PROTOCOL

TITLE:	A Multicenter Study of Ibrutinib and Lenalidomide in Combination with DA-EPOCH-R in Subjects with Relapsed or Refractory Diffuse Large B-cell Lymphoma
PROTOCOL NUMBER:	PCYC-1124-CA
STUDY DRUG:	Ibrutinib (PCI-32765)
IND NUMBER:	102,688
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DATE FINAL:	16 December 2013
AMENDMENT 1 Date:	30 September 2014

PROTOCOL APPROVAL PAGE

Study Title: A Multicenter Study of Ibrutinib and Lenalidomide in Combination with DA-EPOCH-R in Subjects with Relapsed or Refractory Diffuse Large B-cell Lymphoma

Study Number: PCYC-1124-CA

Protocol Date: 16 December 2013

Amendment 1 Date: 30 September 2014

I have carefully read Protocol PCYC-1124-CA entitled "A Multicenter Study of Ibrutinib and Lenalidomide in Combination with DA-EPOCH-R 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, Inc requires that any presentation or publication of study data by clinical Investigators be reviewed by Pharmacyclics, before release, as specified in the protocol.

Principal Investigator's Signature Date

Print Name

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

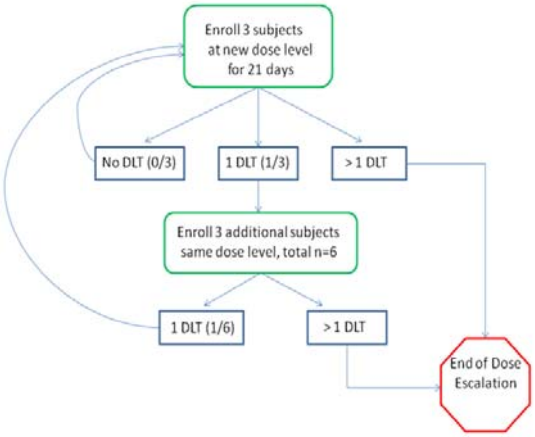
01-Oct-2014

Medical Monitor's Signature Date
Nora Marie Cavazos, M.D.
Medical Director, Clinical Science, Pharmacyclics, Inc.

SYNOPSIS

Title:	A Multicenter Study of Ibrutinib and Lenalidomide in Combination with DA-EPOCH-R in Subjects with Relapsed or Refractory Diffuse Large B-cell Lymphoma
Protocol Number:	PCYC-1124-CA
Phase:	1b/2
Indication:	Relapsed or refractory diffuse large B-cell lymphoma (DLBCL) Part 2 of the study is limited to the non-germinal center B cell-like (non-GCB) subtype, which includes activated B-cell (ABC) DLBCL. The final Part 2 analysis will be performed in subjects with ABC DLBCL profiled by GEP.
Study Drug and Comparator:	Ibrutinib will be supplied as 140 mg hard gelatin capsules for oral (PO) administration. Lenalidomide will be supplied as hard gelatin capsules for PO administration. The following drugs will be commercially supplied as standard of care by the participating sites: Rituximab as 100 mg/10 mL or 500 mg/50 mL solution in single-use vials for IV administration. Cyclophosphamide as 100, 200, 500, 1000 or 2000 mg solution in single-use vials for IV administration. Doxorubicin as 10, 20, 50, 100, 250, 500 and 750 mg solution in single-use vials for IV administration. Vincristine in 1, 2 and 5 mg single use vials for IV administration. Etoposide as a concentrate for parenteral use in 100 mg vials. Prednisone in 20 and 50 mg tablets for oral administration. Pegfilgrastim as a 6 mg-prefilled single-use syringe for subcutaneous administration. *No comparator is used in this study.*
Objectives:	**Part 1** **Primary Objectives:** • To determine the maximum tolerated dose (MTD) of the combination of ibrutinib, lenalidomide and dose-adjusted (DA)-EPOCH-R in relapsed or refractory DLBCL • To determine the safety and tolerability of ibrutinib and lenalidomide in combination with DA-EPOCH-R in relapsed or refractory DLBCL **Secondary Objective:** • To determine the efficacy of ibrutinib and lenalidomide in combination with DA-EPOCH-R in relapsed or refractory DLBCL subjects as assessed by overall response rate (ORR)

	Part 2 **Primary Objective:** • To determine the efficacy of ibrutinib and lenalidomide in combination with DA-EPOCH-R in relapsed or refractory ABC DLBCL subjects as assessed by overall response rate (ORR) **Secondary Objectives:** • To determine the efficacy of ibrutinib and lenalidomide in combination with DA-EPOCH-R in relapsed or refractory ABC DLBCL as assessed by progression-free survival (PFS), duration of response (DOR) and overall survival (OS) • To determine the safety and tolerability of ibrutinib and lenalidomide in combination with DA-EPOCH-R in subjects with ABC DLBCL **Exploratory Objectives:** • To determine the pharmacokinetics (PK) of ibrutinib when dosed with lenalidomide in combination with DA-EPOCH-R • To evaluate biomarkers of sensitivity or resistance to ibrutinib and lenalidomide in combination with DA-EPOCH-R
Study Design:	This is a Phase 1b, open-label, non-randomized multicenter study conducted in 2 parts. In Parts 1 and 2, treatment will be administered in 3-week (21-day) cycles. A standard 3+3 design will be employed in Part 1 to determine the MTD, which will then define the dose to be used in Part 2. <u>Part 1</u>: The dose-escalation part of the study, Part 1, will determine the MTD of the combination of ibrutinib, lenalidomide and DA-EPOCH-R in subjects with DLBCL. Ibrutinib will be administered at a fixed dose of 560 mg and lenalidomide will be dose-escalated at doses of 0, 15, 20 and 25 mg for 7 days of each 21-day cycle. DA-EPOCH-R will be given on Days 1–5 of each 21-day cycle at standard doses. The dose escalation will follow a 3+3 design with 3 subjects in each cohort. Cohort dose escalation will occur if the subject incidence of DLTs during the first 22 days of study treatment is <33%. If one subject within the initial cohort of 3 subjects (dose Level 1) experiences a DLT, an additional 3 subjects may be enrolled at the same dose level. If the initial dose is safe and tolerable with no further DLTs, the next dose level examined will be dose level 2. Dose escalation will continue to dose Level 4. The MTD will be defined as the highest dose level with an observed incidence of DLTs in <33% of the subjects enrolled in the cohort. If in dose Level 4 DLTs occur in <33% of subjects, than the MTD will not be identified. A dose de-escalation of ibrutinib will be permitted from dose Level 1 to dose Level -1 if required based on the number of DLTs.



Part 1			
Dose Level	**Ibrutinib**	**Lenalidomide**	**DA-EPOCH-R**
-1	420 mg	0 mg	Standard doses
1	560 mg	0 mg	Standard doses
2	560 mg	15 mg	Standard doses
3	560 mg	20 mg	Standard doses
4	560 mg	25 mg	Standard doses

A DLT (Dose-Limiting Toxicity) is defined as an Adverse Event (AE) that occurs within the first 22 days (Cycle 1, Cycle 2 Day 1 predose) of dosing that meets the DLT definition, is clinically relevant, and considered at least possibly related to study drug (ibrutinib and/or lenalidomide) in the opinion of the investigator.

Part 2:

For Part 2, the MTD determined in Part 1 will be the dose used for all subjects. If no MTD is identified, then subjects in Part 2 will be treated with the maximum administered doses (MAD, treatment doses from dose Level 4).

The expansion part of the study, Part 2, will only enroll subjects with non-GCB DLBCL. The primary objective is to determine the ORR of ibrutinib and lenalidomide in combination with DA-EPOCH-R in subjects with ABC DLBCL (a subset of non-GCB DLBCL) as analyzed by gene expression profiling.

Approximately 26 subjects will receive ibrutinib at a fixed dose of 560 mg and lenalidomide at the established MTD for 7 days. DA-EPOCH-R will be given on Days 1–5 of each 3-week (21-day) cycle at standard doses.

Part 2		
Ibrutinib	**Lenalidomide**	**DA-EPOCH-R**
560 mg (or 420 mg if toxicity with 560 mg)	TBD	Standard doses

	Subjects in Part 1 and Part 2 will receive therapy until a maximum of six cycles or disease progression, whichever occurs first. Subjects will be restaged after Cycle 3 (Cycle 4 Day 1, -4 days [Cycle 3 Day 19 to Cycle 4 Day 1]) and after Cycle 6 (Cycle 6 Day 21±4 days) of treatment, and then every 3, 4, and 6 months (every 12, 16 and 26 weeks) during post-treatment years 1, 2, and 3, respectively. In this study, immunohistochemisty (IHC) will be performed in Part 1 and Part 2; however IHC will be used to assess subject eligibility with respect to subtype of DLBCL only for Part 2. Gene expression profile (GEP) will be performed in Part 2 to confirm the ABC subtype for analysis purposes. 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. The use of the term "ABC subtype" refers to subjects who have been subsequently (ie, after starting protocol treatment) profiled by GEP and then classified as the true ABC subtype.
Population	Subjects with relapsed or refractory DLBCL who have failed at least 1 prior line of therapy. In Part 1, a minimum of 4 and a maximum of 30 DLBCL subjects will be enrolled. In Part 2, 26 relapsed or refractory de novo DLBCL subjects with non-GCB subtype will be enrolled. Enrollment may be increased to include 26 subjects with confirmed ABC DLBCL depending on data availability. Subjects with ABC subtype from Part 1 that received the MTD or MAD of lenalidomide may be carried over to Part 2.
Centers:	Multicenter – US only
Major Inclusion Criteria:	Note for the complete list of inclusion/exclusion criteria refer to Section 4. Major inclusion criteria: 1. Men and women ≥18 years of age 2. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 3. Pathologically confirmed DLBCL: • Part 1: all subtypes are eligible • Part 2: only non-GCB subtype is eligible 4. Relapsed or refractory disease, defined as either: 1) recurrence of disease after a complete remission (CR), or 2) partial remission (PR), stable disease (SD), or progressive disease (PD) at completion of the treatment regimen preceding entry to the study (residual disease): a) Subjects must have previously received an appropriate first-line treatment regimen. b) For subjects in whom a post-treatment residual computed tomography (CT) scan abnormality exists, and a definitive distinction between residual DLBCL and a non-lymphomatous process (eg, fibrosis) is clinically indicated, those subjects must have biopsy confirmation of residual DLBCL prior to study entry.

	5. Subjects must have ≥1 measurable disease site 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. 6. Subjects must have adequate fresh or paraffin tissue for confirmation of diagnosis and molecular evaluation. Tissue may be from either the initial diagnosis or from relapsed or refractory disease. 7. Meet the following laboratory parameters: a) Absolute neutrophil count (ANC) ≥1,000 cells/mm^3 (1.0 x 10^9/L) b) Platelets ≥75,000 cells/mm^3 (75 x 10^9/L) c) ALT and AST ≤2.5 x ULN unless lymphoma-related d) Bilirubin ≤1.5 x ULN, except ≤2 mg/dL (total) in subjects with Gilbert's syndrome (as defined by >80% unconjugated hyperbilirubinemia) e) Serum Creatinine ≤2.0 mg/dL or creatinine clearance ≥60 mL/min/1.73 m^2 f) Hemoglobin ≥ 8.0 g/dL g) Prothrombin time (PT) and activated partial thromboplastin time (aPTT) must be ≤1.5 x the upper limit of the normal range (ULN); except if, in the opinion of the Investigator, the aPTT is elevated because of a positive Lupus Anticoagulant 8. Left ventricular ejection fraction (LVEF) >45% as assessed by echocardiogram or multigated acquisition scan (MUGA) 9. Able to provide written informed consent and can understand and comply with the requirements of the study 10. 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™. 11. Female subjects of childbearing potential (FCBP) [†] 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 F: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods. 12. 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 F: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods. 13. Life expectancy of more than 3 months

[†] 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 (i.e., has had menses at any time in the preceding 24 consecutive months).

Major Exclusion Criteria	1. Transformed DLBCL or DLBCL with coexistent histologies (eg, follicular or mucosa-associated lymphoid tissue [MALT] lymphoma) for enrollment into Part 2 only 2. Primary mediastinal (thymic) large B-cell lymphoma for enrollment into Part 2 only 3. Known central nervous system lymphoma 4. Any chemotherapy, external beam radiation therapy, or anti-cancer antibodies within 2 weeks prior to the first dose of study drug 5. Radio- or toxin-immunoconjugates within 10 weeks prior to the first dose of study drug 6. Concurrent enrollment in another therapeutic investigational clinical study 7. Previously taken ibrutinib or lenalidomide 8. Major surgery within 4 weeks prior to the first dose of study drug 9. Prior allogenetic stem cell (or other organ) transplant within 6 months or any evidence of active graft-versus-host disease or requirement for immunosuppressants within 28 days prior to first dose of study drug 10. History of other malignancies, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer, or other solid tumors curatively treated with no evidence of disease for ≥ 2 years 11. Currently active, or clinically significant cardiovascular disease such as uncontrolled arrhythmia, congestive heart failure, any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification (Appendix E), or history of myocardial infarction within 6 months prior to first dose with study drug 12. Significant screening electrocardiogram (ECG) abnormalities, including left bundle branch block, 2nd degree atrioventricular (AV) block Type II, 3rd degree block, or QTc ≥470 msec 13. Recent infection requiring intravenous anti-infective treatment that was completed ≤14 days before the first dose of study drug 14. Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 4.03), grade 0 or 1, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia 15. Known bleeding diathesis (eg, von Willebrand's disease) or hemophilia 16. Known history of infection with human immunodeficiency virus (HIV) or chronic or active infection with Hepatitis C virus (HCV) or Hepatitis B virus (HBV). Viral load by PCR must be confirmed negative in equivocal cases for subjects who are Hepatitis B core antibody positive, Hepatitis B surface antigen positive, Hepatitis B surface antibody positive (unless immunized) or Hepatitis C antibody positive. 17. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk 18. Unable to swallow capsules or disease significantly affecting gastrointestinal function and/or inhibiting small intestine absorption such as malabsorption syndrome, resection of the small bowel, or poorly controlled inflammatory bowel disease affecting the small intestine

	19. Received or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 28 days of first dose of study drug 20. Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor 21. Lactating or pregnant women
Endpoints:	**Part 1:** <u>Primary Endpoint: (for all subtypes of DLBCL)</u> • MTD • Safety and tolerability of ibrutinib and lenalidomide in combination with DA-EPOCH-R in relapsed or refractory DLBCL <u>Secondary Endpoint: (for all subtypes of DLBCL)</u> • ORR **Part 2:** <u>Primary Endpoint:</u> • ORR including CR (complete response) and PR (partial response) in ABC DLBCL <u>Secondary Endpoints:</u> *Efficacy:* • Duration of response (DOR) in ABC DLBCL • Progression-free survival (PFS) in ABC DLBCL • Overall survival (OS) in ABC DLBCL *Safety:* • Frequency, severity, and relatedness of AEs • Frequency of AEs requiring discontinuation of study drug or dose reductions *Pharmacokinetics:* • Plasma pharmacokinetics of ibrutinib <u>Exploratory Analyses:</u> • 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. • Change in secreted protein levels (ie, chemokines, cytokines) • Change in peripheral T/B/natural killer (NK) counts and immunophenotypical analysis
Safety plan:	This study will be monitored in accordance with the Sponsor's Pharmacovigilance Committee procedures. AEs and serious adverse events (SAEs) will be reviewed internally on an ongoing basis to identify safety concerns. A Dose Level Review Committee will evaluate safety data from the dose escalation portion of Part 1. 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 and Sub-Investigators.

<table>
<tr><td>Study Treatment:</td><td>
Day 1–7 of each cycle: ibrutinib PO
Day 1–7 of each cycle: lenalidomide PO
Day 1–5 of each cycle: DA-EPOCH-R
Day 6 (with a +48 hour window) of each cycle: Pegfilgrastim
1 cycle = 21 days; maximum 6 cycles
Study follow-up will be for 1 year after the last subject received the first dose.
Part 1:
<table>
<tr><th colspan="4">Part 1</th></tr>
<tr><th>Dose Level</th><th>Ibrutinib</th><th>Lenalidomide</th><th>DA-EPOCH-R</th></tr>
<tr><td>-1</td><td>420 mg</td><td>0 mg</td><td>Standard doses</td></tr>
<tr><td>1</td><td>560 mg</td><td>0 mg</td><td>Standard doses</td></tr>
<tr><td>2</td><td>560 mg</td><td>15 mg</td><td>Standard doses</td></tr>
<tr><td>3</td><td>560 mg</td><td>20 mg</td><td>Standard doses</td></tr>
<tr><td>4</td><td>560 mg</td><td>25 mg</td><td>Standard doses</td></tr>
</table>
Part 2:
<table>
<tr><th colspan="3">Part 2</th></tr>
<tr><th>Ibrutinib</th><th>Lenalidomide</th><th>DA-EPOCH-R</th></tr>
<tr><td>560 mg</td><td>TBD</td><td>Standard doses</td></tr>
</table>
Study treatment will continue for up to 6 cycles and as long as:

subject is deriving clinical benefit (complete remission [CR], partial remission [PR], or stable disease [SD]) and
subject is not experiencing any unacceptable toxicity

</td></tr>
<tr><td>Concomitant Therapy and Clinical Practice:</td><td>Refer to Section 6 for information on concomitant therapy</td></tr>
<tr><td>Statistical Methods:</td><td>
Subjects meeting the stated eligibility requirements will be enrolled in the study. Part 1 of the study is based on a Phase 1 3+3 design described in the Study Design Section. Part 2 of the study is an expansion of the non-GCB subtype of DLBCL population (ABC DLBCL will be subsequently confirmed by GEP). Subjects with the ABC subtype from Part 1 that received the MTD or MAD of lenalidomide may be carried over to Part 2. The study will expand to N=26 relapsed or refractory de novo DLBCL subjects in Part 2, which will provide 81% power when comparing an ORR of 60% versus 85% with 1-sided alpha level 5% by exact test. Enrollment may be increased to include 26 subjects with confirmed ABC DLBCL depending on data availability.
The primary endpoint (ORR) will be reported including an exact 1-sided 95% confidence interval. The secondary efficacy endpoints (DOR, PFS, and OS) will be summarized by Kaplan-Meier analyses with estimated means, medians and ranges reported in months. The secondary safety endpoints will be summarized by incidences and types of clinical AEs.
The final analysis will occur approximately 1 year after the last subject received the first dose. Analyses methods will be detailed in the Statistical Analysis Plan.
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TABLE OF CONTENTS

PROTOCOL APPROVAL PAGE **2**
SYNOPSIS **3**
TABLE OF CONTENTS **11**
LIST OF TABLES **17**
LIST OF FIGURES **17**
LIST OF APPENDICES **17**
LIST OF ABBREVIATIONS AND DEFINITIONS **18**
1. BACKGROUND **21**
1.1. Overall Summary 21
1.2. Diffuse Large B-cell Lymphoma (DLBCL) 21
1.3. Ibrutinib Background 23
1.4. Lenalidomide Background 24
1.5. Combination of Ibrutinib and Lenalidomide in ABC Subtype of DLBCL 26
1.6. Summary of Relevant Nonclinical Data for Ibrutinib 27
1.6.1. Nonclinical Pharmacology Studies 27
1.6.2. Toxicology Studies 27
1.7. Summary of Clinical Studies for Ibrutinib 28
1.7.1. Summary of Clinical Pharmacokinetics 28
1.7.2. Summary of Clinical Safety for Ibrutinib 29
1.7.2.1. Monotherapy Studies 29
1.7.2.2. Combination Therapy Studies 30
1.7.3. Risks 31
1.7.3.1. Bleeding-related Events 31
1.7.3.2. Cardiac 31
1.7.3.3. Cytopenias 31
1.7.3.4. Diarrhea 31
1.7.3.5. Infections 31
1.7.3.6. Other Malignancies 31
1.7.3.7. Rash 32
1.7.3.8. Treatment-related Lymphocytosis 32
1.7.3.9. R-CHOP with Ibrutinib 32
1.8. Summary of Clinical Safety for Lenalidomide in Lymphoma 33
1.8.1. Venous Thromboembolism 33
1.8.2. Second New Cancers 34
1.8.3. R-CHOP with Lenalidomide 34
1.9. Summary of Clinical Safety for DA-EPOCH-R Chemotherapy in Lymphoma 34
1.10. Justification of Study Design and Dose Rationale 35
1.10.1. Dose Selection Rationale for DA-EPOCH-R 35
1.10.2. Dose Selection Rationale for Ibrutinib 35
1.10.3. Dose Selection Rationale for Lenalidomide 36

2. STUDY OBJECTIVES 36
2.1. Primary Objectives 36
2.1.1. Part 1 36
2.1.2. Part 2 36
2.2. Secondary Objectives 36
2.2.1. Part 1 36
2.2.2. Part 2 37
2.3. Exploratory Objectives 37
3. STUDY DESIGN 37
3.1. Overview of Study Design: 37
3.2. Endpoints 37
3.2.1. Part 1: 37
3.2.1.1. Primary Endpoint: (for all subtypes of DLBCL) 37
3.2.1.2. Secondary Endpoint (for all subtypes of DLBCL) 37
3.2.2. Part 2: 38
3.2.2.1. Primary Endpoint 38
3.2.2.2. Secondary Endpoints 38
3.3. Part 1 – Dose Escalation 38
3.4. Part 2 – Expansion 40
3.5. All Subjects in Part 1 and Part 2 40
4. SUBJECT SELECTION 41
4.1. Inclusion Criteria 41
4.2. Exclusion Criteria 43
5. TREATMENT OF SUBJECTS 44
5.1. Treatment Part 1 44
5.2. Treatment Part 2 45
5.3. Dosages Overview 46
5.4. Dose Escalation for Part 1 46
5.5. Dose-Limiting Toxicities for Part 1 47
5.5.1. DLT Definition 47
5.6. Ibrutinib 48
5.6.1. Formulation, Packaging, and Storage of Ibrutinib 48
5.6.2. Dosage and Administration of Ibrutinib 48
5.6.3. Dose Reduction and Discontinuation 49
5.6.4. Overdose Instructions 50
5.6.5. Precautions and Adverse Events 51
5.7. Lenalidomide 51
5.7.1. Formulation, Packaging, and Storage of Lenalidomide 51
5.7.2. Lenalidomide Prescribing Information (applies to US sites only) 51
5.7.3. Pregnancy Testing while Taking Lenalidomide 52
5.7.4. Dosage, Preparation and Administration of Lenalidomide 52

