NCT03145480

IST PROTOCOL

TITLE:	Two-arm phase II trial exploring the use of the targeted agents ibrutinib and obinutuzumab for the treatment of patients with a diagnosis of Richter's Transformation (RT) or Richter's Syndrome (RS)
PROTOCOL NUMBER:	20016
STUDY DRUG:	Ibrutinib (PCI-32765), Obinutuzumab (GA101)
INVESTIGATOR SPONSOR:	Jacqueline Barrientos, MD
DATE FINAL:	April 03, 2017
DATE AMENDED #1:	21-Jun-2018

TABLE OF CONTENTS

TABLE OF CONTENTS **3**
LIST OF APPENDICES **7**
LIST OF IN-TEXT TABLES AND FIGURES **7**
SYNOPSIS **8**
ABBREVIATIONS **15**
1. BACKGROUND **16**
1.1. Disease/Histology 16
1.1.1. Treatment Options 18
1.1.2. Role of BTK in Disease/Histology 19
1.2. Investigational Product Name and Description 19
1.3. Summary of Nonclinical Data 20
1.3.1. Pharmacology 21
1.3.2. Toxicology 21
1.3.2.1. Carcinogenesis, Mutagenesis, Impairment of Fertility 21
1.4. Summary of Clinical Data 22
1.4.1. Pharmacokinetics and Product Metabolism 22
1.5. Summary of Clinical Safety 23
1.5.1. Risks 25
1.5.2. Bleeding-related events 25
1.5.3. Atrial Fibrillation 25
1.5.4. Cytopenias 25
1.5.5. Diarrhea 26
1.5.6. Infections 26
1.5.7. Non-Melanoma Skin Cancer 26
1.5.8. Rash 26
1.5.9. Lymphocytosis and Leukostasis 26
1.5.9.1. Tumor Lysis Syndrome 27
1.5.9.2. Interstitial Lung Disease (ILD) 27
1.6. Obinutuzumab Background 28
1.6.1. Structure and Mechanism of Action of Obinutuzumab 28
1.6.2. Clinical Experience with Obinutuzumab 28
1.6.2.1. Tolerability and Efficacy of Obinutuzumab in Chronic Lymphocytic Leukemia 28
1.6.3. Overview of Safety of Obinutuzumab 32
1.6.4. Risks Associated with Obinutuzumab Therapy 35
1.6.4.1. Hepatitis B Virus Reactivation 35
1.6.4.2. Progressive Multifocal Leukoencephalopathy 36
1.6.4.3. Infusion-Related Reactions 36
1.6.4.4. Tumor Lysis Syndrome 36
1.6.4.5. Infection 37
1.6.4.6. Neutropenia 37
1.6.4.7. Thrombocytopenia 37
1.6.5. Summary of Pharmacokinetic and Pharmacodynamic Data for Obinutuzumab 37
1.7 Overview of Safety of CHOP 38

Risks and side effects related to Cyclophosphamide include: 38
(Table Version Date: May 28, 2013) 38
Risks and side effects related to Doxorubicin include: 39
(Table Version Date: October 24, 2013) 39
Risks and side effects related to Vincristine include: 40
(Table Version Date: May 28, 2013) 40
Risks and side effects related to Prednisone include: 41
(Table Version Date: June 24, 2013) 41
REPRODUCTIVE RISKS: 41
1.8. Study Rationale 42
2. STUDY OBJECTIVE 43
2.1. Primary Objective 43
2.2. Secondary Objectives 43
2.3. Exploratory Objective(s) 43
3. STUDY DESIGN AND TREATMENT 44
3.1. Overview of Study Design 44
3.1.1. Study Schema and Design Overview 45
3.2. Study Design Rationale 45
4. SUBJECT SELECTION 47
4.1. Inclusion Criteria 47
4.2. Exclusion Criteria 48
5. TREATMENT OF SUBJECTS 50
5.1. Study treatment 50
5.2. Study Medication 50
5.2.1. Ibrutinib 50
5.2.1.1. Dose and Administration 51
5.2.1.2. Overdose 51
5.2.1.3. Dose Modification for Adverse Reactions 51
5.2.2. *Obinutuzumab* 53
5.2.3. Obinutuzumab 53
5.2.3.1. Formulation 53
5.2.3.2. Storage 53
5.2.4. Dosage and Administration 54
5.2.4.1. Premedication Requirements 55
5.2.4.2. *Obinutuzumab* Dosing 56
CYCLE AND DAY OF ADMINISTRATION 56
DOSE OF OBINUTUZUMAB 56
CYCLE 1 56
5.2.5. Dosage Modification/Toxicity Management 57
5.2.5.1. Assessment of Hematologic Toxicities 57
5.2.5.2. Dosage Modifications 57
5.2.5.3. Administration of Granulocyte Colony-Stimulating Factor 57
5.2.5.4. Hepatitis B Virus Reactivation 58
5.2.5.5. Management of Infusion-Related Reactions and Anaphylaxis 58

