3A inhibitors will be explored.

10.3.8. Biomarkers

- Identification of signaling pathways or biomarkers that predict sensitivity or resistance to ibrutinib.
- Frequency of tumor mutations (or other molecular markers) between pre and post treatment tissue that predict acquired resistance.

The concordance of the central GEP and central IHC classifiers may be assessed with estimates of sensitivity and specificity of the IHC classifier given the central GEP subtype classification. The SAP will provide additional analysis details.

10.4. Determination of Sample Size

The planned sample size for Phase 2 is approximately 55 subjects to ensure enrollment of at least 49 response-evaluable subjects at 20 mg lenalidomide; approximately 28 additional subjects may be enrolled at 25 mg lenalidomide. The main analysis will be the comparison of response rate to the ORR of a historical control of 40%. The null hypothesis that the true ORR is 40% will be tested against a one-sided alternative that the ORR is 60%. The null hypothesis will be rejected, if 27 or more responses are observed in the 49 subjects. This design yields a 1-sided type I error rate of 0.025 and power of 80% when the true ORR is 60%. This statistical design including number of subjects and number of responders follows the statistical framework of Simon's minmax two-stage design (Simon 1989). Enrollment will continue while the interim analysis is being performed.

10.5. Interim analysis

An interim analysis will be performed including approximately 28 evaluable subjects with adequate tumor response assessment. Enrollment in the 20 mg lenalidomide cohort will continue while the interim analysis is performed. Details of the interim analysis and decision rules will be described in the SAP. At the interim analysis, the review committee could recommend

1. continuation of the study with 20 mg lenalidomide; or
2. increase of the lenalidomide dose to 25 mg, if determined to be safe and tolerated in the Phase 1b, including approximately 28 evaluable subjects with adequate tumor response assessment followed by an interim analysis.

The decisions based on the interim analysis will be made by the Sponsor (at a minimum: the Medical Monitor or designee, a Drug Safety representative and a Biostatistician).

10.6. Safety Analysis

Analysis of safety data will be conducted on the safety analysis population. The baseline value for safety assessments will be defined as the last value on or before the day of the first dose of study drugs if we do not specify. The further details for selecting the baseline value of safety parameters will be described in the SAP. The safety analyses will be based on the monitoring of adverse events, deaths, vital signs measurements, and clinical laboratory results.

The safety variables to be analyzed include adverse events, clinical laboratory test results (hematology and chemistry), physical examination findings, and vital signs measurements. Overall exposure to ibrutinib and the drug combination, and reasons for discontinuation from study treatment will be tabulated. 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.

10.6.1. Adverse Events

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

The verbatim terms used in the eCRF by the Investigator to identify non-hematological adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Treatment-emergent AEs are those AEs events occurring after the first dose of study drugs and within 30 days following the last dose of study drug; any AE that is considered study drug-related regardless of the start date of the event; or any AE that is present at baseline but worsens after the first administration of study drug in severity or is subsequently considered drug-related by the Investigator. All treatment-emergent AEs will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized. The number and percent of subjects with treatment-emergent adverse events will be summarized according to intensity (NCI CTCAE, Version 4.03) 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 SAE.

10.6.2. Clinical Laboratory Tests

Laboratory tests will be summarized separately for hematology and serum chemistry. Local laboratory results will be converted based on the normal ranges and standardized using the SI unit. Selected hematologic and chemistry laboratory parameters are detailed in Section 7.5. Descriptive statistics will be provided for the values of selected clinical laboratory tests at each scheduled on-treatment evaluation including the final value. Percent change from baseline to each scheduled on-treatment evaluation and to the final value will also be summarized. For selected variables, the mean value and mean percent change over time will be presented graphically.

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.

All laboratory values will be converted to standard international units and will be graded using the NCI CTCAE Version 4.03. Standard methods for summarizing laboratory variables will be used, including the use of summary statistics and shift tables.

10.6.3. Dose Level Review Committee

A Dose Level Review Committee will evaluate safety data following the completion of each dose observation period of the Phase 1b portion. The same committee will review safety data in the event that an interim analysis for Phase 2 will be performed. Members of this committee will include the Sponsor (at a minimum: the Medical Monitor or designee, a Drug Safety representative and a Biostatistician) as well as participating Investigators/designees.

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. Adverse Event Definitions and Classifications

11.1.1. Adverse Events

An AE is any untoward medical occurrence in a patient 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 drug, whether or not considered related to the study drug (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.

Disease progression is not an adverse event; rather it may be the cause of an adverse event. The clinical diagnosis that is associated with disease progression must be reported as all other adverse events. "Disease progression" should never be used as an adverse event term.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered 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 DLBCL that were not present before the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (eg, 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 informed consent form 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 to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.
- **Asymptomatic Treatment Related Lymphocytosis:** This event should not be considered an AE. Patients with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.

11.1.2. Serious Adverse Events

A serious adverse event based on 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 patient 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 life-threatening.
- 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 patient'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 life-threatening or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the patient or patient 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. Unexpected Adverse Events

An "unexpected" AE is an AE that is not listed in the Investigator's Brochure/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 Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be "unexpected" (by virtue of greater specificity) if the Investigator's Brochure/ package insert listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the Investigator's Brochure 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.

11.1.4. 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) 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

11.1.5. Causality (Attribution)

The Investigator is to assess the causal relation (ie, whether there is a reasonable possibility that the study drug 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.

11.2. Documenting and Reporting of Adverse Events

The Investigator is responsible for ensuring that all AEs and SAEs observed or reported during the study, as outlined in the prior sections, are recorded on the eCRF. All SAEs must also be reported on the Serious Adverse Event Report Form and submitted to the Sponsor (see Section 11.2.2.2).

11.2.1. Special Reporting Situations

Safety events of interest on a Sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a study drug
- Suspected abuse/misuse of a study drug

- Inadvertent or accidental exposure to a study drug
- Medication error involving a product (with or without subject/patient exposure to the study drug, eg, name confusion)

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the AE eCRF.