5.7.5. Dose Delay, Reduction or Discontinuation of Lenalidomide 52
5.7.5.1. Part 1 Cycle 1 Lenalidomide Dose Modifications 52
5.7.5.2. Part 1 Cycles 2-6 and Part 2 Lenalidomide Dose Modifications 53
5.7.6. Safety Profile 55
5.8. Rituximab 56
5.8.1. Supply 56
5.8.2. Storage 56
5.8.3. Preparation 56
5.8.4. Stability 56
5.8.5. Administration 57
5.8.6. Safety Profile 57
5.9. Cyclophosphamide 58
5.9.1. Supply 58
5.9.2. Storage and Preparation 58
5.9.3. Administration 58
5.9.4. Toxicities 58
5.9.5. Hydration Guidelines 58
5.10. Vincristine/Doxorubicin/Etoposide 59
5.10.1. Central Venous Access 59
5.10.2. Vincristine 59
5.10.2.1. Supply 59
5.10.2.2. Toxicities 60
5.10.3. Doxorubicin 60
5.10.3.1. Supply 60
5.10.3.2. Toxicities 60
5.10.4. Etoposide 60
5.10.4.1. Supply 60
5.10.4.2. Toxicities 60
5.11. Prednisone 60
5.11.1. Supply 60
5.11.2. Doses 61
5.11.3. Toxicities 61
5.12. Pegfilgrastim (Neulasta) 61
5.12.1. Supply 61
5.12.2. Toxicities 61
5.13. Dose Adjustment for EPOCH-R 62
5.13.1. EPOCH-R Dose Adjustment for Part 1 and 2 62
5.13.2. Vincristine Dose Reduction for Ileus Toxicity 63
5.13.3. Vincristine Dose Reduction for Neurological Toxicity 63
5.13.4. Etoposide Dose Reduction for Renal Dysfunction 64
5.13.5. EPOCH-R Dose for Obese Subjects 64
5.13.6. Pretreatment and Dose Modifications for Rituximab 64

5.14. Criteria for Permanent Treatment Discontinuation 65
6. CONCOMITANT MEDICATIONS/PROCEDURES 65
6.1. Permitted Concomitant Medications 65
6.1.1. Prophylaxis of Pneumocystis Jirovecii (Previously Pneumocystis Carinii) 66
6.1.2. Prophylaxis for Tumor Lysis Syndrome (TLS) 66
6.1.3. Recommended Bowel Regimen 66
6.2. Concomitant Medications to be Used with Caution 66
6.2.1. Concomitant Use of CYP3A Inhibitors/Inducers 66
6.2.1.1. Ibrutinib 66
6.2.1.2. Lenalidomide 67
6.2.2. QT Prolongation 67
6.2.3. Antiplatelet Agents and Anticoagulants 67
6.2.3.1. Ibrutinib 67
6.3. Prohibited Concomitant Therapy 68
6.4. Guidelines for Ibrutinib Management with Surgeries or Procedures 68
7. STUDY EVALUATIONS 68
7.1. Description of Procedures 69
7.1.1. Assessments 69
7.1.1.1. Informed Consent 69
7.1.1.2. Confirmation of Eligibility 69
7.1.1.3. Medical History 69
7.1.1.4. Prior and Concomitant Medications 69
7.1.1.5. Adverse Events 70
7.1.1.6. Physical Examination, and Height 70
7.1.1.7. Venous Thromboembolism Risk Assessment 70
7.1.1.8. Vital Signs 70
7.1.1.9. ECOG Performance Status 71
7.1.1.10. Electrocardiogram (ECG) 71
7.1.1.11. Echocardiogram or MUGA 71
7.1.1.12. Bone Marrow Aspirate and Biopsy 71
7.1.1.13. Optional Tumor Biopsy 72
7.1.2. Laboratory 72
7.1.2.1. Hematology 72
7.1.2.2. Serum Chemisty 72
7.1.2.3. Hepatitis Serologies 73
7.1.2.4. Pregnancy Test 73
7.1.2.5. Coagulation Studies 73
7.1.2.6. T/B/NK Cell Count 73
7.1.2.7. Blood Samples for Biomarkers 74
7.1.2.8. Pharmacokinetics (PK) Sample Collection 74
7.1.2.9. Urinalysis 74
7.1.3. Radiological Examinations 74
7.1.4. Overall Response Assessments 75

7.1.5. Survival 75
8. STUDY PROCEDURES 76
8.1. Screening Phase 76
8.2. Treatment Phase 77
8.2.1. Cycle 1 77
8.2.1.1. Cycle 1 Day 1 77
8.2.1.2. Cycle 1 Day 2-6 78
8.2.1.3. Cycle 1 Day 8 and 15 78
8.2.2. Cycles 2-6 79
8.2.2.1. Day 1 79
8.2.2.2. Day 2-6 79
8.2.2.3. Day 8 80
8.2.3. Response Assessments 80
8.2.4. Suspected CR 81
8.3. Follow-up Phase 81
8.3.1. Safety Follow-up Visit 81
8.3.2. Survival Follow-up Visit 82
9. SUBJECT COMPLETION AND WITHDRAWAL 82
9.1. Completion 82
9.2. Treatment Discontinuation 82
9.3. Study Exit/Withdrawal 83
10. STATISTICAL METHODS AND ANALYSIS 83
10.1. General Considerations 83
10.1.1. Response Assessment 83
10.1.2. Safety Monitoring 84
10.2. Definition of Analysis Populations 84
10.3. Endpoint Data Analysis 84
10.3.1. Demographic/Baseline Characteristics and Study Conduct 84
10.3.2. Efficacy Endpoints for Part 1 85
10.3.3. Primary Efficacy Endpoint for Part 2 85
10.3.4. Secondary Efficacy Endpoints for Part 2 85
10.3.4.1. Duration of Response 85
10.3.4.2. Progression-free Survival 85
10.3.4.3. Overall Survival 86
10.3.5. Exploratory/Sensitivity Analysis 86
10.3.6. Safety Endpoint 86
10.3.7. Pharmacokinetics 86
10.3.8. Biomarkers 87
10.4. Handling of Missing Data 87
10.5. Determination of Sample Size 87
10.6. Safety Analysis 88
10.6.1. Adverse Events 88

10.6.2. Clinical Laboratory Tests 88
11. ADVERSE EVENT REPORTING 89
11.1. Adverse Event Definitions and Classifications 89
11.1.1. Adverse Events 89
11.1.2. Serious Adverse Event 90
11.1.3. Unexpected Adverse Events 91
11.1.4. Severity Criteria (Grade 1-5) 91
11.1.5. Causality (Attribution) 92
11.2. Documenting and Reporting of Adverse Events 92
11.2.1. Special Reporting Situations 92
11.2.2. All Adverse Events 93
11.2.2.1. Expedited Reporting Criteria for Serious Adverse Events 93
11.2.3. Events of Special Interest 94
11.2.3.1. Major Hemorrhage 94
11.2.3.2. Intracranial Hemorrhage 94
11.2.4. Other Malignancies 94
11.2.5. Pregnancy 95
11.3. Safety Cohort Review Committee 95
12. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS 95
12.1. Regulatory and Ethical Compliance 95
12.2. Institutional Review Board (IRB), Research Ethics Board (REB) and Independent Ethics Committee (IEC) Approval 95
12.3. Informed Consent 96
12.4. Quality Control and Quality Assurance 96
12.5. Protected Subject Health Information Authorization 96
12.6. Study Files and Record Retention 97
12.7. Case Report Forms and Record Maintenance 98
12.8. Investigational Study Drug Accountability 98
12.9. Study Monitoring/Audit Requirements 99
12.10. Investigator Responsibilities 100
12.11. Sponsor Responsibilities 100
12.12. Financial Disclosure 100
12.13. Liability and Clinical Trial Insurance 101
12.14. Protocol Amendments 101
12.15. Publication of Study Results 101
12.16. Study Discontinuation 102
12.17. Study Completion 102
13. REFERENCE LIST 103
14. APPENDICES 109

LIST OF TABLES

Table 1: Part 1 Dose Levels....40
Table 2: Part 2 Dose Levels....40
Table 3: Part 1 Dosing Levels....45
Table 4: Part 2 Dose Levels....45
Table 5: Dosages....46
Table 6: Part 1 Dosing Levels....47
Table 7: Dose Modification for Ibrutinib Toxicity....50
Table 8: Dose Modification or Interruption for Lenalidomide Toxicity During Administration or for Delay in a Treatment Cycle of Greater Than 1 Week....54
Table 9: Lenalidomide Dose Reduction....55
Table 10: Hydration Guidelines for Cyclophosphamide....58
Table 11: Prednisone Doses per BSA....61
Table 12: EPOCH-R Dose Adjustment....62
Table 13: Doses per Dose Levels for Doxorubicin, Etoposide and Cyclophosphamide....63
Table 14: Sensory Neuropathy Grade and Vincristine Dose Reduction....63
Table 15: Motor Neuropathy Grade and Vincristine Dose Reduction....64
Table 16: Dose Modification for Rituximab Toxicity....64
Table 17: PK Sample Collection Schedule....74

LIST OF FIGURES

Figure 1: 3+3 Dose Escalation Design....39

LIST OF APPENDICES

Appendix A: Schedule of Assessments....110
Appendix B: ECOG Status Scores....113
Appendix C: Inhibitors and Inducers of CYP3A....114
Appendix D: Guidelines for Establishing Response to Treatment....115
Appendix E: New York Heart Association Functional Classification....116
Appendix F: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods....117

LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ABC	Activated B-cell
AE(s)	adverse event(s)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
AV	atrioventricular
BCR	B-cell receptor
BR	bendamustine/rituximab
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CD20	cluster of differentiation 20
CDC	complement dependent cytotoxicity
CEOP	cyclophosphamide, etoposide, vincristine, prednisone
CEPP	cyclophosphamide, etoposide, prednisone, procarbazine
CFR	Code of Federal Regulations
CIV	continuous intravenous infusion
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CR	complete remission (response)
CrCl	creatinine clearance
CRF	case report form
CRi	CR with incomplete bone marrow recovery
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVA	cerebrovascular accident
CYP	cytochrome P450
DA-EPOCH-R	Dose Adjusted Cyclophosphamide, Doxorubicin, Etoposide, Vincristine, Prednisone +/- Rituximab
DLBCL	diffused large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
DVT	Deep Venous thromboembolism
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECHO	Echocardiogram
EDC	electronic data capture
EMR	electronic medical records

Abbreviation	Definition
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FCBP	Females of childbirthing potential
FCR	fludarabine/cyclophosphamide/rituximab
FFPE	Formulin-fixed paraffin embedded tissue
FDA	Food and Drug Administration
FISH	fluorescence *in situ* hybridization
FL	follicular lymphoma
GCB	germinal center B cell-like
GCP	Good Clinical Practice
GDP	gemcitabine, dexamethasone, cisplatin
G-CSF	Granulocyte colony-stimulating factor
GemOx	gemcitabine, oxaliplatin
GEP	gene expression profile
HDT/ASCT	high-dose chemotherapy with autologous stem cell support
HED	human equivalent dose
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	immunohistochemisty
IMiD	immunomodulatory derivatives
IND	Investigational New Drug
INR	international normalized ratio
IRB	institutional review board
IRC	independent review committee
IRF	independent review facility
ITP	idiopathic thrombocytopenic purpura
ITT	Intent-to-treat
IV	Intravenous
LDH	lactate dehydrogenase
LN	lymph node
LVEF	left ventricular ejection fraction
MAD	maximum administered dose
MALT	mucosa-associated lymphoid tissue
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MRI	magnetic resonance imaging

Abbreviation	Definition
MTD	maximum tolerated dose
MUGA	Multigated Acquisition Scan
MM	multiple myeloma
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
Non-GCB	Non-Germinal Center B-cell like
NS	normal saline
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	progressive disease
PE	pulmonary embolism
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PMBL	primary mediastinal B-cell lymphoma
PML	progressive multifocal leukoencephalopathy
PO	per os (oral)
PR	partial remission (response)
PRN	pro re nata, as needed
PT	prothrombin time
QTc	corrected QT interval
R-CHOP	rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone
REB	Research Ethics Board
REMS™	Revlimid Risk Evaluation and Mitigation Strategy
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SCRC	Safety Cohort Review Committee
SD	stable disease
SI	standard international units
SLL	small lymphocytic lymphoma
SOC	system organ class
SOP	standard operating procedures
SPD	sum of the product of the diameters
T_{max}	time to maximum drug concentration
TLS	tumor lysis syndrome
ULN	upper limit of normal
USP	United States pharmacopeial convention
UTI	urinary tract infection
WM	Waldenstrom's Macroglobulinemia

1. BACKGROUND

1.1. Overall Summary

Treatment for relapsed and refractory diffuse large B-cell lymphoma (DLBCL) remains challenging. Following initial therapy, re-induction chemotherapy followed by high-dose therapy with autologous stem cell support (HDT/ASCT) remains the current standard of care. For patients not eligible for stem cell transplant, per NCCN guidelines, a variety of therapies are recommended. However, the overall outcome is relatively poor, with a worse prognosis in the non-GCB subtype including patients with ABC DLBCL. Based on this information, new therapies are needed, particularly for non-transplant eligible subjects with the ABC subtype.

DA-EPOCH-R (dose-adjusted cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone +/- rituximab) is one of the recommended therapies for relapsed DLBCL per NCCN guidelines. Preclinical and clinical data for lenalidomide, another recommended therapy in the relapsed setting, implies it is equally efficacious or perhaps even more efficacious in patients with ABC DLBCL (Yang 2012, Hernandez-Ilizaliturri 2011, Wang 2013). Similarly, clinical data with ibrutinib also implies greater activity in the ABC subtype (de Vos 2013). Since accepted therapy for relapsed DLBCL consists of DA-EPOCH-R, we hypothesize that the addition of ibrutinib and lenalidomide may further enhance the response to chemotherapy in patients with non-GCB (ABC) DLBCL which will be tested in Part 2 of this study. Synergistic activity may also be seen in other forms of DLBCL (ie, transformed, primary mediastinal, germinal center B cell-like [GCB]) which will be tested in a limited number of patients in Part 1.

1.2. Diffuse Large B-cell Lymphoma (DLBCL)

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.

Treatment for relapsed and refractory DLBCL remains challenging. Following initial therapy, the approach of re-induction chemotherapy followed by high-dose chemotherapy with HDT/ASCT for responding patients remains the current standard of care. For patients that are not eligible for stem cell therapy, per NCCN guidelines, a variety of therapies are recommended for second line treatment. These include DA-EPOCH +/- rituximab (Jermann 2004; Wilson 2008), CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) +/- rituximab (Chao 1990), CEOP (cyclophosphamide, etoposide, vincristine, prednisone) +/- rituximab (Bartlett 2001; Moccia 2009), GDP (gemcitabine, dexamethasone, cisplatin) +/- rituximab (Crump 2004), GemOx (gemcitabine, oxaliplatin) +/- rituximab (Lopez 2008; Corazzelli 2009; El Gnaoui 2007), Bendamustine +/- rituximab (Ohmachi 2013; Weidmann 2002; Rigacci 2012), Lenalidomide +/- rituximab (Wiernik 2008; Witzig 2011) and rituximab single-agent therapy (Robach 2002). Despite a number of therapeutic options, the overall outcome remains poor, with a worse prognosis in non-GCB subjects including the ABC subtype. Therefore new treatement regimens are needed.

DA-EPOCH-R (a recommended therapy per NCCN guidelines) was chosen for this study to be used in combination with ibrutinib and lenalidomide. The activity of DA-EPOCH in previously untreated subjects with DLBCL was demonstrated in a study with 50 DLBCL subjects (Wilson 2002). A complete response (CR) was seen in 92% of patients (Wilson 2002). The median follow-up time was 62 months, and progression-free survival (PFS) was 70% and overall survival (OS) was 73% (Wilson 2002). The use of DA-EPOCH in subjects with relapsed or refractory DLBCL and mantle-cell lymphoma (MCL) was demonstrated in another study with 50 subjects (Jermann 2004). The median number of prior chemotherapy regimens was 1.7 (range one to four). Twenty-five subjects had primary DLBCL, 18 had transformed DLBCL and 7 had MCL. The overall response rate (ORR) was 68% (28% CR, 40% PR), median OS was 17.9 months and the projected OS at 1, 2 and 3 years was 66, 42 and 35%, respectively. Median PFS was 11.8 months; projected PFS at 1, 2 and 3 years was 50, 30 and 26%, respectively.

The efficacy of EPOCH in subjects with relapsed and resistant lymphomas was further demonstrated in a study with 131 subjects (Gutierrez 2000). This study included 86 patients (68%) with DLBCL. One hundred and thirty-one patients were assessable for toxicity and 125 patients were assessable for response. Among 125 assessable patients, 93 (74%) achieved objective responses, including 30 (24%) complete and 63 (50%) partial responses. Patients generally had a poor prognosis with high-intermediate or high International Prognostic Index (IPI) scores in 46%. All patients were extensively pretreated having received a median (range) of 8 (1-17) different drugs and 1 (1-5) or 2 (1-7) regimens, respectively, if they had aggressive or indolent histologies. Of the drugs present in the EPOCH regimen, 57% of patients had received all 5 and 88% had received at least 4 of the agents. All but 4 (6%) patients had previously received doxorubicin. To help assess if the infusional schedule increased efficacy, the response to EPOCH in patients who showed no response to their last combination regimen (ie. resistant disease) was analyzed. In this group of 42 patients, 57% responded to EPOCH. Among patients with chemotherapy-sensitive disease, 83% responded with 33% CRs (Gutierrez 2000). EPOCH can also be administered to patients who have received prior anthracyclines because it has low

rates of cardiac toxicity due to the infusional schedule of doxorubicin (Gutierrez 2000). Adding rituximab to DA-EPOCH also showed promising clinical outcome in 72 patients with untreated de novo DLBCL (Wilson 2008). Taken together, DA-EPOCH-R provides an excellent salvage regimen to assess targeted agents and can be administered to previously untreated as well as relapsed and refractory lymphoma patients.

DLBCL gene expression profiling reveals 3 molecular subtypes: activated B cell-like (ABC), germinal center-like (GCB) and primary mediastinal (PMBL). The ABC subtype accounts for ~30% of cases of DLBCL and has an inferior prognosis. 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 the NF-κB pathway (Lenz 2010). This difference in the molecular mechanism of pathogenesis may explain why the ABC subtype is less sensitive to chemotherapy and remains less curable than the GCB subtype. Thus, new strategies for the ABC subtype are needed. Importantly, pre-clinical studies imply synergy when ibrutinib and lenalidomide are combined predominantly but not exclusively in lymphoma cell lines of the ABC subtype.

Previous clinical studies with ibrutinib have shown benefit in the ABC subtype (de Vos 2013), as have trials with lenalidomide (Hernandez-Ilizaliturri 2011). The clinical outcome of the combination of ibrutinib and lenalidomide in DLBCL currently remains unknown. Since patients with DLBCL can be salvaged with DA-EPOCH-R, we hypothesize that the addition of ibrutinib and lenalidomide may further enhance response, and warrants testing in both GCB and non-GCB subtypes of DLBCL.

1.3. Ibrutinib Background

Ibrutinib is a first-in-class, potent, orally administered covalently-binding inhibitor of Bruton's tyrosine kinase (BTK). Inhibition of BTK blocks downstream B-cell receptor (BCR) signaling pathways and thus prevents B-cell proliferation. In vitro, ibrutinib inhibits purified BTK and selected members of the kinase family with 10-fold specificity compared with non-BTK kinases. Ibrutinib (IMBRUVICA®) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of: 1) mantle cell lymphoma (MCL) in patients who have received at least one prior therapy based on overall response rate, 2) chronic lymphocytic leukemia (CLL) in patients who have received at least one prior therapy, and 3) CLL in patients with 17p deletion. Ibrutinib is currently under investigation in various indications.

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 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).

The process of B-cell maturation, including immunoglobulin chain rearrangement and somatic mutation, is tightly regulated. It is thought that B-cell lymphomas and CLL result from

mutations and translocations acquired during normal B-cell development (Shaffer 2002). Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies.

The role of BTK in BCR signal transduction is demonstrated by the human genetic immunodeficiency disease X-linked agammaglobulinemia and the mouse genetic disease X-linked immunodeficiency, both caused by a mutation in the BTK gene. These genetic diseases are characterized by reduced BCR signaling and a failure to generate mature B-cells. The BTK protein is expressed in most hematopoietic cells with the exception of T-cells and natural killer cells, but the selective effect of BTK mutations suggests that its primary functional role is in antigen receptor signaling in B-cells (Satterthwaite 2000).