5.3. Concomitant and Excluded Therapies 59
5.3.1. Concomitant Therapy....59
5.3.1.1. Prophylaxis for Tumor Lysis Syndrome....59
5.3.1.2. Infections Prophylaxis 59
5.3.1.3. Other Concomitant Medications....60
5.4. Criteria for Permanent Discontinuation of Study Drug 60
5.5. Obinutuzumab-Specific Criteria 60
5.6. General Criteria....60
6. CONCOMITANT MEDICATIONS/PROCEDURES 60
6.1. Permitted Concomitant Medications....60
6.2. Medications to be Used with Caution....61
6.2.1. CYP3A- Inhibitors/Inducers 61
6.2.2. Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib 63
6.2.3. QT Prolonging Agents 63
6.2.4. Antiplatelet Agents and Anticoagulants 64
6.3. Prohibited Concomitant Medications 64
6.4. Guidelines for Ibrutinib Management with Surgeries or Procedure 64
6.4.1. Minor Surgical Procedures 64
6.4.2. Major Surgical Procedures....64
6.4.3. Emergency Procedures....65
7. STUDY EVALUATIONS 65
7.1. Screening/Administrative 65
7.1.1. Informed Consent....65
7.1.2. Confirm Eligibility....65
7.1.3. Prior and Concomitant Medications 65
7.1.4. Adverse Events 65
7.1.5. Physical Examination....66
7.1.6. ECOG....66
7.1.7. Vital Signs....66
7.2. Clinical Laboratory Assessments....66
7.2.1. Hematology....66
7.2.2. Chemistry (Serum)....66
7.2.3. Coagulation Studies 66
7.2.4. Hepatitis Serologies 67
7.2.5. β2 -microglobulin 67
7.2.6. Pregnancy Test....67
7.2.7. Flow cytometry surface membrane phenotype 67
7.2.8. IGHVDJ Rearrangement DNA Sequencing 67
7.3. Diagnostics/Procedures....67
7.3.1. ECG....67
7.3.2. Pathological Diagnosis and Bone Marrow Sampling 68
7.4. Biomarkers....68
7.4.1. Genetic and Molecular Prognostic Markers 68
7.5. Efficacy Evaluations 70
7.5.1. Radiographic Imaging....70

7.5.1.1. Radiographic Assessment 70
7.6. Sample Collection and Handling 71
8. STUDY PROCEDURES 71
8.1. Screening Phase 71
8.1.1. Screening Visit 71
8.2. Treatment Phase 71
8.2.1. Cycle 1 Day 1 71
8.2.2. Cycle 1 Day2 72
8.2.3. Cycle 1 Day 3 72
8.2.4. Cycle 1 Day 8 72
8.2.5. Cycle 1 Day 15 72
8.2.6. Cycle 1 Day 28 73
8.2.7. Cycle 2 Day 1 73
8.2.8. Cycle 2 Day 28 74
8.2.9. Cycles 3 – 6, Day 1 74
8.2.10. Cycles 3-7, Day 1 (±3days) 74
8.2.11. Cycles 3-7, Day 15 (±3days) 75
8.2.12. Cycles 8-12, Day 1 (±3days) 75
8.2.13. Suspected PD Visit 75
8.2.13.1. End-of-Treatment Visit 76
8.3. Follow-up Phase 76
9. SUBJECT WITHDRAWAL FROM TREATMENT OR STUDY 77
9.1. Withdrawal from Study Treatment 77
9.2. Withdrawal from Study 77
10. STATISTICAL METHODS AND ANALYSIS 78
10.1. General Consideration 78
10.2. Subject Information - Assignment to ARM A vs. ARM B 78
10.3. Endpoints 78
10.3.1. Primary Endpoint 78
10.3.2. Secondary Endpoints 79
10.3.3. Exploratory Endpoints 80
10.4. Sample Size Determination 80
10.5. Safety Analysis 80
11. DATA AND SAFETY MONITORING PLAN (DSMP) 80
11.1. Risk Assesssment 81
11.2. Ibrutinib Risk Assessment 81
11.3. Obinutuzumab Risk Assessment 81
12. ADVERSE EVENT REPORTING 82
12.1. Definitions 82
12.1.1. Adverse Events 82
12.1.2. Serious Adverse Events 84
12.1.3. Severity Criteria (Grade 1-5) 84
12.1.4. Causality (Attribution) 85
12.2. Expected and Unexpected Adverse Events 86