11.2.2. Adverse Event Reporting Procedures

11.2.2.1. All Adverse Events

All subjects who receive at least one dose of study drug(s) will be considered evaluable for safety assessments. All AEs whether serious or non-serious, will be recorded in the source documents from the time signed and dated ICF is obtained until 30 days following the last dose of study drug. Starting from the time of first dose of study drug, all AEs and SAEs will be entered in the eCRF until 30 days after the date of last dose of study drug. Serious Adverse Events that occur during study conduct including the screening period must be reported to the Sponsor. Serious adverse events occurring more than 30 days following the last dose of study drug should also be reported if considered related to any of the study drugs. Resolution information after 30 days should be provided.

Progressive disease should NOT be reported as an AE, but instead symptoms/clinical signs of disease progression may be reported. Otherwise, all events that meet the definition of a SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

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 (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to Sponsor instructions.

11.2.2.2. Reporting Criteria for Serious Adverse Events

All SAEs occurring during the study must be reported to the Sponsor by the study-site within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to Pharmacyclics using the Serious Adverse Event Report Form, which must be completed by a study physician from the study site, and submitted to Pharmacyclics within 24 hours of the study site becoming aware of the event.

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 drug 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)

11.2.3. Events of Special Interest

Specific AEs or groups of AEs will be followed as part of standard safety monitoring activities by the Sponsor. These events will be reported to Pharmacyclics within 24 hours of awareness irrespective of seriousness (ie, serious and non-serious adverse events) following the procedure described above for SAEs and will require enhanced data collection.

11.2.3.1. Major Hemorrhage

Major hemorrhage is defined as any of the following:

1. Any treatment-emergent hemorrhagic adverse events of Grade 3 or higher*.
2. Any treatment-emergent serious adverse events of bleeding of any grade
3. 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 11.2.3 above.

11.2.4. Other Malignancies

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported as SAEs. This includes any second primary malignancy, regardless of causal relationship to study drug[s], occurring at any time for the duration of the study, from the time of signing the informed consent to 3 years after the last study drug treatment.

Events of second primary malignancy are to be reported using the SAE form; these events must also be documented in the appropriate page(s) of the eCRF and in the subject’s source documents. Documentation of the diagnosis of the second primary malignancy must be provided

at the time of reporting as an SAE (eg, any confirmatory histology or cytology results, X-rays, CT scans, etc.).

11.2.5. 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 consent to 30 days after the last dose of study drug. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of his consent to 90 days after the last dose of study drug. Any female subjects receiving study drug(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.

11.2.5.1. Pregnancy Reporting

Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 30 days after the last dose of study drug must be reported. Any occurrence of pregnancy must be recorded on the Pregnancy Report Form Part I and submitted 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 serious adverse event.

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 local regulations (including US Code of Federal Regulations [CFR] Title 21 and European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

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 (eg, 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 informed consent form 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. Long-Term Retention of Samples for Additional Future Research

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 lenalidomide, to understand DLBCL, to understand sensitivity or resistance to the investigational products tested in this study, and to develop tests/assays related to ibrutinib/lenalidomide and DLBCL. 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.

12.5. 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 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).

12.6. 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.

12.7. 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 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 eCRFs, and documentation of eCRF 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 (eg, 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.

12.8. Case Report Forms and Record Maintenance

Electronic CRFs 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 (eg, physicians' notes, nurses' notes, clinic charts and other study-specific source documents). Authorized study site personnel (ie, listed on the Delegation of Authority log) will complete eCRFs designed for this study according to the completion guidelines that will be provided. The Investigator will ensure that the eCRFs are accurate, complete, legible, and completed within a reasonable amount 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 (eg, paper, CD, or other appropriate media) for archiving at the study site.

12.9. Investigational Study Drug Accountability

Study drug(s) must be kept in a locked limited access room and must not be used outside the context of the protocol. Under no circumstances should the Investigator or other site personnel supply ibrutinib, lenalidomide or rituximab 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, lenalidomide and rituximab 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 Drug Accountability Log must be used for drug accountability. For accurate accountability, the following information must be noted when drug supplies are used during the study:

- Study identification number (PCYC-1123-CA)
- Subject identification number
- Lot number(s) of study drug (s) dispensed for that subject
- Date and quantity of drug dispensed
- Any unused drug returned by the subject

For additional details on investigational product management, please refer to the Pharmacy Manual.

12.10. Study Monitoring/Audit Requirements

Representatives of Pharmacyclics or its designee will monitor this study until study 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 certified copies of all documents are made available during monitoring visits for all screened and enrolled subjects. 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 affiliates, 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.

12.11. Investigator Responsibilities

A complete list of Investigator responsibilities are outlined in the clinical trial research agreement and the Statement of Investigator Form FDA 1572, 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.

12.12. 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.

12.13. Financial Disclosure

A separate financial agreement will be made between each Principal Investigator and Pharmacyclics or its authorized representative before the study drug is delivered.

For this study, each Investigator and Sub-Investigator (as designated on the Form FDA1572) will provide a signed Financial Disclosure Form in accordance with § 21 CFR 54. Each Investigator will notify Pharmacyclics or its authorized representative of any relevant changes during the conduct of the study and for 1 year after study completion.

12.14. 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.

12.15. Protocol Amendments

Only Pharmacyclics can initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/REB/IEC together with, if applicable, a revised model ICF. Written documentation of 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 the increased risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand and sign any revised ICF confirming willingness to remain in the trial.

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

12.16. 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.

In most cases, the Investigators at the sites with the highest accruals of eligible subjects shall be listed as lead authors on manuscripts and reports of study results. The Medical Monitor, Study Director and/or Lead Statistician may also be included in the list of authors. This custom can be adjusted upon mutual agreement of the authors and Pharmacyclics.

12.17. 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.

12.18. Study Completion

The study is expected to be completed 3 years from the last study treatment, the time point all subjects have exited the study for any reason, or study termination at the Sponsor's discretion, whichever occurs first.