Data from Study PCYC-04753 demonstrate that although ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing with ibrutinib is adequate to sustain maximal pharmacodynamic activity for 24 hours postdose at dose levels ≥2.5 mg/kg. In Study PCYC-04753, the BTK occupancies in PBMCs for the 2.5 mg/kg/day to 12.5 mg/kg/day cohorts and for the 560 mg continuous dosing cohort, were all above 90% at either 4 or 24 hours after drug administration. In addition, because of an expected tissue-to-plasma concentration ratio of 50% in more distant compartments, such as blood-forming organs (bone marrow, spleen, and lymph node) and lymphoid tumor tissue (based on ratio data in the range of 0.44 to 0.67 observed in rats), it is reasonable to expect full BTK occupancy in these tissues at doses of 5 mg/kg and above.

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, nonrandomized, 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).

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 IB.

1.4. Lenalidomide Background

The immunomodulating drug lenalidomide (IMiD compound, CC-5013, Celgene) is a structural and functional analogue of thalidomide. The second generation of IMiD compounds were designed to enhance immunologic and anti-cancer properties while potentially decreasing the

neurotoxic and teratogenic adverse effects of the parent compound thalidomide (Barlett 2004). These drugs have been extensively used and have shown clear benefit in other diseases, particularly multiple myeloma and myelodysplastic syndromes. Lenalidomide has been reported to down-regulate key prosurvival cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-8 (IL-8), and vascular endothelial growth factor (VEGF) (Corral 1999). Other immunomodulatory activities of IMiDs include inhibition of T-regulatory cell function (Galustian 2009) and potent T-cell co-stimulatory activity, leading to increased secretion of the T-cell lymphokines interferon (IFN)-γ, and IL-2. This enhances Th1-type cellular immunity and natural killer (NK) T-cell cytotoxicity (Corral 1999, LeBlanc 2004, Chang 2006, Davies 2001). IMiDs have also demonstrated direct antiproliferative effects by inhibiting the Akt pathway and increasing the expression of the p21 tumor suppressor protein, leading to G1 cell cycle arrest (Dredge 2005, Gandhi 2006), as well as its inhibition of angiogenesis (Lentzsch 2003). As described above, lenalidomide has specific activity against ABC DLBCL that appears related to its effect on Type I interferon and the NF-kB pathway.

A Phase 2 study (NCI study NHL-002) of 50 patients with relapsed or refractory aggressive NHL showed moderate single-agent activity with lenalidomide. The study included patients with DLBCL, follicular lymphoma (FL), MCL, and transformed NHL. Lenalidomide (25 mg/d) was administered on Days 1 to 21, every 28 days for 52 weeks as tolerated or until disease progression. The ORR was 35% for all patients, 19% for DLBCL patients and 53% in MCL. Clinical responses were also observed in all lymphoma subtypes. The main adverse event (AE) was hematologic, severe neutropenia being the most common reason for dose reduction. The results from this study suggest that lenalidomide has potentially important activity in aggressive lymphoma (Wiernik 2008). Based on these results, an international Phase 2 trial (NHL-003) of single-agent lenalidomide was initiated for patients with relapsed/refractory aggressive NHL. The preliminary results from the 39 MCL and 73 DLBCL patients enrolled in this study were recently reported. The ORR in patients with MCL was 41%, with five patients (13%) achieving CR/CRu and eleven (28%) reaching PR. The response rate was slightly lower in patients with DLBCL, with an ORR of 29%, with 3 patients (4%) achieving CR and 18 patients (25%) achieving PR. Eleven patients (15%) had stable disease. The drug was well tolerated with a manageable toxicity profile, similar to that observed in NHL-002. These preliminary results further validate the role of lenalidomide in the treatment of patients with relapsed or refractory DLBCL and MCL (Zinzani 2008, Czuczman 2008).

A retrospective analysis was performed on 3 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). Another Phase 2 study

(N=45) evaluated the safety and efficacy of lenalidomide in combination with rituximab in relapsed or refractory NHL (Wang 2013). For the included DLBCL patients (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 (Wang 2013).

1.5. Combination of Ibrutinib and Lenalidomide in ABC Subtype of DLBCL

The ABC subtype of DLBCL has constitutive NF-kB activation. The NF-kB pathway is activated by chronic active BCR signaling and can be additionally activated by certain mutations.

Combined use of functional and structural genomics has revealed the molecular basis for constitutive NF-kB activation in ABC DLBCL. In response to BCR engagement by antigen, the signaling adapter CARD11 coordinates the activation of IkB kinase (IKK), the key regulatory kinase of the NF-kB pathway (Thome 2010). CARD11 is more highly expressed in ABC DLBCL than in other lymphoma subtypes and is continuously required for NF-kB activity and viability of ABC DLBCL cell lines (Ngo 2006). In approximately 10% of ABC DLBCLs, CARD11 acquires activating mutations in its coiled-coil domain, leading to spontaneous aggregation of the mutant isoform, thereby activating IKK and the NF-kB pathway (Lenz 2008). In other DLBCLs, upstream signaling from the BCR engages wild type CARD11 to activate the pathway, a phenomenon termed chronic active BCR signaling (Davis 2010). More than 20% of ABC DLBCL tumors have mutations in the CD79A and CD79B subunits of the BCR that augment BCR signaling to NF-kB, establishing the pathogenetic importance of this pathway for ABC DLBCL (Davis 2010).

MYD88 is the key signaling adapter in toll-like receptor signaling (Ngo 2011). During innate immune responses to microorganisms, toll-like receptors bind to pathogen-associated molecular patterns, leading to the recruitment of a signaling complex composed of MYD88 and the kinases IRAK1 and IRAK4, ultimately engaging the NF-kB, MAP kinase and type I interferon pathways. In ABC DLBCL cell lines, knockdown of MYD88 is lethal due to inhibition of NF-kB and the loss of autocrine IL-6/IL-10 signaling through JAK kinase and STAT3 (Ngo 2011, Lam 2008).

Based on the NF-kB signaling pathway, as exploratory analyses in ABC DLBCL, this study aims to analyze the mutations of CARD11, CD79A, CD79B, and MYD88 and perform correlations with clinical outcome. By affecting different targets involving the B-cell receptor and the NF-kB activation pathway, ibrutinib and lenalidomide are expected to have a synergistic effect in chronically activated ABC subtype tumor cells.

In summary, adding ibrutinib and lenalidomide to a regimen of DA-EPOCH-R is expected to improve the overall clinical outcome in subjects with relapsed and refractory DLBCL, especially in the ABC subtype. Based upon the safety profile of ibrutinib monotherapy and the lack of significant myelosuppression, the combination of lenalidomide and ibrutinib may be well tolerated with the potential to exploit synergistic effects for improvement in outcomes in a frail population with minimal therapeutic options and a poor prognosis.

1.6. Summary of Relevant Nonclinical Data for Ibrutinib

1.6.1. Nonclinical Pharmacology Studies

Ibrutinib was designed as a selective covalent inhibitor of BTK (Pan 2007) and in vitro 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 B-cell receptor and blocks primary B-cell activation (IC_{50} = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression (Herman 2011). Ibrutinib arrested cell growth and induced apoptosis in human B-cell lymphoma cell lines in vitro and inhibited tumor growth in vivo in xenograft models (Herman 2011). Ibrutinib also inhibited adhesion and migration of MCL cells in co-culture and reduced tumor burden in lymph node and bone marrow in a murine model of MCL dissemination and progression (Chang 2013a, Chang 2013b). Therefore, ibrutinib may also disrupt key interactions with the tumor microenvironment.

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

1.6.2. Toxicology Studies

In safety pharmacology assessments, 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 the 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 in 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). Relative to a human dose of 560 mg/day and the no-observed-adverse-effect-level (NOAEL) in 13-week studies in animals, the maximum concentration (C_{max})-based safety margins were 3.7 to 8.4 for male and female rats, respectively and 0.9 to 2.7 for female and male dogs, respectively. The area under the curve (AUC)-based safety margin ratios for the 560 mg/day human dose and the NOAEL in animals were 2.6 to 20.3 for male and female rats, respectively and 0.4 to 1.7 for female and male dogs, respectively.

In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. In a rat embryo-fetal toxicity study, ibrutinib administration was associated with fetal loss and malformations (teratogenicity). The NOAEL for effects on embryo/fetal development was 10 mg/kg/day (human equivalent dose [HED] = 1.6 mg/kg/day).

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

1.7. Summary of Clinical Studies for Ibrutinib

Ibrutinib is under late-stage development as an orally administered anticancer agent with lead indications in the relapsed/refractory setting and in treatment-naïve patients with B-cell malignancies as a single agent. Combination studies with chemoimmunotherapy and immunotherapy have been initiated. There are 20 ongoing and 4 completed company-sponsored clinical studies of ibrutinib. Across all studies, malignancies under investigation include CLL, SLL, MCL, DLBCL, FL, MM, and Waldenstrom's Macroglobulinemia (WM). As of the data cutoff of 06 April 2013, safety data are available for 736 subjects treated with ibrutinib: 506 subjects receiving ibrutinib monotherapy; 100 healthy subjects in the pharmacokinetic (PK)/clinical pharmacology studies; and 130 subjects receiving ibrutinib in combination with 1 or more marketed chemo/immunotherapeutic agents. In addition, approximately 537 subjects have been treated with ibrutinib or placebo in 5 randomized, controlled trials. In Study PCYC-1103-CA, a rollover extension study, 196 subjects continue to be treated with ibrutinib.

1.7.1. Summary of Clinical Pharmacokinetics

Following oral administration of ibrutinib at doses ranging from 1.25 to 12.5 mg/kg/day as well as fixed dose levels of 420, 560, and 840 mg/day, exposure to ibrutinib increased as doses increased with substantial intersubject variability. The mean half-life ($t_{1/2}$) of ibrutinib across 3 clinical studies ranged from 4 to 10 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Administration of 420 mg ibrutinib with a high-fat breakfast in subjects with CLL approximately doubled the mean systemic exposure compared to intake after overnight fasting with median time to T_{max} delayed from 2 to 4 hours. Ibrutinib was extensively metabolized to the dihydrodiol metabolite PCI-45227, a reversible inhibitor of BTK, with approximately 15 times lower inhibitory potency compared to ibrutinib. The metabolite-to-parent AUC ratio ranged from 0.7 to 3.4. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure.

Ibrutinib is minimally cleared renally. The results of a human mass balance study of [^{14}C]-ibrutinib conducted in six healthy male subjects demonstrated that less than 10% of the total dose of [^{14}C]-ibrutinib is renally excreted, whereas approximately 80% is recovered in feces. No specific clinical studies have been conducted in subjects with renal impairment. In Study PCYC-1102-CA, subjects with mild and moderate renal insufficiency (creatinine clearance >30 mL/min) were enrolled. No dose adjustment is needed for subjects with mild or moderate renal impairment (greater than 30 mL/min creatinine clearance) in this study. There is no data in patients with severe renal impairment or subjects on dialysis. The study of ibrutinib in hepatic impaired subjects is currently in progress.

Ibrutinib is primarily metabolized by cytochrome P450 (CYP) 3A. Concomitant use of ibrutinib and drugs that inhibit CYP3A can increase ibrutinib exposure. Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects, increased dose normalized exposure (C_{max} and $AUC_{0\text{-last}}$) of ibrutinib by 29- and 24-fold, respectively. However, in 38 cancer subjects treated with mild and/or moderate CYP3A inhibitors, the ibrutinib exposure (AUC) was ≤2-fold the upper limit of the range of 76 patients not treated concomitantly with CYP3A inhibitors. Clinical safety data in patients treated with weak, moderate or strong CYP3A inhibitors did not reveal meaningful increases in toxicities.

Administration of ibrutinib with strong inducers of CYP3A can decrease ibrutinib plasma concentrations. Physiologically based PK modeling and simulation indicates that rifampin, a strong inducer, can cause a 10-fold decrease in ibrutinib exposure.

The risks associated with ibrutinib and the dihydrodiol metabolite PCI-45227 as potentially affecting the clearance of R-CHOP were assessed in subjects with CD20-Positive B-Cell NHL in Study PCI-32765DBL1002. Vincristine pharmacokinetics were evaluated since CYP3A has been shown to be relevant for vincristine's systemic clearance. No indications for an effect of ibrutinib dosed at 560 mg on vincristine pharmacokinetics were apparent. For the other CHOP compounds, which are not substrates of CYP3A, clinical drug-drug interaction with ibrutinib is much less likely to occur. Regarding the effect of concomitant medication on ibrutinib pharmacokinetic behavior, preliminary pharmacokinetic data for ibrutinib and metabolite PCI-45227 from Study PCI-32765DBL1002 were compared with exposure data derived from PCYC-1104-CA, an ibrutinib monotherapy study in subjects with MCL. Co-administration of R-CHOP and ibrutinib did not affect ibrutinib exposures in a clinically meaningful way. These data are relevant since several of the agents used in the CHOP regimen are similar to that of DA-EPOCH.

1.7.2. Summary of Clinical Safety for Ibrutinib

1.7.2.1. Monotherapy Studies

Pooled safety data for subjects treated with ibrutinib monotherapy in 11 nonrandomized studies (PCYC -1102-CA, PCYC-1117-CA, PCYC-1112-CA [crossover only], PCYC-1104-CA, PCI-32765MCL2001, PCI-32765MCL4001, PCYC-1106-CA, PCYC-1111-CA, PCI-32765FLR2002, PCYC-04753, and PCI-32765-JPN-101) has been evaluated (ibrutinib Investigator's Brochure [IB], version 8.0).

The most frequently reported treatment-emergent adverse events (AEs) in more than 10% of subjects receiving ibrutinib as monotherapy in nonrandomized studies (N=1061) were diarrhea (35.9%), fatigue (28.6%), nausea (20.2%), cough (17.5%), and anemia (15.2%). The most commonly reported Grade 3 or 4 AEs that were hematologic in nature were neutropenia (10.7%), thrombocytopenia (6.2%), and anemia (5.5%). Pneumonia (5.7%), fatigue (2.9%), hypertension (2.7%), and atrial fibrillation (2.6%) were the most frequently reported nonhematologic Grade 3 or 4 adverse events.

The incidence of treatment emergent SAEs reported was 41.3% (N=1061); pneumonia (7.0%), atrial fibrillation (2.8%), and febrile neutropenia (2.3%) were the most commonly reported treatment-emergent SAEs.

In a randomized Phase 3 study in subjects with CLL/SLL (PCYC-1112-CA), the most frequently reported treatment-emergent adverse events in the ibrutinib arm were diarrhea (47.7%), fatigue (27.7%), nausea (26.2%), pyrexia (23.6%), anemia (22.6%), and neutropenia (21.5%). Adverse events reported at a higher incidence (>10% difference) in the ibrutinib arm than in the ofatumumab arm included diarrhea (ibrutinib: 47.7%, ofatumumab: 17.8%), arthralgia (17.4%, 6.8%), and petechiae (13.8%, 1.0%).

The most commonly reported Grade 3 or 4 adverse events in more than 2% of ibrutinib treated subjects that were hematologic in nature were neutropenia (16.4%), thrombocytopenia (5.6%), and anemia (4.6%). Pneumonia (6.7%) was the most frequently reported nonhematologic event. The most frequently reported SAEs in ibrutinib subjects were pneumonia (8.7%), atrial fibrillation (3.1%), pyrexia (3.1%), lung infection (2.6%), lower respiratory tract infection (2.1%) and urinary tract infection (2.1%). For more detailed information please refer to the current version of the IB.

1.7.2.2. Combination Therapy Studies

Pooled safety data for subjects (N=136) treated with ibrutinib as combination therapy in 3 non-randomized studies (ibrutinib + BR or FCR (n=33); ibrutinib + ofatumumab (n=71), and ibrutinib + R-CHOP (n=32) are summarized below. The median duration of treatment was 11.1 months (range: 0.0 to 19.5).

The most frequently reported treatment-emergent adverse events reported in more than 10% of subjects were diarrhea (62.5%), nausea (45.6%), neutropenia (37.5%), fatigue (32.4%), peripheral sensory neuropathy (30.9%), upper respiratory tract infection (26.5%), vomiting (26.5%), anemia (21.3%), and thrombocytopenia (21.3%). The most commonly reported Grade 3 or 4 adverse events were: neutropenia (36.0%), pneumonia (8.1%), febrile neutropenia (7.4%), thrombocytopenia (7.4%), diarrhea (5.1%), anemia (4.4%), cellulitis (4.4%) and urinary tract infection (4.4%).

Treatment-emergent SAEs in subjects receiving ibrutinib as combination therapy (N=136) were reported in 39.0% of subjects. The most frequently reported serious adverse events were pneumonia (8.8%), febrile neutropenia (7.4%), cellulitis (4.4%), and atrial fibrillation (2.9%).

For more detailed information please refer to the current version of the IB.

1.7.3. Risks

1.7.3.1. Bleeding-related Events

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

1.7.3.2. Cardiac

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. In particular subjects with a history of cardiac arrhythmias should be monitored closely.

1.7.3.3. Cytopenias

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

1.7.3.4. Diarrhea

Approximately one-third of subjects treated with ibrutinib monotherapy and two-thirds treated with combination therapy reported diarrhea. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe, with only a small number of Grade 3 events, and no Grade 4 events reported to date.

1.7.3.5. 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). The most commonly reported infections include pneumonia, cellulitis, urinary tract infection and sepsis. Isolated cases of JC virus reactivation resulting in progressive multifocal leukoencephalopathy (PML) have been observed and resulted in death. Two cases in relapsed CLL subjects have been reported. One case occurred after multiple prior rituximab regimens and less than one year after the last dose of rituximab and high dose steroid administration. The second case occurred during concomitant administration of rituximab, bendamustine and ibrutinib.

1.7.3.6. Other Malignancies

Other malignancies, most frequently skin cancers, have occurred in subjects treated with ibrutinib. Across the MCL (PCYC-1104-CA) and CLL/SLL studies (PCYC-1112-CA and PCYC-1102-CA), skin cancers and non-skin cancers were reported in 5.0% (18/357) and 2.5% (9/357) of subjects who received ibrutinib, respectively.

1.7.3.7. Rash

Rash has been commonly reported in subjects treated with either single agend ibrutinib or in combination with chemotherapy. In a randomized Phase 3 study (PCYC-112-CA), rash occurred at a higher rate in the ibrutinib arm than in the control arm. Most rashes were mild to moderate in severity. One case of Stevens-Johnson Syndrome (SJS), with a fatal outcome, was reported in a subject with CLL. The subject received ibrutinib (420 mg/day) and was also receiving various antibiotics and antigout medication (allopurinol) known to be associated with SJS.

1.7.3.8. Treatment-related Lymphocytosis

Similar to other agents targeting BCR signaling, transient lymphocytosis is a pharmacodynamic effect of ibrutinib, in which the inhibition of BTK-mediated cellular homing and adhesion results in a mobilization of tumor cells to the peripheral blood (Stevenson 2011).

Upon initiation of treatment, a transient phase of increase in lymphocyte counts (ie, ≥50% increase from baseline and above absolute count 5000/µL), often associated with reduction of lymphadenopathy, has been observed in most subjects (75%) with relapsed/refractory CLL/SLL treated with ibrutinib. This effect has also been observed in some subjects (33%) with relapsed/refractory MCL treated with ibrutinib. This observed transient lymphocytosis is usually not associated with an AE and should not be considered progressive disease (PD) 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 resolves within a median of 7.1 weeks in the MCL and 18.7 weeks in the CLL subjects.

A substantial increase in the number of circulating lymphocytes (eg, >400,000/µL) has been observed in a subset of subjects. There have been isolated cases of leukostasis reported in subjects treated with ibrutinib.

1.7.3.9. R-CHOP with Ibrutinib

Many of the chemotherapeutic agents used in the R-CHOP regimen are also used in DA-EPOCH-R. Relevant to this, ibrutinib has been evaluated in a Phase 1b study combining ibrutinib with R-CHOP in patients with CD20-positive B-Cell NHL (Younes 2013). Patients received an oral daily dose of ibrutinib (280, 420, or 560 mg) in combination with standard doses of R-CHOP (rituximab, cyclophosphamide, doxorubicin, and vincristine on Day 1, and prednisone on Days 1 through 5 of each 21-day cycle for up to 6 cycles). The primary objective was to determine the recommended Phase 2 dose of ibrutinib in combination with standard R-CHOP. The secondary objectives were to assess safety, ORR, pharmacokinetics, and pharmacodynamic biomarkers.

Seventeen patients (7, 4, and 6 receiving increasing ibrutinib doses) were enrolled: 59% male, median age 65 (Range 46–81) years, 47% DLBCL, 29% MCL and 24% FL. In the 280 mg cohort, 2 patients had dose-limiting toxicity (DLT): 1 with transient syncope and 1 with

periorbital cellulitis; at 560 mg, 1 patient had gastritis (Grade 2). The recommended Phase 2 dose was established at 560 mg ibrutinib.

The most common (≥ 20% of patients) AEs were neutropenia (77%), thrombocytopenia (65%), vomiting (59%), anemia (53%), nausea (47%), fatigue (35%), headache (29%), constipation (24%), diarrhea (24%), and dizziness (24%). To date, 6 patients completed 6 cycles of treatment, and 2 patients discontinued treatment (1 due to noncompliance with the study drug and 1 due to non-DLT AE). Preliminary efficacy assessments showed a favorable response (Younes 2013).

Based on these studies, ibrutinib can be safely combined with systemic chemotherapy and a similar regimen to DA-EPOCH-R produced promising results in patients with newly diagnosed DLBCL.

1.8. 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.

1.8.1. 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).

1.8.2. 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 first step to reducing number of cancer cells) and/or bone marrow transplant then lenalidomide for a long period of time compared to patients treated with induction therapy and/or bone marrow transplant then 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, please refer to the prescribing information (REVLIMID™ Prescribing Information 2013).