12.3. Procedures for Eliciting, Documenting and Reporting of Adverse Events and Serious Adverse Events by Investigators 86
12.3.1. Eliciting Adverse Events 86
12.3.2. Specific Instructions for Recording Adverse Events 87
12.3.2.1. Diagnosis versus Signs and Symptoms 87
12.3.3. Assessment of Adverse Events 87
12.3.4. Adverse Event Reporting 87
12.3.5. Adverse Event Reporting Period 87
12.3.6. Pregnancy 88
12.3.7. Other Malignancies 89
12.3.8. Eye-Related Adverse Events 89
12.3.9. Adverse Events of Special Interest (AESI) 89
12.3.9.1. Major Hemorrhage- Ibrutinib Adverse Event of Special Interest 90
12.3.10. Reporting Requirements for Serious Adverse Events 90
12.3.10.1. Post-Study Adverse Events ..... **Error! Bookmark not defined.**
12.3.10.2. Reconciliation ..... **Error! Bookmark not defined.**
12.4. Safety Reporting Requirements for IND Exempt Studies 92
13. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS 92
13.1. Protocol Amendments 92
13.2. Publication of Study Results 92
13.3. Study Discontinuation 92
13.4. Study Close-Out ..... **Error! Bookmark not defined.**
14. RETENTION OF RECORDS 93
15. REFERENCES 94
16. APPENDICES 101

LIST OF APPENDICES

Appendix 1. Schedule of Assessments 102
Appendix 2. ECOG Status Scores 107
Appendix 3. Inhibitors and Inducers of CYP3A 100
Appendix 4. Guidelines for Establishing Response to Treatment 101
Appendix 5. Correlative Studies 104
Appendix 6. Child-Pugh Score 105
Appendix 7. Cumulative Illness Rating Score 106
Appendix 8. FACIT Fatigue Questionnaire 113

LIST OF IN-TEXT TABLES AND FIGURES

Tables

Table 1. Ibrutinib Dose Modifications 45

Table 2. Obinutuzumab Dosing Schedule ……45

Table 3. Management of Hepatitis B Reactivation ……..49

Figures

Figure 1. Study Design……38

SYNOPSIS

Study Title:	Two-arm phase II trial exploring the use of the targeted agents ibrutinib and obinutuzumab for the treatment of patients with a diagnosis of Richter's Transformation (RT) or Richter's Syndrome (RS)
Protocol Number:	**20016**
Study Phase:	2
Study Duration:	2 years
Investigational Product and Reference Therapy:	• Ibrutinib will be supplied as 140 mg hard gelatin capsules for oral (PO) administration. Additional Drug: • Obinutuzumab (GA-101)
Objectives:	**Primary Objective:** • To determine the efficacy of combining Ibrutinib with obinutuzumab (with or without "CHOP" chemotherapy regimen) as measured by overall response rate (ORR). **Secondary Objectives**: • To assess the safety of Ibrutinib in combination with obinutuzumab as measured by the incidence of prolonged hematologic toxicity in cycle 1 in subjects with a diagnosis of Richter's Transformation (RT), hematologic improvement, progression-free survival (PFS), overall survival (OS), and health-related quality of life (HRQL) measures. • To identify and correlate potential markers predictive of response to the combination therapy and associate pharmacogenetic findings to response and toxicity.
Study Design:	We propose a design to evaluate two study arms, a "**fit"** and a "**frail"** cohort. Each group will follow an independent but parallel