13. REFERENCES

1. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 1993;329(14):987-94.
2. Bishop GA, Haxhinasto SA, Stunz LL, et al. Antigen-specific B-lymphocyte activation. Crit Rev Immunol 2003;23:165–197.
3. Chao NJ, Rosenberg SA and Horning SJ. CEPP(B): an effective and well-tolerated regimen in poor-risk aggressive non-Hodgkin's lymphoma. Blood 1990;76:1293-1298.
4. Cheson BD, Pfistner B, Juweid ME, et al. Revised Response Criteria for Malignant Lymphoma. JCO 2007;25:579-586.
5. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-hodgkin lymphoma: the Lugano classification. JCO 2014; 32:3059-3067.
6. Child CG, Turcotte JG. "Surgery and portal hypertension". In Child CG. The liver and portal hypertension. Philadelphia:Saunders. 1964. pp. 50-64.
7. Christian B, Kuruvilla J, Smith SM et al. A Phase 1 Study of Ibrutinib and Lenalidomide in Patients with Relapsed and Refractory B-Cell Non-Hodgkin's Lymphoma; ASH 2014 abstract #4476 (oral presentation).
8. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03, Published June 14, 2010
9. Corazzelli G, Capobianco G, Arcamone M, et al. Long-term results of gemcitabine plus oxaliplatin with and without rituximab as salvage treatment for transplant-ineligible patients with refractory/relapsing B-cell lymphoma. Cancer Chemother Pharmacol. 2009:64:907-916.
10. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41.
11. Crump M, Baetz T, Couban S, et al. Gemcitabine, Dexamethasone, and Cisplatin in Patients with Recurrent or Refractory Aggressive Histology B-Cell non-Hodgkin Lymphoma: A Phase II Study by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). Cancer 2004;101:1835-1842.
12. Davis RE, Ngo VN, Lenz G, et al. Chronic active B-cell-receptor signaling in diffuse large B-cell lymphoma. Nature 2010;463:88-92.
13. Dunleavy K, Pittaluga S, Czuczman MS, et al. Differential efficacy of bortezomib plus chemotherapy within molecular subtypes of diffuse large B-cell lymphoma. Blood 2009;113:6069-6076.
14. De Vos S, Wilson WH, Gerecitano J et al. The Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib (PCI-32765), Has Preferential Activity In The Activated B Cell-Like (ABC) Subtype of Relapsed/ Refractory (R/R) DLBCL: Interim Phase 2 Results. Haematologica 2013; s1:abstract s1180. (oral presentation)
15. El Gnaoui T, Dupuis J, Belhadj K, et al. Rituximab, gemcitabine and oxaliplatin: an effective salvage regimen for patients with relapsed or refractory B-cell lymphoma not candidates for high-dose therapy. Annals of Oncology 2007;18:1363-1368.
16. Fisher SG, Fisher RI. The epidemiology of non-Hodgkin's lymphoma. Oncogene. 2004;23(38):6524-6534.
17. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28(27):4184-90.

18. Gururajan M, Jennings CD, Bondada S. Cutting edge: Constitutive B cell receptor signaling is critical for basal growth of B lymphoma. Journal of Immunology 2006;176:5715-5719.

19. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 2004;103:275-282.

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

21. Hernandez-Ilizaliturri FJ, Deeb G, Zinzani PL, et al. Higher Response to Lenalidomide in Relapsed/ Refractory Diffuse Large B-Cell Lymphoma in Non-germinal Center B-Cell-Like Than in Germinal Center B-Cell-Like Phenotype. Cancer 2011;117:5058-5066.

22. Holford TR, Zheng T, Mayne ST, McKay LA. Time trends of non-Hodgkin's lymphoma: are they real? What do they mean? Cancer Res 1992;52 (19 Suppl):5443s–5446s.

23. IMBRUVICA® [ibrutinib package insert]. Sunnyvale, CA: Pharmacyclics LLC; Janssen Biotech Inc.; 2015.

24. Investigator's Brochure. Ibrutinib. Version 9: 30June 2015. Pharmacyclics LLC; Janssen Research & Development, LLC.

25. Investigator's Brochure. Revlimid®. Edition 17: 31 Jan 2014. Celgene Corporation; 2014

26. Jermann M, Jost LM, Taverna Ch, et al. Rituximab-EPOCH, an effective salvage therapy for relapsed, refractory or transformed B-cell lymphomas: results of a phase II study. Annals of Oncology 2004;15:511-516.

27. Küppers R. Mechanisms of B cell lymphoma pathogenesis. Nature Reviews Cancer 2005;5:251-262.

28. Lenz G, Staudt LM Aggressive lymphomas. N Engl J Med 2010;362:1417-1429.

29. Leonard J, Jung S, Johnson JL, et al. CALGB 50401: A randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma. [abstract]. 2012 ASCO Annual Meeting. J Clin Oncol 2012;30(suppl); abstr 8000.

30. Lopez A, Gutierrez A, Palacios A, et al. GEMOX-R regimen is a highly effective salvage regimen in patients with refractory/relapsing diffuse large-cell lymphoma: a phase II study. Eur J Haematol. 2008;80:127-132.

31. Lyman GH, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013; 31: 2189-204.

32. MabThera® [EU SmPC]. Welwyn Garden City, United Kingdom: Roche Registration Limited; 2014.

33. Meeker T, Lowder J, Cleary ML, et al. Emergence of idiotype variants during treatment of B-cell lymphoma with anti-idiotype antibodies. N Engl J Med 1985;312:1658-1665.

34. National Cancer Comprehensive Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Non-Hodgkin's Lymphomas. Version 1.2013. http://www.NCCN.org.

35. Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

36. Ohmachi K, Niitsu N, Uchida T, et al. Multicenter Phase II Study of Bendamustine Plus Rituximab in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma. JCO 2013:31:2103-2109.