1.8.3. R-CHOP with Lenalidomide

Lenalidomide has been evaluated in a Phase 1 study with R-CHOP (Nowakowski 2011). Patients with newly diagnosed, untreated DLBCL or Grade III FL were treated with standard doses of R-CHOP and escalating doses of lenalidomide. Doses were tested at 15 mg, 20 mg, and 25 mg on Days 1–10 and no DLT was found. The ORR rate was 100% with a CR rate of 77%. Lenalidomide 25 mg was then used in a Phase 2 study with R-CHOP in newly diagnosed DLBCL or FL Grade III (Nowakowski 2012). Ninety-two % (47 patients) of these patients had DLBCL and 60% (31 patients) had stage IV disease. The most common toxicities were hematological toxicities with Grade 3 and 4 thrombocytopenia (20% for both groups) and Grade 3 and 4 neutropenia (18% and 71%, respectively). Non-hematological toxicities in Grade 3 or higher were seen in 27% of patients and included febrile neutropenia (10%), nausea (4%), urinary tract infection (4%), vascular access complication (4%) and dehydration (4%). One patient developed thrombosis and one patient died secondary to bowel perforation. The ORR was 98% and the CR rate was 83%, with PFS at 12 months being 73%.

Based on these studies, lenalidomide can be safely combined with systemic chemotherapy and a similar regimen to DA-EPOCH-R produced promising results in patients with newly diagnosed DLBCL.

1.9. Summary of Clinical Safety for DA-EPOCH-R Chemotherapy in Lymphoma

A long-term follow-up study evaluated relapsed and refractory lymphoma patients, including 86 patients (68%) with DLBCL (Gutierrez 2000). The toxicity of EPOCH was evaluated over 535 cycles in 131 patients (Gutierrez 2000). A common pattern of toxicity consisted of a brief neutropenia, usually less than 4 days and occurring around day 10 to 14 of treatment, and

minimal gastrointestinal toxicity. Thrombocytopenia below 50,000/μL occurred during 24% of cycles, and neutropenia occurred during 48% of cycles with hospitalization for neutropenia with fever during 18% of cycles. There were 3 infection-related deaths. Gastrointestinal toxicity was mild. Neurological toxicity necessitating vincristine reduction occurred in 10% of cycles, despite prior vincristine exposure in most patients. Cardiac toxicity, a major limitation of doxorubicin, was rarely seen despite unspecified maximum allowable doxorubicin exposure (in 3% of patients). A modest and clinically insignificant decline in the median ejection fraction (EF) over multiple cycles of EPOCH was observed; a paired t-test (p2) analysis comparing Cycle 0-1 vs. Cycle 2-3, Cycle 4-5 and Cycle 6 revealed a difference of -2.58%, (0.13); -5.5%, (0.0038) and -6.32%, (0.020), respectively. Although patients were heavily pretreated, the toxicity profile of EPOCH allowed delivery of 71%, 92%, 92% and 93% of planned cyclophosphamide, doxorubicin, vincristine and etoposide, respectively.

1.10. Justification of Study Design and Dose Rationale

This non-randomized, multicenter, open-label, study is designed to evaluate whether a combination of DA-EPOCH-R, ibrutinib and lenalidomide has clinical benefit in subjects with relapsed or refractory DLBCL. In Part 1 of the study, the MTD of the combination of DA-EPOCH-R, ibrutinib and lenalidomide will be assessed in relapsed or refractory DLBCL. In part 2 of the study, the efficacy in the ABC subtype of DLBCL will be explored. DA-EPOCH-R is one of the recommended therapies per NCCN guidelines for relapsed or refractory DLBCL not eligible for stem cell therapy. The treatment combination of ibrutinib and lenalidomide may prove to be beneficial in both the GCB and non-GCB subtypes.

1.10.1. Dose Selection Rationale for DA-EPOCH-R

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 doses of DA-EPOCH-R are standard doses; doses will be adjusted per ANC as previously described (Wilson 2002).

1.10.2. Dose Selection Rationale for Ibrutinib

The proposed dose for ibrutinib is 560 mg PO once per day (4 x 140-mg capsules) administered from Day 1–7 in each cycle. In the Phase 1 study PCYC-04753 in subjects with NHL, the 560 mg dose administered once daily appeared safe and favorable responses were observed.

Study PCYC-04753 was a first-in-human, Phase 1, dose-escalating study of ibrutinib in 66 subjects with recurrent B-cell lymphoma including NHL, CLL, FL, MCL, and WM. Five sequential cohorts of subjects received ibrutinib from 1.25 to 12.5 mg/kg/day for 28 days of a 35-day cycle and 2 additional cohorts received either a continuous ibrutinib dose of 8.3 mg/kg/day or a 560-mg fixed dose.

Ibrutinib was well tolerated across a broad range of doses (1.25 through 12.5 mg/kg/day) both when given intermittently and continuously on a 35-day cycle. The most common AEs (>20% of subjects) in this population were diarrhea, fatigue, cough, nausea, headache, and pyrexia. AEs were generally mild to moderate (Grade 1 or 2) and readily managed or reversible. There was no apparent relationship between the incidences or severity of AEs and dose or schedule of ibrutinib. In addition, the maximum tolerated dose of ibrutinib was not reached. Pharmacodynamic studies revealed complete BTK active-site occupancy in PBMCs at doses of 2.5 mg/kg and above, including the 560 mg continuous dosing cohort. The 560 mg dose was chosen for this study since it was found to be active in NHL not only in this Phase 1 trial, but also in several Phase 2 studies in patients with NHL.

1.10.3. Dose Selection Rationale for Lenalidomide

The established dose in monotherapy studies of lenalidomide is 25 mg administered orally once daily for 21 days on a 28-day cycle (Witzig 2009). Escalating doses of lenalidomide used in this study are 0, 15, 20 and 25 mg. Thus, the top dose of lenalidomide tested in combination with DA-EPOCH-R and ibrutinib in this study is the established dose of 25 mg.

2. STUDY OBJECTIVES

2.1. Primary Objectives

2.1.1. Part 1

- To determine the maximum tolerated dose (MTD) of the combination of ibrutinib, lenalidomide and dose-adjusted (DA)-EPOCH-R in relapsed or refractory DLBCL
- To determine the safety and tolerability of ibrutinib and lenalidomide in combination with DA-EPOCH-R in relapsed or refractory DLBCL

2.1.2. Part 2

- To determine the efficacy of ibrutinib and lenalidomide in combination with DA-EPOCH-R in relapsed or refractory ABC DLBCL subjects as assessed by overall response rate (ORR)

2.2. Secondary Objectives

2.2.1. Part 1

- To determine the efficacy of ibrutinib and lenalidomide in combination with DA-EPOCH-R in relapsed or refractory DLBCL subjects as assessed by overall response rate (ORR)

2.2.2. Part 2

- To determine the efficacy of ibrutinib and lenalidomide in combination with DA-EPOCH-R in relapsed or refractory ABC DLBCL as assessed by progression-free survival (PFS), duration of response (DOR) and overall survival (OS)
- To determine the safety and tolerability of ibrutinib and lenalidomide in combination with DA-EPOCH-R in subjects with ABC DLBCL

2.3. Exploratory Objectives

- To determine the pharmacokinetics (PK) of ibrutinib when dosed with lenalidomide in combination with DA-EPOCH-R
- To evaluate biomarkers of sensitivity or resistance to ibrutinib and lenalidomide in combination with DA-EPOCH-R

3. STUDY DESIGN

3.1. Overview of Study Design:

This is an open-label, non-randomized multicenter study conducted in 2 parts. In Parts 1 and 2, treatment will be administered in 3-week cycles (21 days each). In Part 1, a minimum of 4 and a maximum of 30 subjects with DLBCL will be enrolled into a standard 3+3 design to determine the MTD which will then be used in Part 2. Approximately 26 subjects with relapsed or refractory de novo DLBCL non-GCB subtype will be enrolled in Part 2 and will receive ibrutinib at a fixed dose of 560 mg and lenalidomide at the established MTD together with DA-EPOCH-R. If no MTD is identified, then subjects in Part 2 will be treated with the maximum administered doses (MAD), which is the treatment dose from Part 1 dose Level 4.

3.2. Endpoints

3.2.1. Part 1:

3.2.1.1. Primary Endpoint: (for all subtypes of DLBCL)

- MTD
- Safety and tolerability of ibrutinib and lenalidomide in combination with DA-EPOCH-R in relapsed or refractory DLBCL

3.2.1.2. Secondary Endpoint (for all subtypes of DLBCL)

- ORR

3.2.2. Part 2:

3.2.2.1. Primary Endpoint

- ORR including CR (complete response) and PR (partial response) in ABC DLBCL

3.2.2.2. Secondary Endpoints

Efficacy:

- Duration of response (DOR) in ABC DLBCL
- Progression-free survival (PFS) in ABC DLBCL
- Overall survival (OS) in ABC DLBCL

Safety:

- Frequency, severity, and relatedness of AEs
- Frequency of AEs requiring discontinuation of study drug or dose reductions

Pharmacokinetics:

- Plasma pharmacokinetics of ibrutinib

Exploratory Analyses:

- 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.
- Change in secreted protein levels (ie, chemokines, cytokines)
- Change in peripheral T/B/natural killer (NK) counts and immunophenotypical analysis

3.3. Part 1 – Dose Escalation

The dose-escalation part of the study, Part 1, will determine the MTD of the combination of ibrutinib, lenalidomide and DA-EPOCH-R in subjects with DLBCL. Subjects will receive ibrutinib at a fixed dose of 560 mg (or 420 mg if there is toxicity associated with 560 mg) and lenalidomide at an escalating dose of 0, 15, 20 and 25 mg on Days 1–7 of each 21-day cycle. DA-EPOCH-R will be given at standard doses on Days 1-5 of each 21-day cycle.

The dose escalation will follow a 3+3 design with 3 subjects in each cohort. Cohort dose escalation will occur if the subject incidence of DLTs during the first 22 days of study treatment is <33%. If one subject within the initial cohort of 3 subjects experiences a DLT, an additional 3 subjects may be enrolled at the same dose level. If the initial dose is safe and tolerable with no further DLTs, the next dose level examined will be dose Level 2. Dose escalation will continue

to dose Level 4. The MTD will be defined as the highest dose level with an observed incidence of DLTs in <33% of the subjects enrolled in the cohort. If in dose Level 4 DLTs occur in <33% of subjects, then the MTD will not be identified and the dose Level 4 dose will be the maximum administered doses (MAD).

In the event of toxicity associated with 560 mg of ibrutinib (DLTs during the first 22 days of study treatment is >33% in dose Level 1), 420 mg of ibrutinib (dose Level -1) may be used for the dose escalation cohorts if it is deemed safe in combination with DA-EPOCH-R. In this case, a maximum of 30 subjects may be enrolled in Part 1 (up to 6 subjects at the -1 level and 4 x 6 = 24 subjects at levels 1, 2, 3 and 4).

At the MTD or MAD, at least 6 subjects will be treated at this level prior to start of Part 2 of the study.

Figure 1: 3+3 Dose Escalation Design

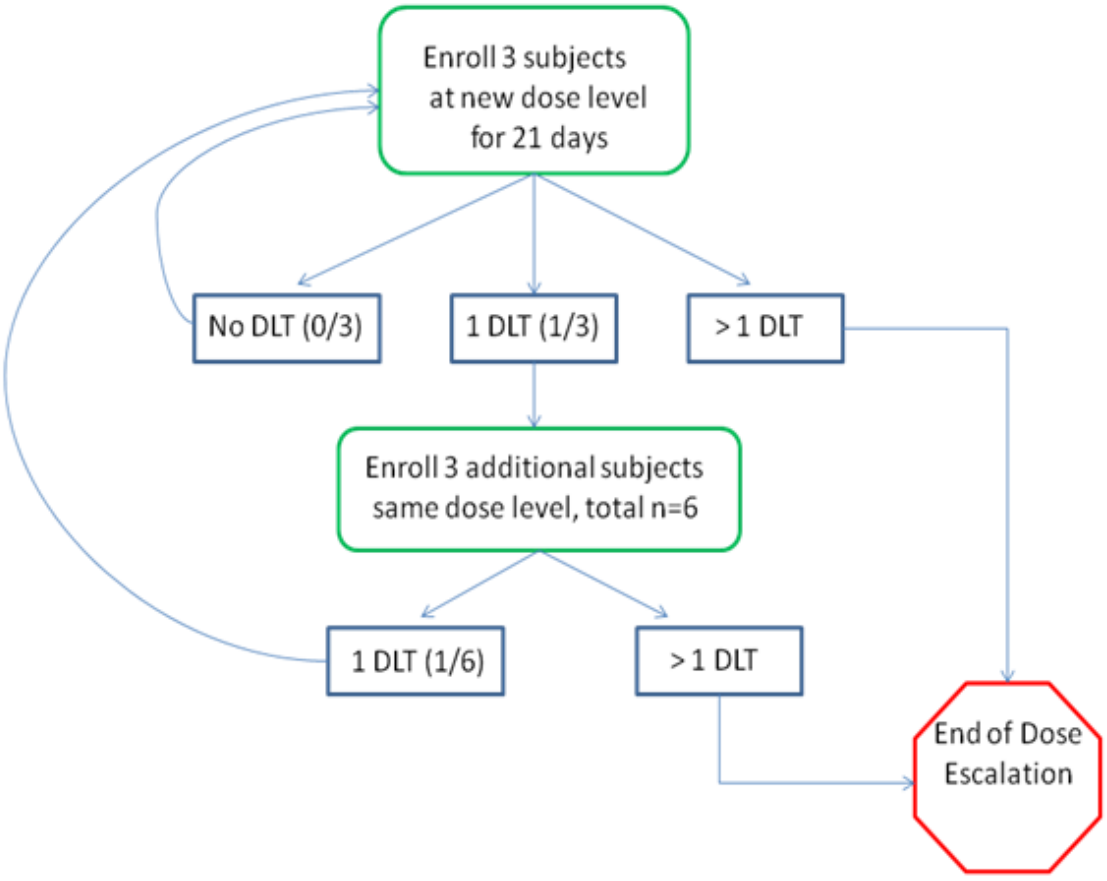

Table 1: Part 1 Dose Levels

Part 1			
Dose Level	**Ibrutinib**	**Lenalidomide**	**DA-EPOCH-R**
-1	420 mg	0 mg	Standard doses
1	560 mg	0 mg	Standard doses
2	560 mg	15 mg	Standard doses
3	560 mg	20 mg	Standard doses
4	560 mg	25 mg	Standard doses

Subjects will be monitored through all cycles of treatment for related toxicities. Dose-limiting toxicities are defined in Section 5.5.

3.4. Part 2 – Expansion

The expansion part of the study, Part 2, will only enroll subjects with non-GCB DLBCL as identified by IHC. The primary objective is to determine the ORR of ibrutinib and lenalidomide in combination with DA-EPOCH-R in subjects with ABC DLBCL as analyzed by gene expression profiling (GEP).

The MTD determined in Part 1 will be the dose used for all subjects. If no MTD is identified, then subjects in Part 2 will be treated with the MAD which is the treatment dose from dose Level 4. Approximately 26 subjects will receive ibrutinib at a fixed dose of 560 mg (or 420 mg if there is toxicity associated with 560 mg, see dose escalation schema above) on Days 1–7 and lenalidomide at the established MTD on Days 1–7. DA-EPOCH-R will be given on Days 1–5 of each 3-week (21-day) cycle at standard doses.

Depending on the number of subjects enrolled at the MTD in Part 1 and depending on the number of subjects with the ABC subtype that will be identified, additional subjects may be enrolled (please see sample size calculation).

Table 2: Part 2 Dose Levels

Part 2		
Ibrutinib	**Lenalidomide**	**DA-EPOCH-R**
560 mg (or 420 mg if toxicity with 560 mg)	TBD	Standard doses

3.5. All Subjects in Part 1 and Part 2

Subjects in Part 1 and Part 2 will receive therapy until a maximum of six cycles or disease progression, whichever occurs first. Subjects will be restaged after cycle 3 (Cycle 4 Day 1, -4 days [Cycle 3 Day 19 to Cycle 4 Day 1]) and after Cycle 6 (Cycle 6 Day 21 ±4 days) of treatment, and then every 3, 4, and 6 months (every 12, 16 and 26 weeks) during post-treatment years 1, 2, and 3 respectively.

In this study, immunohistochemisty (IHC) using Hans method (Hans 2004) will be used to assess subject eligibility with respect to subtype of DLBCL for Part 2. GEP will be performed to confirm the ABC subtype for analysis purposes. 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. The use of the term "ABC subtype" refers to subjects who have been subsequently profiled by GEP and then classified as the ABC subtype by GEP. Subjects with primary mediastinal B cell lymphoma (PMBL) are excluded in Part 2 as they can be erroneously identified by IHC as ABC DLBCL.

Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase.

The Screening Phase will be up to 28 days prior to first dose of study drug, during which the subject's eligibility and baseline characteristics will be determined.

The Treatment Phase will extend from enrollment until study drug discontinuation. Subjects will receive treatment for up to 6 (21-day) cycles as long as the subject is deriving clinical benefit (complete remission [CR], partial remission [PR], or stable disease [SD]) or until the subject experiences any unacceptable toxicity, whichever occurs first. Further information on dosing is provided in Section 5. Regularly scheduled disease assessments are required throughout the Treatment Phase (Section 8.2).

The Post-treatment Phase will extend from the discontinuation of treatment up until the subject has progressive disease or other criteria listed in Section 9. Response evaluations will be continued every 3, 4 and 6 months during post-treatment years 1, 2 and 3 respectively.

Response assessments will be completed by the investigator using the Revised Response Criteria for Malignant Lymphoma (Cheson 2007).

The Investigator will evaluate sites of disease by radiological imaging (primary), physical examination or other procedures as necessary, review of hematology and serum chemistry results, and disease-related symptoms. The same methods of assessment used to assess disease at baseline should be used throughout the study. Local laboratories will perform all hematology and serum chemistry testing for the primary endpoint analysis.

4. SUBJECT SELECTION

4.1. Inclusion Criteria

Subjects will be considered for inclusion in this study if they meet all of the following criteria:

1. Men and women ≥ 18 years of age

2. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2
3. Pathologically confirmed DLBCL:
   - Part 1: all subtypes are eligible
   - Part 2: only non-GCB subtype is eligible
4. Relapsed or refractory disease, defined as either: 1) recurrence of disease after a complete remission (CR), or 2) partial remission (PR), stable disease (SD), or progressive disease (PD) at completion of the treatment regimen preceding entry to the study (residual disease):
   a) Subjects must have previously received an appropriate first-line treatment regimen.
   b) For subjects in whom a post-treatment residual computed tomography (CT) scan abnormality exists, and a definitive distinction between residual DLBCL and a non-lymphomatous process (eg, fibrosis) is clinically indicated, those subjects must have biopsy confirmation of residual DLBCL prior to study entry.
5. Subjects must have ≥ 1 measurable disease site 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.
6. Subjects must have adequate fresh or paraffin tissue for confirmation of diagnosis and molecular evaluation. Tissue may be from either the initial diagnosis or from relapsed or refractory disease.
7. Meet the following laboratory parameters:
   c) Absolute neutrophil count (ANC) ≥1,000 cells/mm^3 (1.0 x 10^9/L)
   d) Platelets ≥75,000 cells/mm^3 (75 x 10^9/L)
   e) ALT and AST ≤2.5 x the upper limit of the normal range (ULN) unless lymphoma-related
   f) Bilirubin ≤1.5 x ULN, except ≤2 mg/dL (total) in subjects with Gilbert's syndrome (as defined by >80% unconjugated hyperbilirubinemia)
   g) Serum Creatinine ≤2.0 mg/dL or creatinine clearance ≥60 mL/min/1.73 m^2
   h) Hemoglobin ≥8.0 g/dL
   i) Prothrombin time (PT) and activated partial thromboplastin time (aPTT) must be ≤1.5 x ULN; except if, in the opinion of the Investigator, the aPTT is elevated because of a positive Lupus Anticoagulant
8. Left ventricular ejection fraction (LVEF) >45% as assessed by echocardiogram or multigated acquisition scan (MUGA)
9. Able to provide written informed consent and can understand and comply with the requirements of the study
10. 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™.

11. Female subjects of childbearing potential (FCBP)[1] 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 F: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.
12. 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 F: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.
13. Life expectancy of more than 3 months

4.2. Exclusion Criteria

Subjects will be ineligible for this study if they meet any of the following criteria:

1. Transformed DLBCL or DLBCL with coexistent histologies (eg, follicular or mucosa-associated lymphoid tissue [MALT] lymphoma) for enrollment into Part 2 only
2. Primary mediastinal (thymic) large B-cell lymphoma for enrollment into Part 2 only
3. Known central nervous system lymphoma
4. Any chemotherapy, external beam radiation therapy, or anti-cancer antibodies within 2 weeks prior to the first dose of study drug
5. Radio- or toxin-immunoconjugates within 10 weeks prior to the first dose of study drug
6. Concurrent enrollment in another therapeutic investigational clinical study
7. Previously taken ibrutinib or lenalidomide
8. Major surgery within 4 weeks prior to the first dose of study drug
9. Prior allogenetic stem cell (or other organ) transplant within 6 months or any evidence of active graft-versus-host disease or requirement for immunosuppressants within 28 days prior to first dose of study drug
10. History of other malignancies, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer, or other solid tumors curatively treated with no evidence of disease for ≥2 years
11. Currently active, or clinically significant cardiovascular disease such as uncontrolled arrhythmia, congestive heart failure, any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification (Appendix E), or history of myocardial infarction within 6 months prior to first dose with study drug

[1] 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 (i.e., has had menses at any time in the preceding 24 consecutive months).