	design. This is a nonrandomized open-label Phase II study of Ibrutinib 560mg daily in combination with Obinutuzumab, 100 mg on day 1 and 900 mg on day 2 of Cycle 1, and 1000 mg on days 8 and 15 of Cycle 1, and 1000 mg on day 1 of Cycles 2–6 in subjects with RT. The addition of the chemotherapy regimen known as "CHOP" (i.e., cyclophosphamide, doxorubicin, vincristine, and prednisone) will depend on the fitness of the subject. The primary objective of the study is to determine the efficacy of this combination regimen in patients with a diagnosis of Richter's Transformation (RT). RT patients are a subtype of chronic lymphocytic leukemia (CLL) patients that develop a more rapidly progressive disease with extremely poor outcomes when treated with chemoimmunotherapy regimens. There is currently no standard of care to treat this condition once a Richter's transformation occurs as life expectancy is only a matter of months once the diagnosis is established. Efficacy for this combination regimen will be assessed by measuring overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). Patients who have no evidence of progressive disease after cycle 3 will be treated for up to three additional 28-day cycles of the infusion regimen based on tolerability and lack of evidence of progressive disease. Ibrutinib will be continued indefinitely until progression of disease or until unacceptable toxicity develops, similar to its current approved usage in CLL and lymphoma patients. Response rates will be reported following completion of all therapy, but the primary efficacy endpoint is ORR following at least 2 cycles of treatment. Up to 50 subjects will be screened for enrollment in the combination treatment groups: ▪ Up to 20 patients will receive the combination ibrutinib and obinutuzumab alone (**frail** patients) and ▪ Up to 23 patients will receive ibrutinib and obinutuzumab in combination with the CHOP regimen (**fit** patients). All enrolled subjects will receive up to 6 cycles of infusion therapy (Obinutuzumab with or without CHOP). Ibrutinib will be given daily continuously until progression of disease or toxicities as it is approved for use in patients with a CLL diagnosis.
Population:	This is a two-arm trial with two cohorts of patients based on their ability to tolerate therapy:

	Arm A – Fit cohort: Age ≤80, CIRS<6 with adequate renal function (estimated creatinine clearance ≥30 ml/min), to be treated with the combination of ibrutinib, obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone; i.e. "IG-CHOP" **Arm B – Frail or unfit cohort:** Age ≤80 years, estimated Creatinine Clearance ≥30 ml/min (Cockcroft-Gault) or with a score on the Cumulative Illness Rating Scale (CIRS) ≥6 for coexisting illnesses not related to CLL, to be treated with ibrutinib (I) and obinutuzumab (G), i.e. "IG".
Centers:	Northwell Health/CLL Research and Treatment Program
Inclusion Criteria: **1.** *Refer to* Section 4.0 *for the complete and detailed list of inclusion/exclusion criteria.*	• Subjects ≥ 18 and ≤80 years of age • Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 • Histologically confirmed Richter's transformation in CLL/SLL patients. Patients can be treatment-naive or have been previously treated • Regimen-specific inclusions: **Fit Group:** Patients with prior BTK agent exposure (including Ibrutinib) may be included on the FIT arm. **Frail Group:** Patients who have had prior BTK inhibitors (including Ibrutinib) should not be included on the Frail arm. • Patients may have had prior exposure to alternative B-cell signaling receptor agents including prior exposure to a Phosphoinositide 3-Kinase Delta (PI3Kd) inhibitor, and a Spleen tyrosine kinase (SYK) inhibitor. • Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations) • Willing and able to participate in all required evaluations and procedures in this study protocol • Adequate hematologic function defined as: → Absolute neutrophil count ≥1000 cells/mm^3 (1.0 x 10^9/L). → Platelet count ≥50,000 cells/mm^3 (50 x 10^9/L).