37. Pan Z, Scheerens H, Li SJ, et al. Discovery of selective irreversible inhibitors for Bruton's tyrosine kinase. ChemMedChem 2007;2:58-61.

38. Park LC, Woo SY, Kim S, et al. Incidence, risk factors and clinical features of venous thromboembolism in newly diagnosed lymphoma patients: results from a prospective cohort study with Asian population. Thromb Res. 2012;130:e6-12.

39. 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.

40. REVLIMID® [lenalidomide package insert]. Summit, NJ: Celgene Corporation; 2015.

41. RITUXAN® [rituximab package insert]. South San Francisco, CA: Genentech, Inc.; 2014.

42. Rosenwald A, Wright G, Chan WC, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med 2002;346:1937 47.

43. Surveillance Epidemiology and End Results, NCI, US National Institutes of Health, Fast Facts; Statistics Stratified by Cancer Site, 2010.

44. Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989;10:1-10.

45. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. Journal of Clinical Oncology. 2006:24: 3187-205.

46. US Food & Drug Administration. Guidance for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. ICH-E2A. March 1995.

47. Tilly H, Vitolo U, Walewski J, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2012;23(s7):vii78-vii82.

48. Wang M, Fowler N, Wagner-Bartak N, et al. Oral Lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular, and transformed lymphoma: a phase II clinical trial. Leukemia 2013; approved online. Doi; 10.1038/leu.2013.95.

49. Weidmann E, Kim SZ, Rost A, et al. Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma. Annals of Oncology 2002;13:1285-1289.

50. Wiernik PH, Lossos IS, Tuscano JM, et al. Lenalidomide Monotherapy in Relapsed or Refractory Aggressive Non-Hodgkin's Lymphoma. JCO 2008;26:4962-4957.

51. Witzig TE, Vose JM, Zinzani PL, et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. Annals of Oncology 2011;22:1622-1627.

52. Yang Y, Shaffer AL, Tolga Emre NC, et al. Exploiting Synthetic Lethality for the Therapy of ABC Diffuse Large B Cell Lymphoma. Cancer Cell 2012;21:723-737.

53. Zhou X, Teegala S, Huen A, et al. Incidence and risk factors of venous thromboembolic events in lymphoma. Am J Med. 2010;123(10):935-41.

54. Ziepert M, Hasenclever D, Kuhnt E, et al. Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. J Clin Oncol 2010; 28:2373-80.

55. Zinzani PL, Pellegrini C, Gandolfi L, et al. Combination of Lenalidomide and Rituximab in Elderly atients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma: A Phase 2 Trial. Clinical Lymphoma, Myeloma & Leukemia 2011; 11:462-466.

14. APPENDICES

Appendix 1. Schedule of Assessments

Cycle		C1				C2		C3			C4	C5	C6		C7 & Beyond	C9 & Beyond	Response Evaluation[o]		EOT	RFU[a]	LTFU
Day		1	8	15	22	1	15	1	15	22-28	1	1	1	22-28	1	22-28					
Visit Window		N/A									+2 days						±7 days		30 days (±7) from last dose	every 3 months (±14 days) until PD	every 3 mon
Study Drug Administration																					
Ibrutinib (continuous)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Lenalidomide (Days 1-21 of each cycle)		X	X	X		X	X	X	X		X	X	X		X		X				
Rituximab (Day 1 of Cycles 1-6)		X				X		X			X	X	X				X				
Review Study Drug Compliance[b]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Procedure	**Screening** Day -28 to -1																				
Informed Consent	X																				
IHC Tumor Sample[c]	X																				
Tumor Sample (Optional)[d]	X																	X[d]			
Medical History & Demographics	X																				
Venous Thromboembolism Assessment	X																				
Lenalidomide Counseling[j]	X	X				X		X			X	X	X		X						
Review Concomitant Medications	X	All medications from 14 days before Cycle 1 Day 1 through 30 days after the last dose of study drugs should be collected.																	X		
Review Adverse Events	X	Continuous starting from consent to 30 days after the last dose of study drugs																	X		
Complete Physical Exam & Weight *(height @ Screening)*	X	X				X		X			X	X	X		X		X		X		
Symptom Directed Physical Exam			X	X	X		X														
Vital Signs[e]	X	X	X	X	X	X	X	X			X	X	X		X		X		X		
ECOG Performance Status	X	X	X	X	X	X	X	X			X	X	X		X				X		
12-Lead ECG	X	If clinically indicated (eg, subjects with palpitations, lightheadedness)																	X		
Bone Marrow Aspirate & Biopsy[f]	X																X[f]				
Confirm Eligibility	X	X																			

Continue Assessment Until Disease Progression

	Cycle	C1				C2		C3			C4	C5	C6		C7 & Beyond	C9 & Beyond	Response Evaluation[o]	Assessment Until Disease	EOT	RFU[a]	LTFU
	Day	1	8	15	22	1	15	1	15	22-28	1	1	1	22-28	1	22-28					
Laboratory Assessment																					
Hematology[g]	X	X	X	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		X		X		X		
Creatinine clearance	X	X				X		X			X	X	X		X						
Coagulation (PT, INR, aPTT)	X																		X		
Thyroid Function Test (TSH)[h]	X							X					X		X[h]				X		
Hepatitis Serologies[i]	X																				
Urinalysis	X																		X		
Pregnancy Test (serum or urine)[j]	X	X	X	X	X	X	X[j]	X	X[j]		X	X	X		X		X		X[j]		
T/B/NK Cell Count[k]		X				X		X			X				X[k]		X[k]		X		
Serum Immunoglobulins (Ig)[l] *(Phase 2)*		X									X[l]				X[l]		X		X		
Biomarker Blood Sample[k]		X				X		X			X				X[k]		X[k]		X		
PK Blood Sampling[m] *(Phase 2)*					X[m]	X[m]															
Radiologic Tumor Assessment																					
CT Neck, Chest, Abdomen, Pelvis[n]	X									X				X		X	X[n,o]			X	
PET or PET/CT[n]	X																X[n,o]			X	
Other																					
Survival Status[p]																					X[p]
Subsequent Anticancer Therapy																				X	X[p]