12. Significant screening electrocardiogram (ECG) abnormalities, including left bundle branch block, 2nd degree atrioventricular (AV) block Type II, 3rd degree block, or QTc ≥ 470 msec
13. Recent infection requiring intravenous anti-infective treatment that was completed ≤ 14 days before the first dose of study drug
14. Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 4.03), grade 0 or 1, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia
15. Known bleeding diathesis (eg, von Willebrand's disease) or hemophilia
16. Known history of infection with human immunodeficiency virus (HIV) or chronic or active infection with Hepatitis C virus (HCV) or Hepatitis B virus (HBV). Viral load by PCR must be confirmed negative in equivocal cases for subjects who are Hepatitis B core antibody positive, Hepatitis B surface antigen positive, Hepatitis B surface antibody positive (unless immunized) or Hepatitis C antibody positive.
17. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk
18. Unable to swallow capsules or disease significantly affecting gastrointestinal function and/or inhibiting small intestine absorption such as malabsorption syndrome, resection of the small bowel, or poorly controlled inflammatory bowel disease affecting the small intestine
19. Received or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 28 days of first dose of study drug
20. Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor
21. Lactating or pregnant women

5. TREATMENT OF SUBJECTS

This is an open-label single-arm study conducted in 2 parts. Subjects will not be blinded to the study treatment nor will they be randomized. Enrolled subjects will receive open-labeled ibrutinib capsules in combination with lenalidomide and DA-EPOCH-R.

All subjects will receive the following treatment regimen: Ibrutinib and lenalidomide will be given on Days 1–7 and DA-EPOCH-R will be given on Days 1–5, repeating each cycle every 3 weeks (=21 days) until disease progression or for a maximum of 6 cycles.

Study follow-up will be for 1 year after the last subject received the first dose.

5.1. Treatment Part 1

Ibrutinib and lenalidomide (lenalidomide dose-escalated in cohorts, Table 3) and DA-EPOCH-R

Day 1–7 of each cycle: ibrutinib PO
Day 1–7 of each cycle: lenalidomide PO

Day 1–5 of each cycle: DA-EPOCH-R
Day 6 (with a +48 hour window) of each cycle: Pegfilgrastim

Table 3: Part 1 Dosing Levels

Part 1			
Dose Level	**Ibrutinib**	**Lenalidomide**	**DA-EPOCH-R**
-1	420 mg	0 mg	Standard doses
1	560 mg	0 mg	Standard doses
2	560 mg	15 mg	Standard doses
3	560 mg	20 mg	Standard doses
4	560 mg	25 mg	Standard doses

Part 1 Cycle 1 and predose Cycle 2 Day 1 (=22 days) is the DLT assessment window. Blood draws on Cycle 2 Day 1 on study Day 22 occur predose. The DLT period ends after the blood draws on Cycle 2 Day 1, before Cycle 2 Day 1 treatment begins. Laboratory samples drawn pre-dose Cycle 2 Day 1 need to be reviewed prior to dosing on Day 22.

5.2. Treatment Part 2

Ibrutinib and lenalidomide (lenalidomide dose as determined in Part 1) and DA-EPOCH-R

Day 1–7 of each cycle: ibrutinib PO
Day 1–7 of each cycle: lenalidomide PO
Day 1–5 of each cycle: DA-EPOCH-R
Day 6 (with a +48 hour window) of each cycle: Pegfilgrastim

Table 4: Part 2 Dose Levels

Part 2		
Ibrutinib	**Lenalidomide**	**DA-EPOCH-R**
560 mg (or 420 mg if there is toxicity associated with 560 mg)	TBD	Standard doses

5.3. Dosages Overview

Table 5: Dosages

Drugs	Dosages & Administration/Schedule
Ibrutinib	560 mg/day taken by mouth Days 1–7
Lenalidomide	Dose escalated as described in Section 5.7.4 and taken by mouth Days 1–7
Prednisone	60 mg/m^2 PO* BID Days 1–5 (first dose should be given 1–12 hours before starting rituximab)
Rituximab	375 mg/m^2 day 1 (before etoposide+doxorubicin+vincristine infusion begins; see Section 5.8.5 for administration instructions)
Etoposide	50 mg/m^2/day CIV Days 1–4 (96-hour infusion)
Doxorubicin	10 mg/m^2/day CIV Days 1–4 (96-hour infusion)
Vincristine	0.4 mg/m^2/day CIV Days 1–4 (96-hour infusion)
Cyclophosphamide	750 mg/m^2 IV Day 5 over 30–60 mins
Pegfilgrastim	6 mg SC on Day 6 (with a +48 hour window)
Cycle Length	Repeat cycle every 21 days, CBCs are checked twice a week every cycle to identify ANC nadir

BID =twice daily; CIV=continuous intravenous infusion; IV=intravenous infusion; PO = oral; SC=subcutaneous
* For subjects who cannot tolerate prednisone PO, please contact the Hospital Pharmacist for guidance on dosing equivalents of other corticosteroid preparations.

Dose adjustment for EPOCH-R: Please see instructions in Section 5.13.

5.4. Dose Escalation for Part 1

The dose-escalation part of the study, Part 1, will determine the MTD of the combination of ibrutinib, lenalidomide and DA-EPOCH-R in subjects with DLBCL. DA-EPOCH-R will be given at standard doses on Days 1–5 of each 21-day cycle. The dose level of lenalidomide will be escalated. Subjects will receive ibrutinib at a fixed dose of 560 mg PO on Days 1–7 and lenalidomide PO at an escalated dose of 0, 15, 20 and 25 mg for 7 days of each 21-day cycle. The dose escalation will follow a 3+3 design with 3 subjects in each cohort.

- The first cohort of 3 subjects will begin at Part 1 dose Level 1; if 0 of 3 subjects experience a DLT within the first 22 days, then the next dose level cohort (Part 1 Level 2) with 3 new subjects will be enrolled.
- If 1 of 3 subjects experiences a DLT, 3 additional subjects will be enrolled at the same dose level for a total of 6 subjects.
- If no additional subjects experience a DLT at that dose level, meaning that no more than 1 of 6 subjects at the same dose level experience a DLT, then the next dose level cohort will be enrolled with 3 new subjects.

- If >1 of the 6 subjects experiences DLT, then the MTD is one dose level below.
- Part 1 cohort 1–4 dose levels are given in the table below.
- Dose Level 4 defines the maximum administered dose (MAD) in this study.

The MTD will be defined as the highest dose level with an observed incidence of DLTs in < 33% of the subjects enrolled in the cohort. If in dose Level 4 DLTs occur in < 33% of the subjects, then the MTD will not be identified. In this case, the MAD of 25 mg lenalidomide from dose Level 4 will be the lenalidomide dose used in Part 2.

Table 6: Part 1 Dosing Levels

Part 1			
Dose Level	**Ibrutinib**	**Lenalidomide**	**DA-EPOCH-R**
-1	420 mg	0 mg	Standard doses
1	560 mg	0 mg	Standard doses
2	560 mg	15 mg	Standard doses
3	560 mg	20 mg	Standard doses
4	560 mg	25 mg	Standard doses

If 2 or more DLTs are seen in dose Level 1, ibrutinib may be reduced to a dose of 420 mg (dose Level -1). If the 420 mg dose of ibrutinib is the MTD that can be combined with DA-EPOCH-R, then dose escalation of lenalidomide will proceed with dose escalation Levels 2, 3, and 4 as outlined above.

In Part 1, during the first 21-day cycle, lenalidomide will NOT be reduced due to toxicity. Lenalidomide toxicity will be considered a Dose-Limiting Toxicity (DLT) during this period (see Section 5.5).

After Cycle 1, EPOCH-R will be dose-adjusted as described below and as previously described (Wilson 2002).

5.5. Dose-Limiting Toxicities for Part 1

A DLT is defined as an Adverse Event (AE) that occurs within the first 22 days (Cycle 1, Cycle 2 Day 1 predose) of dosing that meets the DLT definition below, is clinically relevant, and is considered at least possibly related to study drug (ibrutinib and/or lenalidomide) in the opinion of the investigator.

5.5.1. DLT Definition

DLT assessments will only be conducted during the dose-escalation part during the first 22 days (Cycle 1, Cycle 2 Day 1 predose).

A DLT is defined as any Grade 3 or higher adverse event at least possibly related to study drug (ibrutinib and/or lenalidomide) and occurring during the DLT window with the following clarifications for the toxicities below:

Non-Hematologic:

- Grade 3 or 4 nausea, vomiting or diarrhea despite maximum medical supportive care and persisting ≥ 7 days
- Grade 3 fatigue persisting ≥ 7 days
- 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
- Treatment delay of Cycle 2 ≥ 7 days for toxicity

Hematologic:

- Grade 4 neutropenia (ANC <500/mm^3) lasting for ≥ 7 days
- Grade 4 thrombocytopenia (<25,000/mm^3) that persists for ≥ 7 days
- Grade 3 thrombocytopenia associated with grade 2 or greater bleeding
- Grade 3 anemia lasting for ≥ 7 days or Grade 4 anemia
- Treatment delay of Cycle 2 ≥ 7 days for hematologic toxicity

5.6. Ibrutinib

5.6.1. 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. Please refer to the ibrutinib IB for a list of excipients.

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.

Please refer to the pharmacy manual for additional guidance on study drug preparation, handling and storage.

5.6.2. Dosage and Administration of Ibrutinib

Ibrutinib 560 mg (4 x 140-mg capsules) is administered orally once daily on Days 1–7 with 8 ounces (approximately 240 mL) of water. Grapefruit or Seville orange juice should be avoided due to CYP3A inhibition. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. Each dose of ibrutinib should be taken at least 30 minutes before eating or at least 2 hours after a meal, at approximately the same time

each day. Ibrutinib and lenalidomide which are given PO can be administered together. On Day 1, ibrutinib and lenalidomide will be administered first and infusions will be started within 30 min of the PO doses.

If a dose of ibrutinib is missed, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. No extra capsules to make up missed doses of ibrutinib should be taken.

Ibrutinib will be dispensed to subjects in bottles. All doses of ibrutinib taken in the clinic should be taken from the bottle dispensed to the subject. Unused ibrutinib capsules dispensed during previous visits must be returned to the site and drug accountability records (Section 12.8) must be updated. Returned capsules must not be re-dispensed to anyone. Subjects should return all used bottles to the site when they receive new study drug. For the purpose of drug accountability, empty bottles and returned capsules should be kept at the site until after the review of the site monitor if allowed by local institution policy.

Investigators are prohibited from supplying ibrutinib capsules to any subjects not properly enrolled in this study or to any physicians or scientists except those designated as subinvestigators on Food and Drug Administration (FDA) Form 1572. The investigator must ensure that subjects receive ibrutinib capsules only from personnel who fully understand the procedures for administering the drug.

Treatment will continue for up to 6 cycles of treatment until disease progression or other reason for treatment discontinuation as outlined in Section 9.

Dose modifications for toxicity are outlined in Section 5.6.3.

5.6.3. Dose Reduction and Discontinuation

Outside of the DLT window in Part 1 and in Part 2 of the study, the ibrutinib dose should be held for any unmanageable, potentially ibrutinib-related toxicity.

Note: During Part 1, ibrutinib may be reduced from 560 mg to a dose of 420 mg (dose Level -1). If this is the case, apply the table below using recommendations for 1 dose level lower than that used for 560 mg.

Please see Section 11.2.3 for event of special interest reporting of major hemorrhage (Section 11.2.3.1) and intracranial hemorrhage (Section 11.2.3.2).

The action in Table 7 should be taken for the following ibrutinib-related toxicities:

- Grade 4 ANC (<500/μL) for more than 7 days. The use of neutrophil growth factors is permitted per American Society of Clinical Oncology (ASCO) guidelines (Smith 2006) and must be recorded in the electronic case report form (eCRF).

- Grade 3 thrombocytopenia (<50,000/μL) for subjects with normal platelet count at baseline; or for subjects with baseline thrombocytopenia, a platelet decrease of 50% to 74% from baseline in the presence of >Grade 2 bleeding
- Grade 4 thrombocytopenia (<25,000/μL) for subjects with normal platelet count at baseline; or for subjects with baseline thrombocytopenia, a platelet decrease of ≥75% from baseline or <20,000/μL, whichever is higher
- Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy
- Any other Grade 4 toxicity or unmanageable Grade 3 toxicity.

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 anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation (Section 6.2.3.1).

Table 7: Dose Modification for Ibrutinib Toxicity

Occurrence	Action to be Taken
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 (420 mg per day)
Third	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (280 mg per day)
Fourth	Discontinue ibrutinib

An ibrutinib-related toxicity that results in a dose delay of greater than 1 week should result in a dose reduction as per the table above.

At the investigator's discretion, the dose of ibrutinib may be re-escalated after a dose reduction in the absence of a recurrence of the toxicity that led to the reduction.

Please see Section 6.2.1 for guidelines for management of ibrutinib in subjects who require treatment with a strong CYP3A inhibitor.

Dose modifications of ibrutinib must be recorded in the eCRF.

5.6.4. Overdose Instructions

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any SAE criterion must be reported as an SAE in the appropriate time frame and documented as clinical sequelae to an overdose. There is no specific antidote for ibrutinib. In the event of an overdose, subjects should be closely monitored and given appropriate supportive treatment.

5.6.5. Precautions and Adverse Events

The most common AEs reported for subjects across studies with ibrutinib have included diarrhea, nausea, and fatigue. Additional common AEs such as cough, muscle spasm, urinary tract infection, headache, vomiting, pyrexia, arthralgia, constipation, and rash have been reported in 15–25% of subjects. The remaining more common AEs reported for 10–15% of subjects include peripheral edema, anemia, contusion, dyspepsia, insomnia, abdominal pain, dyspnea, myalgia, dizziness, pain in extremity, and thrombocytopenia. In addition, Events of Special Interest are outlined in Section 11.2.3. For complete information on precautions, please refer to the IB.

5.7. Lenalidomide

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

5.7.1. 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 1 cycle of dosing. Lenalidomide must be dispensed in the original packaging with the label clearly visible. **Only 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.

5.7.2. 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 the Revlimid REMS™ program of Celgene Corporation. Per standard Revlimid REMS™ requirements all physicians who prescribe lenalidomide for research subjects enrolled into this study, and all research subjects enrolled into this study, must be registered in and must comply with all requirements of the Revlimid REMS™ program. Prescriptions must be filled within 7 days for females of childbearing potential and within 14 days for all other risk categories. Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site for IND studies. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

5.7.3. Pregnancy Testing while Taking Lenalidomide

Please refer to Appendix F: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

5.7.4. Dosage, Preparation and Administration of Lenalidomide

The first dose of lenalidomide will be administered PO on Cycle 1 Day 1 of the Treatment Phase, after which lenalidomide will be self-administered daily by the subjects on Days 1-7 of each cycle.

Lenalidomide and ibrutinib which are given PO can be administered together. On Day 1, ibrutinib and lenalidomide will be administered first and infusions will be started within 30 min of the PO doses.

Lenalidomide should be administered with water. The capsule should be swallowed intact and subjects should not attempt to chew capsules, open capsules or dissolve them in water. Results from human in vitro studies show that lenalidomide is neither metabolized by nor inhibits or induces the CYP450 pathway.

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 1–7 of each cycle. 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 for up to 6 cycles of treatment until disease progression or other reason for treatment discontinuation as outlined in Section 9.

Dose modifications for toxicity are outlined in Section 5.7.5, Table 8, and Table 9.

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

5.7.5. Dose Delay, Reduction or Discontinuation of Lenalidomide

5.7.5.1. Part 1 Cycle 1 Lenalidomide Dose Modifications

During the first cycle in Part 1 which is the DLT period, the lenalidomide dose will not be reduced.

5.7.5.2. Part 1 Cycles 2–6 and Part 2 Lenalidomide Dose Modifications

A new course with 7-day lenalidomide treatment may begin on Day 1 of a new cycle if

- ANC ≥ 1,000/μL and
- Platelet count ≥ 50,000/μL and
- No lenalidomide-related ≥ Grade 3 toxicity

If the criteria are not met, per investigator's discretion, assessments may be repeated.

The initiation of lenalidomide should be delayed until subject meets criteria to receive drug as planned. Once a 7-day cycle has initiated, if lenalidomide must be held for toxicity during dosing (Day 1–7), lenalidomide will not resume until Day 1 of the next cycle, provided the subject meets criteria above, with dose adjustments as per Table 8.

If a lenalidomide-related toxicity occurs after dosing between Day 8 and 21, lenalidomide may resume at Day 1 of the next cycle, provided the subject meets criteria above. No dose adjustment is required if the next cycle resumes on schedule or is delayed less than 1 week. If the next treatment cycle is delayed more than 1 week due to a lenalidomide-related toxicity, then dose adjustments should be undertaken as per Table 9.

Dose adjustments are to be made according to the system showing the greatest toxicity. If a patient experiences several toxicities and there are conflicting recommendations, the recommended dose adjustment that reduces the dose to the lowest level will be used. The major toxic effects which limit dose are: vomiting, diarrhea, neuropathy, thrombocytopenia, neutropenia and anemia. In the event a patient is diagnosed with a thyroid condition or experiences a drop in creatinine clearance to <60 mL/min please refer to Table 8 for further instructions.

Table 8: Dose Modification or Interruption for Lenalidomide Toxicity During Administration or for Delay in a Treatment Cycle of Greater Than 1 Week

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 for remainder of cycle • Reduce lenalidomide by 1 dose level (5 mg) at Day 1 next cycle if patient meets cycle initiation criteria (see Section 5.7.5.2). • Minimum dose 5 mg daily
Neutropenia: • ANC <1,000/μL for at least 7 days, OR • ANC <1,000/μL with an associated temperature ≥38.5°C, OR • ANC <500/μL	• Interrupt lenalidomide for remainder of cycle • Reduce lenalidomide by 1 dose level (5 mg) at Day 1 next cycle if patient meets cycle initiation criteria (see Section 5.7.5.2). • Minimum dose 5 mg daily
Rash: • Any Grade desquamating (blistering) • Grade 4 non-blistering	• Discontinue lenalidomide
Venous thromboembolism ≥ Grade 3	• Interrupt lenalidomide for remainder of cycle • Initiate therapeutic anticoagulation as clinically indicated, please evaluate interactions with other study drugs • Resume lenalidomide without dose modification at Day 1of next cycle if benefit of therapy outweighs bleeding risk
Hyperthyroidism or hypothyroidism	• Interrupt lenalidomide treatment for remainder of cycle • Evaluate etiology & initiate appropriate therapy • Reduce lenalidomide by 1 dose level (5 mg) at Day 1 next cycle. Start new cycle when patient meets cycle initiation criteria (see Section 5.7.5.2). • Minimum dose 5 mg daily

Creatinine Clearance <60 mL/min (CrCl, Cockcroft-Gault)	• Interrupt lenalidomide for remainder of cycle
	• Reduce lenalidomide according to recommendations below based upon CrCl at Day 1 of next cycle if patient meets cycle initiation criteria (see Section 5.7.5.2).
	• Minimum dose 5 mg daily
	  ○ CrCl 30–60 mL/min: 10 mg every 24 hours
	  ○ CrCl <30 mL/min (not requiring dialysis): 15 mg every 48 hours
	• If CrCl becomes >60mL/min for a minimum of 2 cycles one may re-escalate to the prior dose at investigator's discretion

Any other Grade 3/4 non-hematologic toxicities attributed to lenalidomide	• Interrupt lenalidomide for remainder of cycle • Reduce lenalidomide by 1 dose level (5 mg) at Day 1of next cycle if patient meets cycle initiation criteria (see Section 5.7.5.2). • Minimum dose 5 mg daily

Table 9: Lenalidomide Dose Reduction

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

5.7.6. Safety Profile

Please see prescribing information for lenalidomide/REVLIMID®.

There are boxed warnings for lenalidomide, embryo-fetal toxicity (please see Appendix F), hematologic toxicity and venous thromboembolism. Lenalidomide can cause significant neutropenia and thrombocytopenia; for venous thromboembolism please see background section (clinical safety).

In addition, there are warnings regarding allergic reactions, tumor lysis syndrome, tumor flare reaction and second primary malignancies.

Allergic reactions

Hypersensitivity, angioedema, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Tumor lysis syndrome

Fatal instances of tumor lysis syndrome have been reported during treatment with lenalidomide. The subjects at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. These subjects should be monitored closely and appropriate precautions taken.

Tumor flare reactions

Serious tumor flare reactions have occurred during investigational use of lenalidomide for chronic lymphocytic leukemia and lymphoma.

Adverse Events

Most frequently reported adverse events reported during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, UTI,

Upper respiratory infection, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures.

Second new cancers

Please see Section 1.8.2 Summary of Clinical Safety.

Complete and updated adverse events are available in the IB and the IND Safety Letters.

5.8. Rituximab

All subjects in both parts of this study will receive rituximab and will follow guidelines for rituximab dosing and toxicity management. Please refer to the FDA approved package insert for complete product information.

5.8.1. Supply

Rituximab is 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.

5.8.2. Storage

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.

5.8.3. Preparation

Rituximab will be diluted to a final volume of 0.9% Sodium Chloride or 5% Dextrose Injection to prepare a standard product with concentration of 2 mg/mL. Caution should be taken during the preparation of the drug, as shaking can cause aggregation and precipitation of the antibody.

5.8.4. Stability

After dilution, rituximab is stable at 2ºC to 8ºC (36ºF to 46ºF) for 24 hours and at room temperature for an additional 24 hours.

5.8.5. Administration

Per prescribing information:

First Infusion: The rituximab solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted with other drugs.