	→ Hemoglobin >8.0 g/dL • Adequate hepatic and renal function defined as: → Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 2.5 x upper limit of normal (ULN). → Estimated Creatinine Clearance ≥30 ml/min (Cockcroft-Gault) → Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin) → PT/INR <1.5 x ULN and PTT (aPTT) <1.5 x ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder). When treated with warfarin or other vitamin K antagonists, then INR≤3.0)
Exclusion Criteria:	• Regimen-specific exclusions: o **Fit Group:** known hypersensitivity to any of the agents in the combination regimen or having a comorbidity that may affect patient's ability to tolerate the therapy at the investigator's discretion. Patients with prior BTK agent exposure (including Ibrutinib) may be included on the FIT arm. o **Frail Group:** Known grade 4 hypersensitivity, severe allergy, or anaphylactic reaction to a monoclonal antibody. Patients who have had prior BTK inhibitors (including Ibrutinib) should not be included on the Frail arm. • Inability to swallow capsules or any of the following: uncontrolled malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction • Unwilling or unable to participate in all required study evaluations and procedures • Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations) • Lactating, pregnant or unwilling to follow precautions to avoid an unintended pregnancy • Concomitant use of warfarin or other Vitamin K antagonists • Subjects who received a strong cytochrome P450 (CYP) 3A4 inhibitor within 7 days prior to the first dose of ibrutinib or

	subjects who require continuous treatment with a strong CYP3A inhibitor (see Appendix 3) • Chemotherapy ≤21 days prior to first administration of study treatment • Biologic immunotherapy ≤10 days prior to first administration of study treatment • BCR inhibitors ≤24 hours days prior to first administration of study treatment • Major surgery, excluding diagnostic tissue biopsies required to diagnose Richter's transformation, within 4 weeks of first dose • History of other malignancies, except: o Malignancy treated with curative intent and with no known active disease present for ≥2 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician o Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease o Adequately treated carcinoma in situ without evidence of active or residual disease • Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 4), grade 0 or 1, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia. • 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. • Recent infection requiring systemic treatment that was completed ≤14 days before the first dose of study drug. • Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody or hepatitis B surface antigen or Hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded. • Any uncontrolled active systemic infection. • Known bleeding disorders (e.g., von Willebrand's disease) or hemophilia. • History of stroke or intracranial hemorrhage within 6 months prior to enrollment.

	• Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization. • Currently active, clinically significant hepatic impairment Child-Pugh class C according to the Child Pugh classification • Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.
Study Treatment:	Ibrutinib (PCI-32765), Obinutuzumab (GA101) plus or minus CHOP
Concomitant Therapy:	*Refer to Section* 6 *for information on concomitant therapy.*
Safety Plan:	*Refer to Section 11 for information on safety follow up measures.*
Statistical Methods and Data Analysis:	**Primary Efficacy Analysis:** The primary endpoint variable is the overall response rate evaluated following at least two months after start of therapy. ORR conforms to the published Revised Response Criteria for malignant lymphoma **Secondary Efficacy Analysis:** Secondary endpoints include: incidence of prolonged hematologic toxicity in cycle 1 in subjects with a diagnosis of Richter's Transformation (RT), hematologic improvement, progression-free survival (PFS), overall survival (OS), and health-related quality of life (HRQL) measures **Exploratory Efficacy Analysis:** Peripheral blood, lymph node and/or bone marrow samples (depending on the site of disease activity) will be obtained pre-therapy. In addition, peripheral blood and possibly lymph node and bone marrow samples (depending on the site of disease activity) will be obtained on C1D15, C1D28, C2D28 of therapy and at the end of the study or at the time of disease progression.

	These samples will be tested to determine correlation with observed outcomes.
Sample Size Determination	Simon's two-stage design (Simon, 1989) will be used for each of the two study groups (fit and frail groups). For the frail group, the study will be designed to test the ORR at 55% (the alternative hypothesis) against the estimated true response rate of 30% (the null hypothesis). In the first stage, 8 patients will be accrued. If there are 2 or fewer responses in these 8 patients, the study will be stopped. Otherwise, 12 additional patients will be accrued for a total of 20. The null hypothesis will be rejected if 9 or more responses are observed in 20 patients. This design yields a type I error rate of alpha=0.1 and power of 80% when the true response rate is 55%. For the fit group, the study will be designed to test the ORR at 60% (the alternative hypothesis) against the estimated true response rate of 35% (the null hypothesis). In the first stage, 10 patients will be accrued. If there are 4 or fewer responses in these 10 patients, the study will be stopped. Otherwise, 13 additional patients will be accrued for a total of 23. The null hypothesis will be rejected if 11 or more responses are observed in 23 patients. This design yields a type I error rate of alpha=0.1 and power of 80% when the true response rate is 60%. For the frail (fit) group, the null hypothesis will be rejected if there are 9 (11) or more responses in the 20 (23) patients, 9/20=45% (11/23=48%). Therefore, the study will require a total of 20+23=43 patients (fit and frail groups).