Abbreviations: C=cycle; CT=computed tomography; D=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End-of-Treatment Visit; LTFU=Long-Term Follow Up; RE=Response Evaluation; PD=progressive disease; PET=positron emission tomography; PO=oral; RFU=Response Follow Up

Footnotes for PCYC-1123-CA Schedule of Assessments:

a. CT/MRI and PET scans may be done per the Investigator's discretion during the response follow-up period.

b. Study Drug diary must be provided to the subjects at the beginning of each Day 1 visit to record daily dosing. Site personnel must instruct the subjects to bring the completed diary card with any used and unused study drugs at each study visit. Site personnel must reconcile and document the returned capsules from the subjects at each visit to ensure compliance.

c. **Phase 2 only:** A fresh tissue sample, archived unstained slides or an archived paraffin block must be sent to central lab for determination of DLBCL subtype by GEP and IHC using the Hans method **at Screening to confirm eligibility for enrollment.** For subjects in **Phase 1b**, available tissue (archived or fresh) will be sent to central lab at Screening for DLBCL subtyping. (Local laboratory results for DLBCL subtype for subjects in the Phase 1b may be collected).The tumor sample(s) can be archival tissue from original diagnosis, from relapsed or refractory disease, or a fresh (recent) biopsy, if done to confirm eligibility for this study.

d. A subject who consents to participate in the optional **pre-treatment** lymph node biopsy, the sample must be collected since the completion of the most recent treatment regimen. A subject who is discontinued from study treatment due to disease progression may consent to an optional post-progression tumor tissue sample (see Section 7.6.5). For a subject who consents to participate in the optional tumor tissue sample assessment, the lymph node biopsy must be collected within 30 (±7) days after the last dose of ibrutinib or prior to the start of a new anticancer treatment and as early as possible on or before the EOT visit. See Laboratory Manual/Flow Chart for details regarding specimen collection and processing.

e. Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed after the subject has rested in the sitting position for ≥3 minutes.

f. A unilateral bone marrow aspirate and biopsy will be done at Screening or up to 28 days before the first administration of study drug. If a bone marrow biopsy and aspirate were done within 28 days of the first dose of study drug, the sample may be used. Thereafter, a bone marrow aspirate and biopsy will only be required to confirm CR if result was positive at Screening. (See Section 8.3.18)

g. Hematology includes complete blood count with differential and platelet counts.

h. TSH will be performed at Screening, on pre-dose Day 1 of every 3 cycles for the first year, then every 6 cycles thereafter and at the EOT Visit.

i. Hepatitis C antibody, hepatitis B surface antigen and antibody and hepatitis B core antibody will be evaluated. If hepatitis B core antibody or hepatitis B surface antigen is positive, then hepatitis B PCR to quantitate hepatitis B DNA must be performed. DNA PCR needs to be confirmed negative prior to enrollment in subjects who are hepatitis B core antibody or hepatitis B surface antigen positive. For subjects who are hepatitis C antibody positive, hepatitis C PCR needs to be confirmed negative prior to enrollment.

j. Must be done in accordance with Celgene Revlimid REMS™ program (US Sites) or global Pregnancy Prevention Program (PPP) guidelines (Ex-US Sites) for females of childbearing potential (FCBP). Day 15 of each Cycle only applies if a subject's menstruation is irregular. Serum or urine depending on site standard method. If positive at Screening Visit, the subject is not eligible to enroll. See Appendix 7 and Appendix 8 for pregnancy testing frequency requirements.

k. T/B/NK cell count and biomarkers should be done at pre-dose on Day 1 of Cycles 1, 2, 3, at response evaluation (ie, Day 1 Cycles 4, 7, 10, 13, 16, 19, 22, 25, and then every 6 cycles thereafter) and EOT Visits.

l. **Phase 2 only:** Serum Ig will be taken pre-dose Day 1 Cycle 1. Samples will also be taken at all response evaluation visits (eg, Cycle 4, 7, 10, etc.) and EOT Visit.

m. **Phase 2 only:** PK samples will be drawn according to the schedule Table 9. For subjects who must take strong or moderate CYP3A inhibitors while on treatment with ibrutinib, additional PK blood samples for evaluation of ibrutinib exposure is requested.

n. Pretreatment tumor assessment should be performed within 28 days before the first dose. A CT scan (with contrast unless contraindicated) of the neck, chest, abdomen, and pelvis and any other disease sites and a PET or PET/CT scan are required for the pretreatment tumor assessment. Thereafter, a PET scan is to be performed to confirm CR if PET result was positive at Screening or may be performed at anytime if clinically indicated. During treatment, CT/MRI scans will be done for tumor assessments within 7 days prior to Day 1 of Cycle 4 and Cycle 7, then every 3 cycles up to Cycle 25, and then every 6 cycles thereafter, until PD or use of alternative anticancer therapy. In the event that CT contrast is contraindicated, MRI of the abdomen and pelvis with contrast and CT of the chest and neck may be performed as an alternative. Lesions in anatomical locations that are not well visualized by CT may be measured at baseline from MRI instead and should continue to be measured from MRI until disease progression. Follow the Cheson 2007 (Phase 1b) Appendix 5 and Cheson 2014 (Phase 2) Appendix 6.

o. Response evaluation (RE) should be performed in alignment with the CT/MRI and/or PET scans schedules. The RE is to be performed within 7 days of Day 1 of Cycle 4 and Cycle 7, then every 3 cycles up to Cycle 25, and then every 6 cycles thereafter, or at any time during the study if indicated per the Investigator.

p. Subjects will be contacted about every 3 months to assess subsequent anticancer therapies, information about second malignancies & survival status.