If hypersensitivity or infusion reactions do not occur, the infusion rate may be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If a hypersensitivity (non-IgE-mediated) or an infusion reaction develops, the infusion should be temporarily slowed or interrupted. The infusion can continue at one-half the previous rate upon improvement of subject symptoms.

Subsequent Infusions: If the subject tolerated the first infusion well, subsequent rituximab infusions can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr as tolerated. If the subject did not tolerate the first infusion well, follow the guidelines for the first infusion.

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

5.8.6. Safety Profile

The information below is based on the information given in the package insert for rituximab. Please see the package insert for more information.

Rituximab is contraindicated in patients with known anaphylaxis or IgE-mediated hypersensitivity to murine proteins or to any component of the drug product.

In addition, there are boxed warnings for rituximab. These include severe infusion reactions, tumor lysis syndrome and severe mucocutaneous reactions.

Other severe reactions to rituximab include allergic reactions, cardiac arrhythmias, renal toxicity and progressive multifocal leukoencephalopathy (PML).

The most common side effects of rituximab (in more than 30% of 356 subjects with B-cell lymphoma included in clinical studies) were fever and chills, infection and lymphopenia. Serious infections including reactivation of viral infections have been seen.

Other side effects of rituximab (in more than 10% of 356 subjects with B-cell lymphoma included in clinical studies) were general weakness, headache, abdominal pain, general pain, back pain, low blood pressure, nausea diarrhea, vomiting, low white blood cells, low platelets, cough, runny nose, throat irritation, general swelling, joint pain, dizziness, night sweats, rash and itching.

5.9. Cyclophosphamide

Refer to the FDA approved package insert for complete product information.

5.9.1. Supply

Commercially available in white crystalline formulation for intravenous injection, in vials containing 100 mg, 200 mg, 500 mg, 1 gm, and 2 gm.

5.9.2. Storage and Preparation

Intact vials are stable at room temperature (not to exceed 30°C). Reconstitute with appropriate amounts of 0.9% NaCl to produce a final concentration of 20 mg/mL. Discard solution after 24 hours at room temperature. Stable up to 6 days if refrigerated (2ºC to 8°C).

5.9.3. Administration

Cyclophosphamide will be diluted in 100 mL of D5W or 0.9% NaCl and infused over 30 minutes or according to institutional standard. Subjects will be instructed to drink an adequate amount of fluids and empty their bladders frequently during cyclophosphamide administration.

5.9.4. Toxicities

Myelosuppression, nausea and vomiting, hemorrhagic cystitis, and alopecia. Cystitis can be largely prevented by maintaining a good state of hydration and good urine flow during and after drug administration using the following. Please refer to the package insert for a complete listing of all toxicities.

5.9.5. Hydration Guidelines

All subjects should receive 0.9%NS at the following volumes (based on cyclophosphamide dose levels) and rates with half the specified volume given before starting cyclophosphamide administration and half the volume given after completion of the cyclophosphamide administration.

Table 10: Hydration Guidelines for Cyclophosphamide

Cyclophosphamide Dosage Levels (please refer to Table 13 with dosage levels for Doxorubicin, Etoposide and Cyclophosphamide)	**Fluid Volume and Administration Rate**
Levels 1 & 2	1000 mL 0.9%NS @ 300–500 mL/h
Levels 3, 4, & 5	2000 mL 0.9%NS @ 300–500 mL/h
Levels ≥6	2500 mL 0.9%NS @ 300–500 mL/h

5.10. Vincristine/Doxorubicin/Etoposide

Stability studies conducted by the Pharmaceutical Development Service, Pharmacy Department, NIH Clinical Center, have demonstrated that admixtures of vincristine, doxorubicin, and etoposide in 0.9% Sodium Chloride Injection, USP at concentrations, respectively, of 1, 25 and 125 mcg/mL; 1.4, 35 and 175 mcg/mL; 2, 50 and 250 mcg/mL; and 2.8, 70 and 350 mcg/mL are stable for at least 36 hours at room temperature when protected from light. Also admixtures containing vincristine, doxorubicin and etoposide concentrations of 1.6, 40 and 200 mcg/mL are stable for at least 30 hours at 32ºC.

For this study, vincristine, doxorubicin, and etoposide comprising a daily dose (a 24-hour supply) will be diluted in 0.9%NS. Product containers will be replaced every 24 hours to complete the planned duration of infusional treatment. Product volumes will be determined by the amount of etoposide present in a 24-hour supply of medication. For daily etoposide doses ≤130 mg, admixtures will be diluted in approximately 500 mL 0.9%NS. For daily etoposide doses >130 mg, admixtures will be diluted in approximately 1000 mL 0.9%NS.

Vincristine + doxorubicin + etoposide admixtures will be administered by continuous IV infusion over 96 hours with a suitable rate controller pump via a central venous access device.

5.10.1. Central Venous Access

Central Venous Access is required for EPOCH administration. Possible lines include:

- Temporary internal jugular line (preferred);
- PICC lines via the brachial vein;
- semi-permanent HICKMAN;
- GROSHONG catheters; or
- medi-port implanted devices.

All devices will have nursing supervision to include subject self-care and cleaning/flushing of the devices.

5.10.2. Vincristine

Refer to the FDA approved package insert for complete product information.

5.10.2.1. Supply

Commercially available in 1 mg, 2 mg, and 5 mg vial sizes. Each ml contains 1 mg of vincristine, 100 mg mannitol, 1.3 mg methylparaben, and 0.2 mg propylparaben. Drug should be stored at 2ºC to 8^{o}C and should be protected from light.

5.10.2.2. Toxicities

Peripheral neuropathy, autonomic neuropathy, and alopecia. Local necrosis if injected subcutaneously. Please refer to the package insert for a complete listing of all toxicities.

5.10.3. Doxorubicin

Refer to the FDA approved package insert for complete product information.

5.10.3.1. Supply

Commercially available in 10, 20, 50, 100, and 150 mg vials with 50, 100, 250, 500, and 750 mg, of lactose, respectively.

5.10.3.2. Toxicities

Myelosuppression, stomatitis, alopecia, nausea and vomiting, and acute and chronic cardiac toxicity, manifested as arrhythmias or a congestive cardiomyopathy, the latter uncommon at total cumulative doses less than 500 mg/m^2. The drug causes local necrosis if infiltrated into subcutaneous tissue. Please refer to the package insert for a complete listing of all toxicities.

5.10.4. Etoposide

Refer to the FDA approved package insert for complete product information.

5.10.4.1. Supply

Commercially available as a concentrate for parenteral use in 100 mg vials; each ml contains 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80, 650 mg of polyethylene glycol 300, and 30.5% alcohol.

5.10.4.2. Toxicities

Myelosuppression, nausea, vomiting, anaphylactoid reactions, alopecia, and hypotension if infusion is too rapid. Please refer to the package insert for a complete listing of all toxicities.

5.11. Prednisone

Refer to the FDA approved package insert for complete product information.

5.11.1. Supply

Commercially available in a large number of oral dosage strengths including pills and liquid formulations. Tablets should be stored in well-closed containers at temperatures between 15–30^{o}C.

5.11.2. Doses

Prednisone utilization will be simplified by using only 20- and 50-mg tablets to produce individual doses and by stratifying prednisone doses by a subject's body surface area (BSA), as follows:

Table 11: Prednisone Doses per BSA

BSA (m^2)	Each Dose
1.25–1.49	80 mg
1.5–1.83	100 mg
1.84–2.16	120 mg
2.17–2.41	140 mg
2.42–2.6	150 mg
2.7–3	170 mg

5.11.3. Toxicities

Proximal muscle weakness, glucose intolerance, thinning of skin, redistribution of body fat, Cushingoid facies, immunosuppression, and propensity to gastrointestinal ulceration. Please refer to the package insert for a complete listing of all toxicities.

5.12. Pegfilgrastim (Neulasta)

Refer to the FDA approved package insert for complete product information.

5.12.1. Supply

Commercially available in a prefilled single use syringe containing 6 mg pegfilgrastim, supplied with a 27-gauge, 1/2-inch needle with an UltraSafe® Needle Guard. The needle cover of the prefilled syringe contains dry natural rubber (a derivative of latex). Neulasta is provided in a dispensing pack containing one syringe (NDC 55513-190-01).

Store refrigerated between 2°C to 8°C (36°F to 46°F) in the carton to protect from light. Do not shake. Discard syringes stored at room temperature for more than 48 hours. Avoid freezing; if frozen, thaw in the refrigerator before administration. Discard syringe if frozen more than once. Pegfilgrastim will be given by subcutaneous injection; subject or other caregiver will be instructed on proper injection technique.

5.12.2. Toxicities

Rare anaphylactic reactions with the first dose; bone pain at sites of active marrow with continued administration. Local reactions at injection sites. Constitutional symptoms, increased alkaline phosphatase, LDH, uric acid; worsening of pre-existing inflammatory conditions. Splenic rupture and acute respiratory distress syndrome (ARDS) can occur in subjects receiving Neulasta, including fatal cases. Please refer to the package insert for a complete listing of all toxicities.

5.13. Dose Adjustment for EPOCH-R

5.13.1. EPOCH-R Dose Adjustment for Part 1 and Part 2

- Dose adjustments for DA-EPOCH-R are based on twice weekly CBC obtained between cycles. Nadir ANC and platelets are usually observed between Day 10–14 and Day 11–16, respectively.
- Dose adjustments above starting dose level (Level 1) apply to etoposide, doxorubicin and cyclophosphamide.
- Dose adjustments below starting dose level (Level 1) apply to cyclophosphamide only.
- Drug doses based on previous cycle ANC nadir:

Table 12: EPOCH-R Dose Adjustment

• If Nadir ANC ≥ 500/μL on all measurements:	↑ One dose level above last cycle
• If Nadir ANC < 500/μL on 1 or 2 measurements:	Same dose level as last cycle
• If Nadir ANC < 500/μL ≥ 3 measurements:	↓ One dose level below last cycle
Or	
• If nadir platelet < 25,000/μL on ≥ 1 measurement:	↓ One dose level below last cycle

- If ANC ≥1000/μL and platelets ≥75,000/μl on Day 22, begin treatment (even if ibrutinib and/or lenalidomide are withheld due to ibrutinib- or lenalidomide-related toxicity).
- If ANC <1000/μL or platelets <75,000/μl on Day 22, delay up to 1 week. If EPOCH-R cannot be administered then ibrutinib and lenalidomide will also be delayed. Filgrastim may be started for ANC <1000/μL and stopped 24 hours before treatment. If counts still low after 1 week delay, ↓ 1 dose level below last cycle.
- Important: Measurement of ANC nadir based on twice weekly CBC only (3 days apart, e.g. on Monday & Thursday or Tuesday & Friday to assure that counts are checked every 3 to 4 days). Only use results from twice weekly CBCs for dose adjustment, even if additional (daily) CBC's are obtained. Note: Not all the CBC blood draws for the dose adjustment are included in the schedule of assessments; please draw twice weekly for the dose adjustment of EPOCH and as clinically indicated.
- The Investigator or his designee must be consulted on all dose adjustments.
- Note: The Investigator may use discretion in adjusting doses in subjects with compromised bone marrow function due to involvement by lymphoma. Subjects with severe cytopenias due to compromised marrow function from lymphoma will have repeat bone marrow biopsies and will only be retreated if there is evidence of tumor response. This judgment may be made by the investigator in consultation with the local hematopathologists.

Table 13: Doses per Dose Levels for Doxorubicin, Etoposide and Cyclophosphamide

Drugs	Doxorubicin, Etoposide & Cyclophosphamide Doses per Dose Levels							
	-2	-1	1	2	3	4	5	6
Doxorubicin (mg/m^2/day)	10	10	10	12	14.4	17.3	20.7	24.8
Etoposide (mg/m^2/day)	50	50	50	60	72	86.4	103.7	124.4
Cyclophosphamide (mg/m^2/day)	480	600	750	900	1080	1296	1555	1866

5.13.2. Vincristine Dose Reduction for Ileus Toxicity

Symptomatic ileus/constipation may occur. Because the severity of constipation is dose related, it is usually unnecessary to stop the vincristine altogether. Every effort should be made to not unnecessarily reduce vincristine doses. Ileus/constipation is usually worse during the first cycle, so prophylactic bowel care is essential. If vincristine dose is reduced for this toxicity, it can often be increased to full dose on subsequent cycles without recurrence of severe ileus/constipation. The following guidelines for symptomatic ileus on a previous cycle should be followed.

1. Clinical ileus <8 days with abdominal pain requiring narcotics and/or persistent nausea/vomiting >2 days: Reduce vincristine dose 25%.
2. Clinical ileus 8–12 days with abdominal pain requiring narcotics and/or persistent nausea/vomiting >2 days: Reduce vincristine dose 50%.
3. Clinical ileus >12 days with abdominal pain requiring narcotics and/or persistent nausea/vomiting >2 days: Hold vincristine on next cycle. May restart at 50% reduction on subsequent cycle.

5.13.3. Vincristine Dose Reduction for Neurological Toxicity

Table 14: Sensory Neuropathy Grade and Vincristine Dose Reduction

Grade	% Dose of Vincristine
2	100
3	50
4	0

Table 15: Motor Neuropathy Grade and Vincristine Dose Reduction

Grade	% Dose of Vincristine
1	100
2	75
3	25
4	0

5.13.4. Etoposide Dose Reduction for Renal Dysfunction

Etoposide should be reduced 25% for creatinine clearance 15- 50 mL/min/1.73 m^2. Etoposide should be returned to full dose (or escalated if indicated) once creatinine clearance > 50 mL/min/1.73 m^2. Data are not available in patients with creatinine clearance < 15 mL/min/1.73 m^2. Note: Entry criteria for this study require creatinine clearance ≥ 60 mL/min/1.73 m^2 so this situation pertains to renal dysfunction on treatment.

5.13.5. EPOCH-R Dose for Obese Subjects

All dosing is based on the patient's BSA as calculated from actual weight without capping. There is no clearly documented adverse impact of treatment of obese subjects when dosing is performed according to actual body weight.

5.13.6. Pretreatment and Dose Modifications for Rituximab

Pretreatment for rituximab with diphenhydramine and acetaminophen using standard medical practice may be used. Side effects of rituximab may be infusion-rate related and may be reduced by slower administration or premedication. At the investigator's discretion, rituximab may be discontinued for the duration of the cycles in subjects with allergic reactions and may be administered on the following cycles using slower infusion rates.

At the investigator's discretion, the rituximab dose should be held for any unmanageable, potentially rituximab-related toxicity. The dose of rituximab should be modified according to the dose modification guidelines in Table 16 if any Grade 4 or unmanageable Grade 3 non-hematologic toxicity attributed to rituximab occurs.

Table 16: Dose Modification for Rituximab Toxicity

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

5.14. Criteria for Permanent Treatment Discontinuation

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. If the subject meets any of the following criteria, then withdrawal from the study treatment is mandatory:

- Subject has confirmed PD.
- Subject has an intercurrent illness or AE that prevents further study drug administration.
- Subject decides to withdraw from study.
- Subject requires a prohibited concomitant medication.
- Investigator decision (such as chronic noncompliance, significant protocol deviation, or best interest of the subject)
- Study termination by Sponsor
- Subject becomes pregnant.

Subjects who withdraw for any reason other than those specified in Section 9 will not be replaced. A Safety Follow-up visit (Section 8.3.1) is required for all subjects except for those subjects who have withdrawn full consent (see Section 9.3).

6. CONCOMITANT MEDICATIONS/PROCEDURES

6.1. Permitted Concomitant Medications

Blood and platelet transfusions and supportive medications (such as for emesis, diarrhea, etc.) in accordance with standard practice are permitted.

In Part 1, erythropoietic and hematopoietic growth factors (filgrastim and pegfilgrastim except for what is included in the EPOCH regimen) should only be given during the DLT period (ie, Cycle Day 1 through Cycle 2 Day 1 pre-dose [22 days total]) for Grade 3 or greater events, or if the patient fits the criteria for a DLT. During subsequent cycles in Part 1 and in Part 2, erythropoietic growth factors (eg, erythropoietin) and hematopoietic growth factors filgrastim and pegfilgrastim are allowed per institutional policy and in accordance with the ASCO guidelines (Smith 2006).

Short courses of corticosteroids (< 14 days) for non-cancer-related medical reasons (eg, treatment for rash, arthritis, asthma) at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted.

6.1.1. Prophylaxis of Pneumocystis Jirovecii (Previously Pneumocystis Carinii)

Adult subjects will receive prophylaxis for Pneumocystis Jiroveci during EPOCH chemotherapy. Trimethoprim/sulfamethoxazole 1 DS PO QD on Monday, Wednesday, Friday is the preferred schedule.

Subjects allergic to either component may receive inhaled pentamidine 300 mg once a month or other standard treatments.

6.1.2. Prophylaxis for Tumor Lysis Syndrome (TLS)

At the discretion of the principal investigator, subjects with high tumor burden may be treated with allopurinol 600 mg PO x 1 dose following by 300 mg PO daily for up to 7 days. Hospitalization with aggressive IV hydration and urinary alkalization may be used.

6.1.3. Recommended Bowel Regimen

The goal is to have at least 1 soft bowel motion every 24 hours while receiving treatment.

Adult Subjects: Sodium Docusate 100 mg capsule; take 1 to 2 capsules once a day on Day 1–7 of each cycle. If needed can double the frequency to 2 capsules every 12 hours. If needed add oral lactulose 15–30 mL prn / q 6-hourly.

6.2. Concomitant Medications to be Used with Caution

For subjects taking digoxin, periodic monitoring of digoxin plasma levels is recommended due to increased Cmax and AUC with concomitant lenalidomide therapy (please see prescribing information).

Subjects taking concomitant therapies such as erythropoietin stimulating agents or estrogen containing therapies, may have an increased risk of venous thromboembolism (please see prescribing information and lenalidomide background section).

6.2.1. Concomitant Use of CYP3A Inhibitors/Inducers

6.2.1.1. Ibrutinib

Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.
Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects increased dose normalized exposure, C_{max} and $AUC_{0\text{-}last}$, of ibrutinib by 29- and 24-fold, respectively.
The maximal observed ibrutinib exposure (AUC) was ≤ 2-fold in 37 subjects treated with mild and/or moderate CYP3A inhibitors when compared with the ibrutinib exposure in 76 subjects not treated concomitantly with CYP3A inhibitors. Clinical safety data in 66 subjects treated with moderate (n=47) or strong CYP3A inhibitors (n=19) did not reveal meaningful increases in toxicities. Co-administration of strong CYP3A inhibitors (eg, ketoconazole, indinavir, nelfinavir,

ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, and nefazadone) should be avoided. If a strong CYP3A inhibitor must be used, consider reducing the ibrutinib dose to 140 mg or withhold treatment temporarily. Subjects should be monitored for signs of ibrutinib toxicity.

If the benefit outweighs the risk and a moderate CYP3A inhibitor must be used, monitor subject for toxicity and follow dose modification guidance as needed (Section 5.6.3). Subjects should avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A.

Co-administration of ibrutinib with strong CYP3A inducers, rifampin, in healthy subjects decrease ibrutinib plasma concentrations by approximately 10-fold. Avoid concomitant 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 or inducers is provided in Appendix C; a comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/table.aspx. This website is continually revised and should be checked frequently for updates.

6.2.1.2. Lenalidomide

Results from human in vitro studies show that lenalidomide is neither metabolized by nor inhibits or induces the cytochrome P450 pathway suggesting that lenalidomide is not likely to cause or be subject to P450-based metabolic drug interactions (please see lenalidomide prescribing information).

6.2.2. QT Prolongation

Any medications known to cause QT prolongation should be used with caution; periodic ECG and electrolyte monitoring should be considered.

6.2.3. Antiplatelet Agents and Anticoagulants

6.2.3.1. Ibrutinib

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Ibrutinib should be used 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 6.4.

For subjects requiring the initiation of therapeutic anticoagulation therapy (eg, atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib 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 ibrutinib is restarted.

6.3. Prohibited Concomitant Therapy

Chemotherapy, anticancer immunotherapy, corticosteroids for cancer-related reasons (except for the corticosteroids included in the DA-EPOCH-R regimen), experimental therapy, or radiotherapy are prohibited while the subject is receiving ibrutinib.

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

6.4. Guidelines for Ibrutinib Management with Surgeries or Procedures

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

- 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 serosanguinous drainage or the need for drainage tubes.
- For minor procedures (such as a central line placement, needle biopsy, 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 for these procedures.
- For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

7. STUDY EVALUATIONS

The Schedule of Assessments is provided in Appendix A. Descriptions of the scheduled evaluations are outlined below.

Before study entry, throughout the study, and at the follow-up evaluations, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and efficacy assessments. Clinical evaluations and laboratory assessments may be repeated more frequently if clinically indicated.

7.1. Description of Procedures

7.1.1. Assessments

7.1.1.1. Informed Consent

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

7.1.1.2. Confirmation of Eligibility

Perform all necessary procedures and evaluations to document that the subject meets each eligibility criterion (Section 4). De-identified copies of the pathology report confirming diagnosis of DLBCL (tumor biopsy and bone marrow biopsy), a list of prior anticancer therapies and best responses, and the radiology report from screening CT scan (or MRI if indicated) and positron emission tomography (PET) will need to be submitted to the sponsor as part of the enrollment process. In addition, DLBCL subtype should be provided (IHC testing at local laboratory) at the time of eligibility verification.

To be eligible, all subjects must also have archival tissue for central IHC and GEP. Formulin-fixed paraffin embedded tissue (FFPE), a minimum of 10 slides, however 15–30 slides or a paraffin block is preferred, must be provided for central confirmation of DLBCL subtype (results not required for enrollment). Tumor samples can be archival tissue from original diagnosis or from relapsed or refractory disease, or a fresh (recent) biopsy. Refer to the laboratory manual for a more detailed description of the archival tissue preparation and handling.