ABBREVIATIONS

Include all abbreviations used in the text. If a term is used less than 3 times, it should be spelled out on each use. Each term should be spelled out the first time it is used in the Synopsis, and again the first time it is used in the text. Refer to AMA Manual of Style for standard abbreviations.

CRF	case report form (paper or electronic as appropriate for this study)
DCF	data clarification form
DMC	Data Monitoring Committee
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4th edition)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDC	electronic data capture
EQ-5D-5L	EuroQoL Five-Dimension utility measure
FACT-Leu	Functional Assessment of Cancer Therapy: Leukemia questionnaire
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
HRQL	health-related quality of life
IAC	Interim Analysis Committee
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVRS	interactive voice response system
IWRS	interactive web response system
LC-MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
MRU	medical resource utilization
PD	Pharmacodynamic
PK	Pharmacokinetic
PQC	Product Quality Complaint
PRO	patient-reported outcome(s)
RS	Richter's Syndrome
RT	Richter's Transformation
USP	United States Pharmacopeia

1. BACKGROUND

1.1. Disease/Histology

Chronic lymphocytic leukemia (CLL) is the most common form of adult leukemia in the United States and Europe. According to the SEER database, the annual incidence is ~15,000 new cases with a median age at diagnosis of 72. Clinically, CLL is characterized by a marked degree of heterogeneity, ranging from patients that harbor highly stable disease who do not require treatment to patients with a rapidly progressive disease that require immediate intervention after diagnosis due to the presence of lymphadenopathy, hepatomegaly or splenomegaly, and bone marrow failure. "B" symptoms (i.e., fever, night sweats, and weight loss), general fatigue, and recurrent infections are common in patients with late-stage CLL but can occasionally be found earlier in the course of the disease (Gribben 2011). While clinical staging systems have been developed to risk stratify CLL patients (Rai 1975, Binet 1981), the outcome for a given patient ultimately depends on complex relationships between the characteristics of the patient (age, gender, comorbidity, performance status), the disease (burden, kinetics and biology of the tumor), as well as sensitivity of the disease to treatment. Thus, clinical staging is only one of the parameters in this complex interaction (Montserrat 2006). As previously described by our research group, the observed clinical heterogeneity extends to the molecular biology of CLL clones as CLL cases can be divided into two subgroups based on the presence or absence of significant numbers of *IGHV* somatic mutations (Fais 1998). This molecular distinction has been found to correlate with the heterogeneity in clinical course and survival observed in CLL patients (Damle 1999, Hamblin 1999).

The use of chemoimmunotherapy for CLL as initial therapy is associated with high response rates, with the most active combination being the three-drug regimen of fludarabine, cyclophosphamide, and rituximab (FCR) (Keating 2005, Hallex 2010). Despite excellent responses and remission durations obtained with this regimen, patients with cells that use an unmutated *IGHV* gene (UM-CLL) have inferior rates of survival compared with those that use a mutated *IGHV* gene (M-CLL) (Damle 1999, Hamblin 1999), due to a significantly shorter complete remission duration in the UM-CLL group (Lin 2009). The worse prognosis predicted by unmutated IGHV genes is conceivably due to the enrichment of some genetic lesions that confer higher aggressiveness (e.g., mutations of TP53 or NOTCH1) among UM-CLLs, as well as to the greater predisposition of UM-CLLs, compared with M-CLLs, to undergo clonal evolution (Shanafelt 2006, Stilgenbauer 2007, Fabbri 2011, Puente 2011, Rossi 2012).

The excellent clinical activity of a regimen such as FCR is counterbalanced by its significant toxicities including persistent cytopenias, infections, and the development of therapy-related secondary malignancies (Fischer 2013). Novel treatment strategies have been developed for use in CLL patients that are not appropriate candidates for this regimen due to their co-existing medical comorbidities. Agents such as bendamustine, alemtuzumab, and ofatumumab have shown activity in CLL (Knauf 2009, Hillmen 2007, Wierda 2010) and have been approved by the FDA for use in CLL as monotherapy or in combination regimens. Over the past few months, two new targeted agents with unprecedented activity and safety have been approved for use in CLL patients:

the Bruton's Tyrosine Kinase (BTK) inhibitor ibrutinib and the monoclonal antibody targeting CD20, obinutuzumab. The activity and duration of remission for both agents was also observed in patients that were traditionally excluded from participation in clinical trials due to their known inability to tolerate intensive regimens.