Appendix 2. ECOG Status Scores

Status	Eastern Cooperative Oncology Group (ECOG) Performance Status**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, 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, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: 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 3. Cockcroft-Gault Formula for Estimating Creatinine Clearance

$$C_{cr} = \frac{(140 - \text{age}) \times \text{Body Weight (kg)}}{(\text{Serum creatinine mg/dL}) \times 72}$$

Note:

- Multiply by 0.85 for women
- Use with caution in cirrhosis and muscle wasting
- To convert µmol (micromoles)/L of creatinine to mg/dL, divide by 88.4.

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

Appendix 4. Inhibitors and Inducers of CYP3A

Inhibitors and inducers of CYP3A enzymes are defined as follows. Refer to Section 6.1.2.1 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	
Moderate inhibitors:	
aprepitant	
amprenavir	
amiodarone	
atazanavir	
ciprofloxacin	
crizotinib	
darunavir/ritonavir	
dronedarone	
erythromycin	
diltiazem	
fluconazole	
fosamprenavir	
grapefruit juice	
Seville orange juice	
verapamil	
voriconazole	
imatinib	
Weak inhibitors:	
cimetidine	
fluvoxamine	
All other inhibitors:	
chloramphenicol	
delaviridine	
diethyl-dithiocarbamate	
gestodene	
mifepristone	
norfloxacin	
norfluoxetine	
star fruit	

Appendix 5. Revised International Working Group Response Criteria for Malignant Lymphoma (Cheson 2007) – Phase 1b Only

Response Categories				
Response	**Definition**	**Nodal Masses**	**Spleen, Liver**	**Bone Marrow**
CR	Disappearance of all evidence of disease	a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved sites b) Variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specific
SD	Failure to attain CR/PR or PD	a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node > 1cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, (^{18}F) fluorodeoxyglucose; PET, positron emission tomography; CT, computerized tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease

Appendix 6. Revised International Working Group Response Criteria for Malignant Lymphoma or Lugano Classification (Cheson 2014) – Phase 2 only

Evaluation, Staging, and Response Assessment for Non-Hodgkin Lymphoma: The Lugano Classification (according to Cheson 2014)

Evaluation, staging, and response criteria are summarized in 3 Tables below.

Table 1: Criteria for Involvement of Site

Tissue Site	Clinical	FDG Avidity	Test	Positive Finding
Lymph nodes	Palpable	FDG-avid histologies	PET-CT	Increased FDG uptake
		Non avid disease	CT	Unexplained node enlargement
Spleen	Palpable	FDG-avid histologies	PET-CT	Diffuse uptake, solitary mass, miliary lesions, nodules
		Non avid disease	CT	>13 cm in vertical length, mass, nodules
Liver	Palpable	FDG-avid histologies	PET-CT	Diffuse uptake, mass
		Non avid disease	CT	Nodules
CNS	Signs, symptoms		CT	Mass lesion(s)
			MRI	Leptomeningeal infiltration, mass lesions
			CSF assessment	Cytology, flow cytometry
Other (eg, skin, lung, GI tract, bone, bone marrow)	Site dependent		PET-CT[a], biopsy	Lymphoma involvement

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.
a: PET-CT is adequate for determination of bone marrow involvement and can be considered highly suggestive for involvement of other extralymphatic sites. Biopsy confirmation of those sites can be considered if necessary.

Table 2: Staging System for Primary Nodal Lymphomas

Stage	Involvement	Extranodal (E) Status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky[a]	II as above with “bulky” disease	Not applicable
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

NOTE: Extent of disease is determined by positron emission tomography–computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

[a] Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

Table 3: Criteria for Response Assessment of Non-Hodgkin's Lymphoma

Response	Site	PET-CT-Based Response	CT-Based Response
Complete	Lymph nodes and extralymphatic sites	Complete metabolic response	Complete radiologic response (all of the following)
		Score 1, 2, or 3[a] with or without a residual mass on 5PS[2] 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 determinate, IHC negative
Partial	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
	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

Response	Site	PET-CT-Based Response	CT-Based Response
No response or stable disease	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	Individual target nodes/nodal masses Extranodal lesions	Progressive metabolic disease Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	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
	Non measured lesions	None	New or clear progression of preexisting nonmeasured lesions
	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.

[a] A score of 3 in many subjects 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 7. Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods (for US Sites only)

Risks Associated with Pregnancy

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

All study participants must be registered into the mandatory Revlimid REMS™ program, and be willing and able to comply with the requirements of Revlimid REMS™. **(for US sites only)**

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

The Investigator must ensure that:

- Females of childbearing potential comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Females NOT of childbearing potential acknowledge that she understands the hazards and necessary precautions associated with the use of lenalidomide
- Male patients taking lenalidomide acknowledge that he understands that traces of lenalidomide have been found in semen, that he understands the potential teratogenic risk if engaged in sexual activity with a female of childbearing potential or pregnant female, and that he understands the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a female of childbearing potential or pregnant female.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) throughout the entire duration of lenalidomide treatment; 3) during dose interruptions; and 4) for at least 28 days after lenalidomide discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:

  Intrauterine device (IUD)

  Hormonal (birth control pills, injections, implants)

  Tubal ligation

  Partner's vasectomy
- Additional effective methods:

  Male condom

  Diaphragm

  Cervical Cap

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting lenalidomide

Female Patients:

FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to prescribing lenalidomide. The first pregnancy test must be performed within 10-14 days prior to prescribing lenalidomide and the second pregnancy test must be performed within 24 hours prior to prescribing lenalidomide. The patient may not receive lenalidomide until the Investigator has verified that the results of these pregnancy tests are negative.

Male Patients:

Must agree to practice complete abstinence or agree to use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 90 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following lenalidomide discontinuation.

Female Patients:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of lenalidomide treatment, including dose interruptions and then every 28 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 28 following lenalidomide discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days of lenalidomide treatment, including dose interruptions, and then every 14 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 14 and Day 28 following lenalidomide discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control at each visit during the time that birth control is required.
- If pregnancy or a positive pregnancy test does occur in a study patient, lenalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide treatment must be temporarily discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after lenalidomide discontinuation.