7.1.1.3. Medical History

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 anti-cancer treatments, dates administered, and responses and duration of response to these treatments, also will be recorded.

7.1.1.4. Prior and Concomitant Medications

All medications from 14 days before the start of study drug administration through 30 days after the last dose of study drug will be documented.

7.1.1.5. Adverse Events

All AEs whether serious or non-serious, will be documented in the source documents from the time signed and dated ICF is obtained until 30 days following the last dose of study drug. Only SAEs will be reported to the Sponsor prior to the first dose of study drug. From the first dose of study drug, AEs/SAEs will be recorded in the eCRFs and will continue until 30 days after the last dose of study drug.

Laboratory abnormalities which result in signs and symptoms, require intervention or follow-up and are considered clinically significant should be recorded as AEs. AEs will be recorded at each visit or as reported during the treatment period.

7.1.1.6. Physical Examination, and Height

The physical examination will include, at a minimum, the general appearance of the subject, examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities and lymphatic system. The musculoskeletal system and nervous system may be included in the examination if clinically indicated. A complete physical examination will be performed at Screening, Response Assessment Visits, Day 1 of each Cycle and at the Safety Follow-Up Visit. Symptom-directed physical examinations may be performed at all other visits. Only physicians, physician assistant, or oncology nurse practitioners should perform the lymphatic system examination. As much as possible, the same person should perform all the lymphatic examinations for a given subject.

Height will be collected at Screening only.

7.1.1.7. 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 6.2.3). It is recommended that protocol appropriate VTE prophylaxis be used in subject's 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 8 for dose modification in the event a VTE occurs while on treatment.

7.1.1.8. Vital Signs

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

Weight will also be collected.

7.1.1.9. ECOG Performance Status

The ECOG performance index is provided in Appendix B.

7.1.1.10. Electrocardiogram (ECG)

Subjects should be in supine position and resting for at least 10 minutes before study-related ECGs. During visits in which both ECGs and blood draws are performed, ECGs should be performed first.

12-lead ECGs will be done in triplicate (≥1 minute apart); the calculated QTc average of the 3 ECGs must be <470 msec for eligibility.

Abnormalities noted at Screening should be included in the medical history.

Unscheduled ECGs should be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset dyspnea.

7.1.1.11. Echocardiogram or MUGA

An echocardiogram (ECHO) or MUGA will be performed at Screening on all subjects to assess cardiac function and measure ejection fraction. Abnormalities noted at screening should be included in the medical history, as appropriate.

Additional ECHO or MUGA examinations may be performed at any time during the study, as determined by the investigator.

7.1.1.12. Bone Marrow Aspirate and Biopsy

For Eligibility

A unilateral bone marrow aspirate and biopsy must be obtained at Screening or up to 28 days prior to the first administration of study drug. Subjects who have a bone marrow aspirate and biopsy result since completion of their last therapy for DLBCL may use those bone marrow results, provided the biopsy/aspirate was done <28 days prior to first dose of study drug.

Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572. De-identified copies of all bone marrow biopsy/aspirate results must be provided to the Sponsor.

For Response Confirmation

If the subject's physical examination findings, laboratory evaluations, and radiographic evaluations suggest that CR has been achieved in all response parameters, and the screening bone marrow evaluation was positive for lymphoma, a repeat bone marrow aspirate and biopsy must be obtained to confirm the CR and to evaluate minimal residual disease (MRD). In cases

where cytopenic progression is suspected, a bone marrow aspirate or biopsy should be performed to distinguish autoimmune and drug-related cytopenias.

7.1.1.13. Optional Tumor Biopsy

Patients with accessible tumor tissue who agree to have an optional biopsy performed will be biopsied prior to treatment. Patients who have a partial or complete response and later develop recurrent disease will be encouraged to have an additional biopsy at the time of recurrence. Molecular characterization of this sample may identify altered signaling patterns or mutations that associate with response or resistance to ibrutinib treatment.

For a subject who consents to participate in the optional tumor tissue sample assessment, fresh, frozen and/or formalin-fixed, paraffin-embedded (FFPE) tissue will be collected at least 3 days prior to the start of ibrutinib/lenalidomide for pre-treatment biopsies, and within 30 (±7) days after the last dose of ibrutinib or prior to the start of a new anti-cancer treatment for post treatment biopsies. Please refer to the laboratory binder for additional instructions on collecting and processing this sample.

Material from the biopsy may be used for exploratory analysis including gene expression profiling, sequencing to look for mutations in BTK, related kinases or other critical genes.

7.1.2. Laboratory

7.1.2.1. Hematology

During scheduled visits, hematology parameters will include a complete blood count: white blood cells, red blood cells, hemoglobin, hematocrit, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils, bands (if reported), and atypical lymphocytes (if reported). Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

During Cycles 1-6, standard of care, hematology blood draws for dose adjustments to EPOCH regimen should include at a minimum, white blood cells, neutrophils, bands if present, and platelets, and should be checked twice weekly on days 4 or 5, 11 or 12, 15 and 18 or 19 (e.g. on Monday (Day 1) & Thursday or Friday (Day 4 or 5), or Tuesday (Day 1) & Friday or Saturday (Day 4 or 5) to assure that counts are checked every 3 to 4 days).

7.1.2.2. Serum Chemisty

Chemistry must include albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

7.1.2.3. Hepatitis Serologies

Hepatitis serologies include Hepatitis C antibody, Hepatitis B surface antigen, Hepatitis B surface antibody, and Hepatitis B core antibody. Viral load by PCR must be confirmed negative in equivocal cases for subjects who are Hepatitis B core antibody positive, Hepatitis B surface antigen positive, Hepatitis B surface antibody positive (unless immunized) or Hepatitis C antibody positive.

7.1.2.4. Pregnancy Test

A pregnancy test (urine or serum) with a sensitivity of 25 mIU/mL must be done in accordance with Celgene Revlimid REMS™ 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 prescribing 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 15–21 of each cycle. A pregnancy test may be performed more frequently if required by local and national requirements.

7.1.2.5. Coagulation Studies

Coagulation includes PT, PTT and INR. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

7.1.2.6. T/B/NK Cell Count

The blood sample(s) for T/B/NK cell count (CD3+, CD4+, CD8+, CD19+, CD16/56+) must be taken predosePercentages and absolute counts of CD3+, CD4+, CD8+, CD19+, and CD16/56+ cells will be collected. Testing will be performed at the central laboratory.

7.1.2.7. Blood Samples for Biomarkers

Samples collected may be used for pharmacodynamic and biomarker assessments including BTK and other kinase activity and signaling, determination of BTK active-site occupancy, gene expression profiling (GEP), sequencing, circulating tumor DNA, flow cytometry and secreted protein analyses. Cytokines, chemokines and exploratory investigations of predictive biomarkers and mechanisms of resistance may also be performed. Testing will be performed at the central laboratory or by the sponsor.

Sample Collection and Handling

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

Instructions for the collection, handling and shipment of samples are found in the laboratory manual that will be provided for sample collection and handling.

7.1.2.8. Pharmacokinetics (PK) Sample Collection

PK samples will be collected in all patients in Part 2. Please refer to Table 17 for the pharmacokinetic sample schedule.

Table 17: PK Sample Collection Schedule

Cycle	Day	Predose	Time After Dosing*			
			1 h ± 15 min	2 h ± 15 min	4 h ± 30 min	6 h ± 30 min
1	5	x	x	x	x	x

* Time after dosing of ibrutinib

On the day of the sampling visit, the subject will not take lenalidomide or ibrutinib dose before arrival at the clinic. Study drug intake will be observed by clinic staff. The time of the PK sample and the time of the study drug dose will be recorded in the CRF.

7.1.2.9. Urinalysis

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

7.1.3. Radiological Examinations

Pretreatment tumor assessment will be performed within 21 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 (eg, extremity) and a positron emission tomography (PET) scan are required for the pretreatment tumor assessment. 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 and CT of the chest and neck without contrast. In this case, neck nodes cannot be used as target lesions.

There must be radiographically measurable disease at Screening (at least one lymph node ≥ 1.5 cm in the longest diameter). Up to 6 measurable lymph nodes (target lesions ≥1.5 cm in the longest diameter), clearly measurable in 2 perpendicular dimensions, will be followed as target lesions for each subject. Measurable sites of disease should be chosen such that they are representative of the subject's disease. In addition, selection of target lesions should be from as disparate regions of the body as possible when these areas are significantly involved.
If additional lesions are present but are not included in the target lesion assessment, they can be added as non-target lesions and followed throughout the study.

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.

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.

7.1.4. Overall Response Assessments

Overall response assessments will include evaluation of physical examinations, recording of symptoms, hematological evaluations, and radiographic evaluations as per the schedule of assessments (see Appendix A). Subjects will be restaged after Cycle 3 (Cycle 4 Day 1, -4 days [Cycle 3 Day 19 to Cycle 4 Day 1]) and after Cycle 6 (Cycle 6 Day 21 ± 4 days) of treatment, then every 3, 4, and 6 months during post-treatment years 1, 2 and 3 respectively. Response assessments will be performed according to the revised International Working Group Response Criteria for NHL (Cheson 2007), as assessed by investigators (see Appendix D).

7.1.5. Survival

After progression, survival status will be assessed approximately every 12 weeks until death, withdrawal by subject, lost to follow-up, or study terminated by Sponsor, whichever comes first.

At the time of the interim analysis and at study closure, a survival sweep will be conducted. All subjects who are on study and not known to have died prior to the survival sweep will be contacted at that time.

8. STUDY PROCEDURES

The study is divided into a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Schedule of Assessments Table (Appendix A) summarizes the frequency and timing of efficacy, PK, biomarker, and safety measurements applicable to this study. The PK assessments are detailed in the PK Sample Collection Schedule (Table 17).

8.1. Screening Phase

Screening procedures will be performed up to 28 days before Cycle 1, Day 1, unless otherwise specified. All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, screening, and being deemed eligible for entry, subjects will be enrolled in the study.

Screening Procedures

- Informed consent
- Review of eligibility criteria
- Tumor sample for eligibility
- Medical history
- Adverse events
- Prior and concomitant medications (including chemotherapy, radiation, over-the-counter drugs, vitamins and herbs)
- Complete physical examination
- Venous Thromboembolism Risk Assessment
- Vital signs
- ECOG performance status
- 12-lead ECG (in triplicate)
- Echocardiogram
- Bone marrow biopsy and aspirate (within 28 days of randomization)
- Laboratory Tests
    - Hematology
    - Serum chemistry
    - Hepatitis Serologies

- Pregnancy test (for women of childbearing potential only)
- Coagulation parameters
- Urinalysis

- Radiologic examination by CT/PET
- Optional Tumor Biopsy: Where possible, tumor biopsies will be obtained by core needle biopsy or surgery at least 3 days prior to first dose of ibrutinib and lenalidomide.

8.2. Treatment Phase

Following completion of the Screening Visit and once eligibility has been confirmed by PCYC, subjects must begin the Treatment Phase of the study within 7 days of enrollment. If laboratory tests are required to be collected pre-dose of Day 1 of Cycle 1, subject must continue to meet all eligibility criteria to begin treatment. After Cycle 1, pre-dose assessments may be performed up to 2 days prior to Day 1 of a cycle expect where otherwise noted.

In the Treatment Phase, subjects will receive therapy until disease progression or a maximum of six cycles of 21 days each whichever occurs first.

Study drug treatment should be continued until disease progression, unacceptable treatment-related toxicity, or other reasons outlined in Section 9.2. Local laboratory results will be used to guide all dosing-related decisions. Hematology results during the first cycle to assess dose adjustments for EPOCH-R will be performed as previously described (Wilson 2008).

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

8.2.1. Cycle 1

8.2.1.1. Cycle 1 Day 1

Pre-Dose

The following procedures will be performed prior to dosing Cycle 1, Day 1 visit unless otherwise noted. Screening tests may be used at baseline if done within 28 days of Cycle 1 Day 1 where indicated.

- Confirmation of eligibility
- Update medical history
- Adverse events
- Prior and concomitant medications (including chemotherapy, radiation, over-the-counter drugs, vitamins and herbs)
- Complete physical examination

- Vital signs
- ECOG performance status
- Laboratory Tests
  - Hematology
  - Serum chemistry
  - Pregnancy test (for women of childbearing potential only)
  - T/B/NK cell count
  - Biomarker blood sample

Dosing and Post-Dose

- Administration of ibrutinib, lenalidomide, rituximab and EPOCH
- Dispense ibrutinib and lenalidomide
- Review of AEs
- Concomitant medications (including over-the-counter drugs, vitamins and herbs)

8.2.1.2. Cycle 1 Day 2–6

Pre-dose

- Review of AEs (Days 2–5)
- Concomitant medications (including over-the-counter drugs, vitamins and herbs)
- Vital Signs (Days 2–5)

Dosing and Post Dose

- Administration of ibrutinib and lenalidomide
- Administration of EPOCH (Days 2–4), Cyclophosphamide (Day 5) and Pegfilgrastim (Day 6 with a +48 hour window) as standard of care (Table 5)
- Review of AEs (Days 2–5)
- Concomitant medications (including over-the-counter drugs, vitamins and herbs, Days 2–5)
- Pharmacokinetics (Part 2 only)
  - PK pre- and post-dose Cycle 1, Day 5

8.2.1.3. Cycle 1 Day 8 and 15

- Review of AEs
- Concomitant medications (including over the counter drugs, vitamins and herbs)
- Vital Signs
- Laboratory Tests

- Hematology
- Serum chemistry
- Pregnancy test (for women of childbearing potential only, Day 15 only)
- Biomarker blood sample

8.2.2. Cycles 2–6

8.2.2.1. Day 1

- Review of Adverse events
- Concomitant medications (including over-the-counter drugs, vitamins and herbs)
- Complete physical examination
- Vital signs
- ECOG performance status
- Laboratory Tests
  - Hematology
  - Serum chemistry
  - Pregnancy test (for women of childbearing potential only; pregnancy testing can be collected on Day 15–21 of previous cycle to ensure delivery by Day 1 of new cycle)
  - T/B/NK cell count (Day 1 of Cycles 2, 3, and 6)
  - Biomarker blood sample (Day 1 of Cycles 2, 3, and 6)
- Administration of ibrutinib, lenalidomide, rituximab and EPOCH

8.2.2.2. Day 2–6

Predose

- Review of AEs (Days 2–5)
- Concomitant medications (including over the counter drugs, vitamins and herbs, Days 2–5)
- Vital Signs (Days 2–5)

Dosing and Post-Dose

- Administration of ibrutinib and lenalidomide
- Administration of EPOCH (Days 2–4), Cyclophosphamide (Day 5) and Pegfilgrastim (Day 6 with a +48 hour window) as standard of care (Table 5)
- Review of AEs (Days 2–5)
- Concomitant medications (including over the counter drugs, vitamins and herbs, Days 2–5)

8.2.2.3. Day 8

- Review of Adverse events
- Concomitant medications (including over-the-counter drugs, vitamins and herbs)
- Vital signs
- Laboratory Tests
  - Hematology
  - Serum chemistry
  - Biomarker blood sample (Cycle 2 only)

8.2.3. Response Assessments

Subjects will be restaged at the following timepoints (per Cheson 2007):

- After Cycle 3 (Cycle 4 Day 1, minus up to 4 days [Cycle 3 Day 19 to Cycle 4 Day 1])
- After Cycle 6 (Cycle 6 Day 21 ±4 days)
- Every 12 weeks during post treatment year 1 (±7 days)
- Every 16 weeks post-treatment year 2 (±7 days)
- Every 26 weeks post-treatment year 3 (±7 days)

Response Assessment procedures will be performed in conjunction with standard visits as described below:

- Review of AEs
- Concomitant medications (including over the counter drugs, vitamins and herbs)
- Complete physical examination
- Vital Signs
- ECOG Status
- Laboratory Tests
  - Hematology
  - Serum chemistry
  - T/B/NK cell count
  - Biomarker blood sample
- Radiologic examination by CT or MRI scan
- PET (repeat to confirm CR if positive at screening)
- Bone marrow biopsy and/or aspirate for MRD analysis (repeat to confirm CR if positive at screening) and possibly for other biomarkers

- Overall response assessment

8.2.4. Suspected CR

The Suspected CR visit should be performed at any time during the study, if the investigator suspects CR based on clinical, radiographic and/or laboratory evaluation. The following procedures are required to confirm CR:

- Imaging by CT or MRI; and PET if applicable
- Bone marrow aspirate/biopsy (only if biopsy at Screening was positive)

The following assessments should also be performed after CR is confirmed:

- Review of AEs
- Concomitant medications (including over-the-counter drugs, vitamins and herbs)
- T/B/NK cell count
- Biomarker blood sample

8.3. Follow-up Phase

8.3.1. Safety Follow-up Visit

The Safety Follow-Up Visit should occur 30 days (±7 days) after the last dose of study drug.

The following procedures will be performed at the Safety Follow-Up visit:

- Review of AEs
- Concomitant medications (including over the counter drugs, vitamins and herbs)
- Complete physical examination including weight
- Vital Signs
- ECOG Performance Status
- 12-lead ECG (in triplicate)
- Laboratory tests:
  - Hematology
  - Serum chemistry
  - Pregnancy test for FCBP
  - Coagulation studies
  - T/B/NK cell count
  - Biomarker blood sample

- Urinalysis

8.3.2. Survival Follow-up Visit

Once subjects progress or start use of alternative antineoplastic therapy (for subjects who have not withdrawn consent), they will be contacted approximately every 12 weeks (±7 days) from last dose by clinic visit or telephone to assess survival and the use of alternative antineoplastic therapy and stem cell transplant, up to 1 year after the first dose of the last subject enrolled. Subjects will be contacted until death, subject withdrawal, lost to follow-up, or study termination by the Sponsor, 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. Treatment Discontinuation

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

- Subject has confirmed progressive disease.
- Subject has an intercurrent illness or AE that prevents further study drug administration.
- Subject decides to withdraw from study.
- Subject requires a prohibited concomitant medication.
- 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 (with the exception of withdrawal of consent) will undergo a Safety Follow-Up visit and be followed for progression and survival.

The Investigator should notify the Sponsor within 24 hours if a subject discontinues study treatment due to disease progression and should provide documentation of disease progression for review by the Sponsor's Medical Monitor. 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. Study Exit/Withdrawal

Exit 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 Statistical Analysis Plan (SAP).

10.1. General Considerations

Part 1 of this study is a dose-escalation study. All safety and efficacy assessments will be summarized by dose group.

Part 2 of this single-arm study is designed to assess the efficacy and safety of ibrutinib in combination with multiple anti-tumor agents (defined in Section 5) in subjects with relapsed or refractory de novo non-GCB DLBCL. Non-GCB subtype subjects will be enrolled by IHC but the primary analysis will be in ABC subjects only as classified by GEP.

10.1.1. Response Assessment

Response assessments will be made by investigators. Tumor response will be assessed by the investigator using the revised International Working Group Response Criteria for NHL (Cheson 2007).

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

10.1.2. Safety Monitoring

This study will be monitored in accordance with the Sponsor's Pharmacovigilance Committee procedures. AEs and serious adverse events (SAEs) will be reviewed internally on an ongoing basis to identify safety concerns. A Dose Level Review Committee will evaluate safety data from the dose escalation portion of Part 1. 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 and Sub-Investigators.

10.2. Definition of Analysis Populations

The following definitions will be used for the efficacy and safety analysis sets. Analyses in Part 1 will be performed across subtypes of DLBCL (eg, GCB, non-GCB, PMBL, ABC). Part 2 analyses will be performed on the ABC subtype of DLBCL, with sensitivity analyses for the efficacy endpoints performed using the non-GCB subtype of DLBCL as determined by IHC.

- **All-treated analysis population:** All-treated analysis population will include subjects who have enrolled in the study and received at least 1 dose of any of the study treatments. This is the primary analysis population for efficacy endpoints for Part 1.
- **Safety analysis population:** All enrolled subjects who have received at least 1 dose of any of the study treatments. Safety analysis will be performed using the safety population.
- **Response evaluable population:** All enrolled subjects who have received at least 1 dose of any of the study treatments and have measurable disease at baseline and have at least one adequate post treatment disease assessment by investigator before the start of subsequent anti-cancer therapy. This is the analysis population for sensitivity analyses for the efficacy endpoints.
- **Combined efficacy population:** All enrolled analysis population includes subjects who have received at least 1 dose of any of the study treatments and were enrolled in the MTD/MAD Part 1 or Part 2. This population is the subset of the all treated analysis population that will be used to analyze all efficacy endpoints for Part 2.

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 burden, 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 Part 1

The efficacy endpoints for Part 1 of this trial are overall response (ORR) defined as the proportion of subjects who achieve either a CR or a PR according to the International Working Group Response Criteria for NHL as assessed by the investigators (Cheson 2007). The ORR of Part 1 and its 95% 2-sided exact confidence interval (CI) will be calculated for the All Treated Population of Part 1b.

10.3.3. Primary Efficacy Endpoint for Part 2

The primary efficacy endpoint for Part 2 is the ORR (CR+PR) as assessed by investigators. The ORR will be calculated for the combined efficacy population of Part 2 for each subtype of DLBCL as determined by GEP. The corresponding 95% 1-sided exact CI will be derived for each subtype. If the lower bound of the CI around the ORR is greater than or equal to 60% for the ABC subtype of DLBCL, then the hypothesis that the ORR of ibrutinib combination treatment in the ABC subtype of DLBCL is equal to or lower than 60% will be rejected at the $\alpha = 5\%$ level.

10.3.4. Secondary Efficacy Endpoints for Part 2

The secondary efficacy endpoints of Part 2 of this trial are DOR, PFS and OS.