Male Patients:

- Must practice complete abstinence or use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 90 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the Investigator must be notified immediately.
- Male patients should not donate semen or sperm during therapy or for at least 90 days following discontinuation of lenalidomide.

Additional Precautions

- Patients should be instructed never to give lenalidomide to another person.
- Patients should not donate blood during therapy and for at least 28 days following discontinuation of lenalidomide (90 days for male subjects).
- Only enough lenalidomide for one cycle of therapy may be prescribed with each cycle of therapy.
- Any unused lenalidomide must be returned as instructed through the Revlimid REMS™ program (for US sites only).

Appendix 8. Lenalidomide Pregnancy Prevention Risk Management Plans (for ex-US sites only)

1. LENALIDOMIDE PREGNANCY PREVENTION PLAN FOR SUBJECTS IN CELGENE CLINICAL TRIALS

The Pregnancy Prevention Plan (PPP) applies to all subjects receiving lenalidomide within a clinical trial. The following PPP documents are included:

1. The Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 2) provides the following information:
    - Potential risks to the fetus associated with lenalidomide exposure
    - Definition of female of childbearing potential (FCBP)/female not of childbearing potential (FNCBP)
    - Requirements for counseling of all subjects receiving lenalidomide about pregnancy precautions and the potential risks of fetal exposure to lenalidomide
    - Acceptable birth control methods for both female subjects of childbearing potential and male subjects receiving lenalidomide in the study
    - Pregnancy testing requirements for subjects receiving lenalidomide who are FCBP
2. The Lenalidomide Education and Counseling Guidance Document for each gender (female and male; Section 3 and Section 4 respectively) must be completed and signed by a trained counselor at the participating clinical center prior to each dispensing of lenalidomide. A copy of this document must be maintained in the subject's records for each dispense.
3. The Lenalidomide Information Sheet (Section 5) will be given to each subject receiving lenalidomide. The subject must read this document prior to starting lenalidomide and each time the subject receives a new supply of lenalidomide.

2. LENALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

2.1. Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. A teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a pregnancy prevention program must be followed.

2.1.1. Definition of Females of Childbearing Potential

A FCBP is a female who: 1) has achieved menarche at some point; or 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

2.1.2. Definition of Females Not of Childbearing Potential

Females who do not meet the above definition of FCBP should be classified as FNCBP.

2.2. Counseling

2.2.1. Females of Childbearing Potential

For a FCBP, lenalidomide is contraindicated unless all of the following are met (ie, all FCBP must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting lenalidomide, throughout the entire duration of lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide
- She understands and agrees to inform the Investigator if a change or stop of method of contraception is needed
- She must be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence lenalidomide as soon as it is dispensed following a negative pregnancy test
- She understands and accepts the need to undergo pregnancy testing based on the frequency outlined in this plan (Section 2.4) and in the Informed Consent
- She acknowledges that she understands the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

The Investigator must ensure that a FCBP:

- Complies with the conditions of the pregnancy prevention plan, including confirmation that she has an adequate level of understanding
- Acknowledges the aforementioned requirements.

2.2.2. Females Not of Childbearing Potential

For a FNCBP, lenalidomide is contraindicated unless all of the following are met (ie, all FNCBP must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She acknowledges she understands the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

2.2.3. Males

Traces of lenalidomide have been found in semen. Male subjects taking lenalidomide must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a FCBP
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a FCBP
- Understand the potential teratogenic risk if the subject donates semen or sperm.

2.3. Contraception

2.3.1. Female Subjects of Childbearing Potential

Females of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) while taking lenalidomide; 3) during dose interruptions; and 4) for at least 28 days after the last dose of lenalidomide.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified provider of contraception methods to determine the medically effective contraception method appropriate to the subject. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [eg, desogestrel])
  - Tubal ligation
  - Partner's vasectomy
- Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in subjects with neutropenia.

2.3.2. Male Subjects

Male subjects must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 90 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.

2.4. Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCBP.

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The subject may not receive lenalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking lenalidomide, at study discontinuation, and at Day 28 following the last dose of lenalidomide.

Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide.

2.5. Pregnancy Precautions for Lenalidomide Use

2.5.1. Before Starting Lenalidomide

2.5.1.1. Female Subjects of Childbearing Potential

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The subject may not receive lenalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential must use two reliable forms of contraception simultaneously, or practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact for at least 28 days before starting lenalidomide.

2.5.1.2. Male Subjects

Male subjects must agree to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 90 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.

2.5.2. During and After Study Participation

2.5.2.1. Female Subjects

- Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking lenalidomide, at study discontinuation, and at Day 28 following the last dose of lenalidomide.
- Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control if not committing to complete abstinence, or confirm commitment to complete abstinence.
- If a FCBP considers the need to change or to stop a method of contraception, the Investigator must be notified immediately.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.

- If pregnancy or a positive pregnancy test does occur in a subject, lenalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.

2.5.2.2. Male Subjects

- Must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 90 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.
- Must not donate semen or sperm while receiving lenalidomide, during dose interruptions or for at least 90 days after the last dose of lenalidomide.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male subject while taking lenalidomide, the Investigator must be notified immediately.

2.5.3. Additional Precautions

- Subjects should be instructed to never give lenalidomide to another person.
- Subjects should be instructed to return any unused capsules to the study doctor.
- Subjects should not donate blood while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide (90 days for male subjects).
- No more than a 28-day lenalidomide supply may be dispensed with each cycle of lenalidomide.

3. LENALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR FEMALE SUBJECTS

To be completed prior to each dispensing of lenalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

Check one risk category:

- ☐ FCBP (Female of childbearing potential): a female who: 1) has achieved menarche (first menstrual cycle) at some point, 2) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)
- ☐ NOT FCBP

3.1. Female of Childbearing Potential:

1. I have verified and counseled the subject regarding the following:

   ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking lenalidomide. Females of childbearing potential must agree not to become pregnant while taking lenalidomide.

   ☐ That the required pregnancy tests performed are negative.

   ☐ The subject confirmed that she is using TWO reliable methods of birth control at the same time, or complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact (at least 28 days prior to receiving lenalidomide, while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide).

   One highly effective method and one additional method of birth control must be used AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:

   – Examples of highly effective methods:
     - Intrauterine device (IUD)
     - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [eg, desogestrel])
     - Tubal ligation

- Partner's vasectomy

– Examples of additional effective methods:

- Male condom
- Diaphragm
- Cervical Cap

☐ The subject confirmed that even if she has amenorrhea she must comply with advice on contraception.

☐ Pregnancy tests before, during administration of lenalidomide and at the last dose of lenalidomide, even if the subject agrees not to have reproductive heterosexual contact.

☐ Frequency of pregnancy tests to be done:

– Two pregnancy tests will be performed prior to receiving lenalidomide, one within 10 to 14 days, and a second within 24 hours of the start of lenalidomide.

– Every week during the first 28 days of this study and a pregnancy test every 28 days while the subject is taking lenalidomide if menstrual cycles are regular.

– Every week during the first 28 days of this study and a pregnancy test every 14 days while the subject is taking lenalidomide if menstrual cycles are irregular.

– If the subject missed a period or has unusual menstrual bleeding.

– When the subject is discontinued from the study and at Day 28 after the last dose of lenalidomide if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at Days 14 and 28 after the last dose of lenalidomide.

☐ The subject confirmed that she will stop taking lenalidomide immediately in the event of becoming pregnant and to call her study doctor as soon as possible.

☐ The subject confirmed that she has not and will not breastfeed a baby while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.

☐ The subject has not and will never share lenalidomide with anyone else.

☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.

☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.

☐ The subject confirmed that she will return unused lenalidomide capsules to the study doctor.

2. I have provided the Lenalidomide Information Sheet to the subject.

3.2. Female Not of Childbearing Potential (Natural Menopause for at Least 24 Consecutive Months, a Hysterectomy, or Bilateral Oophorectomy):

3. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject has not and will never share lenalidomide with anyone else.
   - ☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
   - ☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.
   - ☐ The subject confirmed that she will return unused lenalidomide capsules to the study doctor.
4. I have provided the Lenalidomide Information Sheet to the subject.

Do Not Dispense Lenalidomide if:

- **The subject is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence from heterosexual contact) at least 28 days prior to receiving lenalidomide, while receiving lenalidomide and during dose interruptions.**
- **The subject stated that she has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

4. LENALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR MALE SUBJECTS

To be completed prior to each dispensing of lenalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject confirmed that he has practiced complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or used a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or FCBP, while taking lenalidomide, during dose interruptions and for at least 90 days after the last dose of lenalidomide.
   - ☐ The subject confirmed that he has not impregnated his female partner while in the study.
   - ☐ The subject confirmed that he will notify his study doctor if his female partner becomes pregnant and the female partner of a male subject taking lenalidomide confirmed that she will call her healthcare provider immediately if she becomes pregnant.
   - ☐ The subject has not and will never share lenalidomide with anyone else.
   - ☐ The subject confirmed that he has not donated and will not donate semen or sperm while taking lenalidomide or during dose interruptions and that he will not donate semen or sperm for at least 90 days after the last dose of lenalidomide.
   - ☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 90 days after the last dose of lenalidomide.
   - ☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.
   - ☐ The subject confirmed that he will return unused lenalidomide capsules to the study doctor.
2. I have provided the Lenalidomide Information Sheet to the subject.

Do Not Dispense Lenalidomide if:

- **The subject stated that he has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

5. LENALIDOMIDE INFORMATION SHEET

For subjects enrolled in clinical research studies

Please read this Lenalidomide Information Sheet before you start taking lenalidomide and each time you get a new supply. This Lenalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about lenalidomide?

1. **Lenalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Lenalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects.

   If you are a female who is able to become pregnant:

   - **Do not take lenalidomide if you are pregnant or plan to become pregnant**
   - **You must practice complete abstinence from sexual contact with a male or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting lenalidomide
     - while taking lenalidomide
     - during breaks (dose interruptions) of lenalidomide
     - for at least 28 days after the last dose of lenalidomide
   - **You must have pregnancy testing done at the following times:**
     - within 10 to 14 days prior to the first dose of lenalidomide
     - 24 hours prior to the first dose of lenalidomide
     - weekly for the first 28 days
     - if you have regular menstrual periods: every 28 days after the first month
     - if you have irregular menstrual periods: every 14 days after the first month
     - if you miss your period or have unusual menstrual bleeding
     - 28 days after the last dose of lenalidomide (14 and 28 days after the last dose if menstrual periods are irregular)
   - **Stop taking lenalidomide if you become pregnant while taking lenalidomide**
     - If you suspect you are pregnant at any time during the study, you must stop lenalidomide immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to Celgene Corporation.
   - **Do not breastfeed while taking lenalidomide and for at least 28 days after the last dose of lenalidomide**
   - The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not able to become pregnant:

In order to ensure that an unborn baby is not exposed to lenalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

A small amount of lenalidomide is found in human semen. The risk to an unborn baby in females whose male partner is receiving lenalidomide is unknown at this time.

- Male subjects (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
  - While you are taking lenalidomide
  - During breaks (dose interruptions) of lenalidomide
  - For at least 90 days after the last dose of lenalidomide
- **Male subjects should not donate sperm or semen** while taking lenalidomide, during breaks (dose interruptions) and for at least 90 days after the last dose of lenalidomide.
- **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they become pregnant.**

2. **All subjects:**

- **Do not share lenalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.**
- **Do not donate blood** while you take lenalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of lenalidomide (90 days for male subjects).
- **Do not break, chew, or open lenalidomide capsules at any point.**
- You will get no more than a 28-day supply of lenalidomide at one time.
- Return unused lenalidomide capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

Appendix 9. 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.