10.3.4.1. Duration of Response

For subjects achieving objective response as assessed by investigators, their DOR as assessed by investigators 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 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).

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

10.3.4.2. Progression-free Survival

Progression-free survival will be measured as time from first study drug administration to disease 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 and before the initiation of alternative anticancer therapy.

Progression-free survival will be calculated using assessments by investigators. Kaplan-Meier methodology will be used to estimate event-free curves and corresponding quartiles (including the median) using the combined efficacy population.

10.3.4.3. Overall Survival

The duration of overall survival (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 of the last known to be alive.

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

10.3.5. Exploratory/Sensitivity Analysis

Exploratory subgroup analyses and sensitivity analyses using the non-GCB subtype of DLBCL as determined by IHC from the combined efficacy population will be conducted focusing on key efficacy parameters such as ORR, DOR, PFS and OS.

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 (ibrutinib, lenalidomide, and DA-EPOCH-R).

AEs 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

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. Ibrutinib and PCI-45227 data will be listed for all subjects with available plasma concentrations. Subjects will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study agent; concentration data not sufficient for PK parameter calculation due to missing PK draws at multiple visits; or early discontinuation from the study).

Derived PK parameters may be subjected to further explore PK/pharmacodynamic correlation between exposure and relevant clinical or biomarker information.

Bioanalytical data from this study may also 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 using NONMEM. Available subject characteristics (demographics, laboratory variables, genotypes, etc) will be tested as potential covariates affecting PK parameters. The results of the population PK analyses (if performed) will be presented in a separate report.

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.

Additional analysis details will be provided in the SAP.

10.4. Handling of Missing Data

General Considerations: Subjects lost to follow-up (or who dropped out) will be included in statistical analyses up to the point of their last evaluation.

10.5. Determination of Sample Size

The planned sample size for Part 2 is approximately 26 subjects. The main analysis will be the comparison of the response rate within the ABC subtype of DLBCL to the ORR of a historical control of 60%. In subjects with relapsed and refractory DLBCL, EPOCH was observed to have a response rate of between 68–75% (Gutierrez 2000, Jermann 2004), and since the response rate is expected to be lower in the more aggressive ABC subtype, an ORR of 60% has been selected for the historic control value. A Part 2 sample size of 26 subjects will have 81% power to test the null hypothesis that ORR will be ≤60% versus the alternative hypothesis that ORR will be ≥85% at the 1-sided significance level α=5% when the exact test method is used.

10.6. Safety Analysis

Analysis of safety data will be conducted on the safety population, which includes enrolled subjects who receive at least 1 dose of any of the study treatments. 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 not specified. 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, survival status, ECOG performance status, vital sign measurements, and clinical laboratory results.

The safety variables to be analyzed include AEs, clinical laboratory test results (hematology and chemistry), physical examination findings, and vital sign measurements. Exposure to ibrutinib and other study drugs 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

AE 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 Investigators to identify non-hematological adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are those AEs 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 severe or a serious AE.

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 7.1.2. 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.

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 subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an 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 AE; rather it may be the cause of an AE. AEs that occur due to disease progression must be reported as all other treatment-emergent AEs. "Disease progression" should never be an AE term.

AEs 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 after the ICF is signed and for 30 days following the last dose of study drug.

- 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 an AE:

- **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.
- **Preplanned or elective hospitalization:** A hospitalization planned before signing the ICF is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.
- **Diagnostic testing and procedures:** Testing and procedures should not 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 also not be considered an AE. Subjects with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.
- **DA-EPOCH induced neutropenia or thrombocytopenia:** The dose-adjustment paradigm was designed to produce a period of shallow neutropenia resulting in ANC nadirs of between 0.499 and 0.1×10^9/L in 34% of cycles, with more severe neutropenia (ANC $< 0.1 \times 10^9$/L) in 15% of cycles (Wilson, 2002). Therefore, EPOCH-induced neutropenia or thrombocytopenia should not be recorded as an AE, unless neutropenia is accompanied by fever (febrile neutropenia) or infection, or if thrombocytopenia is accompanied by bleeding, or the event meets criteria for serious.

11.1.2. Serious Adverse Event

An SAE 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 subject was at risk of death at the time of the event. It does not refer to an event that 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 inpatient hospitalization >24 hours or prolongation of existing hospitalization

- results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions)
- is a congenital anomaly/birth defect
- is an important medical event that may not result in death, be immediately life-threatening or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject, or subject may require intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsion that does not result in hospitalization; or development of drug dependency or drug abuse.

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

11.1.3. 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 CTCAE (version 4.03) will be used for grading the severity (intensity) of AEs. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE v4.03, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences that are usually transient, requiring no special treatment, and do not interfere with the subject's daily activities.
- Grade 2 (Moderate AE) – experiences that introduce some level of inconvenience or concern to the subject, and that may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
- Grade 3 (Severe AE) – experiences that 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 that cause the subject to be in imminent danger of death.
- Grade 5 (Death related to AE) – experiences that 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 that are observed or reported during the study, as outlined in the prior sections, are recorded on the eCRF. All SAEs also must be reported on an SAE Worksheet and submitted to the Sponsor (see Section 11.2.2.1)

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 serious AE should be recorded on the serious AE page of the eCRF.

11.2.2. All Adverse Events

All subjects who receive at least 1 dose of study drug(s) will be considered evaluable for toxicity. All AEs (with the exception of disease progression) and special reporting situations, whether serious or non-serious, will be recorded in the source documents from the time a 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. All Grade 3 or Grade 4 adverse events considered related to study drug must be followed until recovery to baseline or Grade ≤1. The unresolved aforementioned events will be followed for a maximum of 6 months.

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 (e.g., 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 AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

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

11.2.2.1. Expedited Reporting Criteria for Serious Adverse Events

All SAEs occurring during the study must be reported to the Sponsor contact person within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the Sponsor using the SAE Form/MedWatch or Council for International Organizations of Medical Sciences (CIOMS), which must be completed by a physician from the study site, and submitted to the Sponsor within 24 hours of when the investigator becomes 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 the sponsor within 24 hours of awareness irrespective of seriousness (ie, serious and nonserious AEs) 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 hemorrhagic event that is Grade 3 or greater in severity or that results in one of the following: intraocular bleeding causing loss of vision, any hemorrhagic event which results in the need for a transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization, or prolongation of hospitalization.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 11.2.3 above.

11.2.3.2. Intracranial Hemorrhage

Any intracranial hemorrhage AE, including subdural hematoma/hemorrhage, epidural hematoma/hemorrhage and intracerebral hemorrhage, of any grade severity, will be captured as an AESI 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 for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

11.2.5. Pregnancy

All initial reports of pregnancy must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, stillbirth, and congenital anomaly) are considered SAEs and must be reported in a timely fashion. Any subject who becomes pregnant during the study must discontinue further study treatment. Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

11.3. Safety Cohort Review Committee

A Safety Cohort Review Committee (SCRC) will review safety data in Part 1 after at least 3 subjects are enrolled and complete one cycle of therapy. 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 and Sub-Investigators. All investigators who enrolled subjects in the safety cohort must agree on the course of action based on the safety findings. At least 2/3 of these investigators who enrolled subjects in the trial must attend the committee meeting, the rest can provide their vote by e-mail or other correspondence. Based on the safety findings and recommendations of the SCRC, enrollment may continue at the current dose level, commence with the next dosing level of lenalidomide, be halted, or undergo modifications in dose until the MTD is established.

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 the Sponsor or its authorized representative before entering subjects in this study: (1) a copy of the IRB/REB/IEC letter that grants formal approval; and (2) a copy of the IRB/REB/IEC-approved ICF.

12.3. Informed Consent

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

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

12.4. Quality Control and Quality Assurance

Sponsor shall implement and maintain quality control and quality assurance procedures to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2008) and all revisions thereof, and in accordance with 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).

12.5. Protected Subject Health Information Authorization

Information on maintaining subject confidentiality in accordance to individual local and national subject privacy regulations must be provided to each subject as part of the informed consent process (refer to Section 12.3), either as part of the ICF or as a separate signed document (for example, in the US, a site-specific HIPAA consent may be used). The Investigator or designee must explain to each subject that for the evaluation of study results, the subject's

protected health information obtained during the study may be shared with the Sponsor and its designees, regulatory agencies, and IRBs/REBs/IECs. The Sponsor 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.

12.6. Study Files and Record Retention

The Investigator must keep a record that lists all subjects considered for enrollment (including those who did not undergo screening) 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 CRFs, and documentation of CRF corrections, SAE forms transmitted to the Sponsor, or designee, 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 the Sponsor and obtain written approval from the Sponsor 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.

The Sponsor must be notified in advance of, and the Sponsor 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 the Sponsor to store such documents in sealed containers away from the study site so that they can be returned sealed to the Investigator for audit purposes.

12.7. Case Report Forms and Record Maintenance

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 CRFs designed for this study according to the completion guidelines that will be provided. The Investigator will ensure that the CRFs are accurate, complete, legible, and completed as soon as reasonably possible, after completion of each subject's visit. At all times, the Investigator has final responsibility for the accuracy and authenticity of all clinical data.

The CRFs exists within an electronic data capture (EDC) system with controlled access managed by the Sponsor or its authorized representative for this study. Study staff will be appropriately trained in the use of CRFs 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 CRFs 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.

12.8. Investigational Study Drug Accountability

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

Accountability records for ibrutinib and any comparator must be maintained and readily available for inspection by representatives of the Sponsor 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:

1. Study identification number (PCYC-1124-CA)
2. Subject identification number
3. Lot number(s) of ibrutinib or comparator dispensed for that subject
4. Date and quantity of drug dispensed
5. Any unused drug returned by the subject

At study initiation, the monitor will evaluate and approve the site's procedure for investigational product disposal/destruction to ensure that it complies with the Sponsors' requirements. If the site cannot meet the Sponsors' requirements for disposal/destruction, arrangements will be made between the site and the Sponsor or its representative, for return of unused investigational product. Before disposal/destruction, final drug accountability and reconciliation must be performed by the monitor.

All study supplies and associated documentation will be regularly reviewed and verified by the monitor.

12.9. Study Monitoring/Audit Requirements

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

To assure the accuracy of data collected in the CRFs, 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. 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 the Sponsor, its designated agents and authorized employees of the appropriate regulatory authority to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

The Sponsor 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, the Sponsor will be available to assist in the preparation. All pertinent study data should be made available as requested to the regulatory authority for verification, audit, or inspection purposes.

12.10. Investigator Responsibilities

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

12.11. Sponsor Responsibilities

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

12.12. Financial Disclosure

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

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

12.13. Liability and Clinical Trial Insurance

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

If a bodily injury is sustained, resulting directly from the use of the study drug, the Sponsor will reimburse for reasonable physician fees and medical expenses necessary for treatment of only the bodily injury which is not covered by the subject's medical or hospital insurance, provided that the injury is not due to a negligent or wrongful act or omission by the Investigator/ study staff. The ICF will include a description of this reimbursement policy, incorporating country-specific national regulations and/or local laws. Financial compensation for lost wages, disability or discomfort due to the study is not available.

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

12.14. Protocol Amendments

The Sponsor will 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 the Sponsor 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 effected without the mutual agreement of the Investigator and the Sponsor.

12.15. Publication of Study Results

The Sponsor 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, the Sponsor reserves the right to preview all manuscripts and abstracts related to this study, allowing the Sponsor 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 the Sponsor.

12.16. Study Discontinuation

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

12.17. Study Completion

The study is expected to be completed approximately 1 year after the last subject is enrolled and receives the first dose.

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14. APPENDICES

Appendix A: Schedule of Assessments

Study Drug Administration

Study Cycles (21 days each)	**1–6**						
Study Cycle Week	**1**						
Study Cycle Days	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study Drug Administration							
Ibrutinib PO (Days 1–7 of each cycle)	X	X	X	X	X	X	X
Lenalidomide (Days 1–7 of each cycle) [a]	X	X	X	X	X	X	X
Rituximab (Day 1 of each cycle)	X						
Etoposide, Doxorubicin, Vincristine Days 1–4 of each cycle	X	X	X	X			
Prednisone (Days 1–5 of each cycle)	X	X	X	X	X		
Cyclophosphamide (Day 5 of each cycle)					X		
Pegfilgrastim[b]						X	

Footnote:

a. Lenalidomide is not dosed for patients in Dose Level -1 or 1.

b. Pegfilgrastim is administered on Day 6 of each cycle with a +48 hour window and can be self-administrated.

Schedule of Assessments

Study Cycles (21 days each)	Screening	1							2–6						Response Assessment[a]	Safety Follow-up
Study Cycle Week		1					2	3	1					2		
Study Cycle Days		1	2	3	4	5	8	15	1	2	3	4	5	8	Cycles 3, 6, q12w Yr 1, q16w Yr 2, q26w Yr 3 until PD	30 days after last dose of study drug
Visit Window	-28 days															±7 days
Procedures																
Informed Consent	x															
Tumor Sample for Eligibility[b]	x															
Medical History	x	x														
Adverse Event Assessment [c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant Medications[d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical Exam[e]	x	x							x						x	x
Venous Thromboembolism Risk Assessment[t]	x															
Vital Signs[f]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECOG Status	x	x							x						x	x
12-lead ECG[g]	x															x
Echocardiogram	x	If clinically indicated (eg, subjects with palpitations, lightheadedness)														
Bone Marrow Aspiration/Biopsy[h]	x	only required to confirm complete response														
Optional Tumor Biopsy [i]	x															
Laboratory Assessments																
Hematology[j]	x	x					x	x	x					x	x	x
Serum Chemistry[k]	x	x					x	x	x					x	x	x
Hepatitis Serologies[l]	x															
Pregnancy Test [m]	x	x						x	x					x		x
Coagulation Parameters (PT, PTT, INR)	x															x
T/B/NK Cell Count[n]		x							x						x	x
Biomarker Blood Sample[o]		x					x	x	x					x	x	x
PK [p]						x										
Urinalysis[q]	x															x
Radiological Exams																
CT Neck, Chest, Abdomen, Pelvis[r]	x														x	
PET or PET/CT[r]	x														x	
Survival Status[s]																

Abbreviations: CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; INR= International Normalized Ratio; PD=progressive disease; PET=positron emission tomography; PO=oral; PT=prothrombin time; PTT=partial thromboplastin time; Yr=year; DLT=dose-limiting toxicities

Footnotes:

a. Response Assessments occur at the end of Cycle 3 (-4 days of Cycle 4 Day 1) and after Cycle 6 (±4 days) during treatment; post treatment Q12 weeks in year 1, Q16 weeks in year 2, and Q26 weeks in year 3 (±7 days) until PD or study end.

[b.] Tumor Tissue: Either unstained slides (minimum of 10 slides, preferably 15-30 or a paraffin block) must be sent to the central laboratory for determination of DLBCL subtype within 3 weeks of enrollment. 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.

[c.] Adverse Events: Adverse events are collected from consent through 30 days after the last dose of study drug. DLT assessment window is Part 1 starting from Cycle 1 Day 1 to predose Cycle 2 Day 1 (=22 days). Laboratory samples drawn pre-dose on Cycle 2 Day 1 need to be reviewed prior to dosing.

[d.] Concomitant medications are collected from within 14 days before the first dose through 30 days after the last dose of study drug.

[e.] Physical Exam: A complete physical examination performed at Screening, Day 1 of each Cycle, Response Assessments, and Safety Follow-up will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, lymphatic system. The musculoskeletal and nervous systems may be included if clinically indicated. A symptom-directed physical exam may be perfomed at all other visits.

[f.] 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.

[g.] ECG: 12-lead ECG will be done in triplicate (≥1 minute apart). The calculated QTc average of the 3 ECGs must be <470 msec for eligibility. Subjects should be in a supine position and resting for at least 10 minutes before ECGs. Unscheduled ECG's may be performed at the investigator's discretion, particularly in subject with arrhythmic symptoms (eg, palpitations, lightheadedness) or new dyspnea.

[h.] Bone Marrow Biopsy: A unilateral bone marrow aspirate and biopsy must be obtained at screening or up to 28 days before the first administration of study drug. 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/biopsy required for this study, provided the biopsy/aspirate was done < 28 days of first dose of study drug. Thereafter, bone marrow aspirate and biopsy will only be required to confirm any complete remission if result was positive at screening.

[i.] Optional Tumor Biopsy: Where possible, tumor biopsies will be obtained by core needle biopsy or surgery prior to treatment in Cycle 1 only. Subjects with partial or complete response who later develop recurrent disease are encouraged to have an additional biopsy at time of recurrence. Snap freeze and store tissue biopsies at -80°C.

[j.] During Cycles 1-6, modified hematology blood draws should include at a minimum, white blood cells, neutrophils, bands if present, and platelets, and should be checked twice weekly on days 4 or 5, 11 or 12, 15, and 18 or 19 (e.g. on Monday (day 1) & Thursday or Friday (Day 4 or 5), or Tuesday (Day 1) & Friday or Saturday (Day 4 or 5) to assure that counts are checked every 3 to 4 days).

[k.] Serum chemistry: 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

[l.] Hepatitis serologies include Hepatitis C antibody, Hepatitis B surface antigen, Hepatitis B surface antibody and Hepatitis B core antibodyViral load by PCR must be confirmed negative in equivocal cases for subjects who are Hepatitis B core antibody positive, Hepatitis B surface antigen positive, Hepatitis B surface antibody positive (unless immunized) or Hepatitis C antibody positive.

[m.] Pregnancy Test: Must be done in accordance with Celgene Revlimid REMS™ program guidelines and protocol Section 7.1.2.4 for women of childbearing potential only.

[n.] T/B/NK cell count (ie, CD3+, CD4+, CD8+, CD16/56+, CD19+) done at predose on Day 1 of Cycle 1 and then on Day 1 of Cycles 2, 3, and 6; at Response Assessments post treatment period and at Safety Follow-up visit.

[o.] Biomarker Blood Sample: done at predose Cycle 1 Day 1, Day 8 and Day 15; Cycle 2 Day 1 and Day 8, Cycle 3 Day 1, Cycle 6 Day 1, at each posttreatment response assesment and at Safety Follow-up visit.

[p.] Phamacokinetic samples will be drawn for all subjects in Part 2 of protocol according to the schedule in Table 17.

[q.] Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose

[r.] CT and PET or PET/CT: A CT scan (with contrast unless contraindicated) of the neck, chest, abdomen, and pelvis and any other disease sites (eg, extremity) and a PET or PET/CT scan are required for the pretreatment tumor assessment within 21 days of the first dose. During treatment, CT scans will be done for tumor assessments within 4 days of the end of Cycles 3, (-4 days of Cycle 4 Day 1) and ±4 days of the end of Cycle 6 and then at each response assessment time point thereafter, until PD or use of alternative antineoplastic therapy. PET or PET/CT is mandatory to confirm a CR. In the event that CT contrast is contraindicated, MRI of the abdomen and pelvis and CT of the chest and neck without contrast 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.

[s.] Survival status is to assess survival and the use of alternative antineoplastic therapy and stem cell transplant up to 1 year after the first dose of the last subject enrolled. Survival status will be assessed approximately every 12 weeks (±7 days) from last dose.

[t.] Refer to Section 7.1.1.7 for a description of the venous thromboembolism assessment

Appendix B: ECOG Status Scores

Status	Eastern Cooperative Oncology Group (ECOG) Performance Status**
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

** Oken, 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.

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Appendix C: Inhibitors and Inducers of CYP3A

Inhibitors of CYP3A are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to Section 6.2.1.1 on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib.

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
TELITHROMYCIN	Pioglitazone
Moderate inhibitors:	Rifabutin
aprepitant	Rifampin
erythromycin	St. John's Wort
diltiazem	Troglitazone
fluconazole	
grapefruit juice	
Seville orange juice	
verapamil	
Weak inhibitors:	
cimetidine	
All other inhibitors:	
amiodarone	
NOT azithromycin	
chloramphenicol	
boceprevir	
ciprofloxacin	
delaviridine	
diethyl-dithiocarbamate	
fluvoxamine	
gestodene	
imatinib	
mibefradil	
mifepristone	
norfloxacin	
norfluoxetine	
star fruit	
telaprevir	
troleandomycin	
voriconazole	

Source: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Appendix D: Guidelines for Establishing Response to Treatment

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	If infiltrate present at screening, infiltrate cleared on repeat biopsy; if indeterminate by morphology, immune-histochemistry 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; ≥1 PET positive at previously involved site (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 specified
SD	Failure to attain CR/PR or progressive disease	(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		

Abbreviations: CR = complete remission, CT = computed tomography, FDG = [^{18}F]fluorodeoxyglucose, PET = positron emission tomography, PR = partial remission, SD = stable disease, SPD = sum of the product of the diameters

*Change in target lesion measurement by CT, unless MRI used as the assessment modality for lesions in anatomical locations not amenable to CT

Progressive disease for Non-Hodgkin's lymphoma is characterized by any new lesion or increase by ≥ 50% of previously involved sites from nadir for example:

- Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of >1 node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis
- Lesions PET positive if FDG-avid lymphoma or PET positive before therapy
- >50% increase from nadir in the SPD of any previous lesions in the liver or spleen
- New or recurrent involvement in the bone marrow
- An increase of ≥50% in blood lymphocytes with ≥5 x 10^9/L B-cells only in setting of enlarging lymph node, liver, or spleen (note: an isolated elevation of white blood cell count by itself will not be considered progressive disease unless subject becomes symptomatic from this).

Appendix E: New York Heart Association Functional Classification

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.
Class	**Objective Assessment**
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

Appendix F: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of 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®.

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 3 months 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 3 months 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 3 months 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.
- 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.