While the availability of agents such as FCR and ibrutinib and obinutuzumab has improved clinical outcomes in CLL, therapy is not curative. The clinical course for the majority of patients with CLL has been predictable, with a response to initial treatment, eventual recurrence, reduced likelihood for response with subsequent treatments, and shorter duration of response with each remission (Wierda 2006). Retreatment typically yields progressively less satisfactory responses than the prior treatment, eventually leading to refractory disease. The predisposition to clinical progression of CLL is influenced by the genetic lesions of the leukemic clone. At the time of CLL diagnosis, mutations such as TP53 disruption, ATM deletion, NOTCH1, and SF3B1, have all been shown to predict a worse outcome (Gaidano 2012). Currently available treatment options for relapsed disease tend to have increased toxicity and decreased anti-neoplastic activity with each subsequent therapy, hence the need for the development of agents that target different pathways that can overcome the acquired resistance that stems from clonal evolution.

Despite all the recent advances in therapeutic interventions for CLL patients, a subset of CLL patients will eventually transform into a high-grade Diffuse Large B-Cell Lymphoma (DLBCL), a type of Non-Hodgkin's lymphoma (NHL). When transformation occurs, it is known as a Richter's Transformation (RT) or Richter's syndrome (RS) (referred to in this document as RT). Incidence has been reported to be approximately 2-8% of CLL patients (Tsimberidou 2006), though a single institution experience reported on the outcomes of 185 previously untreated CLL patients and found a cumulative incidence of RT at 5 and 10 years after CLL diagnosis at 13% and 16%, respectively, higher than historical records (Rossi 2008). Since RT diagnosis requires a pathological assessment, heterogeneity in biopsy policies among institutions could represent a major factor influencing the reported rate in different CLL series. In this respect, the high rate of RT in this particular cohort may reflect the intensive biopsy policy, hence the need for biopsies to determine whether the clinical presentation is a Richter's transformation vs relapsed/refractory CLL. The clinical manifestations of RT include a rapid increase in size of lymphadenopathy, splenomegaly, worsening "B" symptoms (fevers, night sweats, and weight loss of over 10%) accompanied by a rise in lactic acid dehydrogenase (Tsimberidou 2006), though as mentioned above, these symptoms could also be attributed to relapsed or refractory CLL. The mechanism by which this transformation to an aggressive lymphoma occurs is still poorly understood. Most importantly, we currently lack predictors of transformation and prognostic markers to determine a response to treatment (Tsimberidou 2005). TP53, NOTCH1, and MYC abnormalities are the most frequent recurrent genetic lesions observed in patients that develop RT. Because these abnormalities are frequently acquired at the time of transformation (Rossi 2011), next-generation ultra-deep sequencing studies can aid in the identification of additional genetic lesions acquired at the time of transformation from CLL to RT. The high prevalence of TP53 mutation in RT suggests clonal selection driven by previous CLL treatments. Nevertheless, despite morphologic and phenotypic similarities with non-germinal center (non-GC) *de novo* DLBCL (a more benign and responsive form of DLBCL), the molecular profile of genomic abnormalities in RT is different. Most genetic changes that are observed in *de novo* DLBCL are rare or absent in RT. The increased frequency of unmutated *IGHV* genes observed in RT is in sharp contrast with the genetic

characteristics of *de novo* DLBCL, which show mutated *IGHV*s in virtually all cases. This disparity could reflect differences in the cell of origin or the microenvironment.

1.1.1. Treatment Options

Once a CLL patient develops RT, there are no consensus guidelines on its therapy and there is currently no standard of care management recommendations. If the patient is fit and able to tolerate chemotherapy, treatments for a Richter's transformation include the use of aggressive lymphoma combination regimens, such as CHOP, ESHAP, and Hyper-CVAD or CVXD in combination with the anti-CD20 monoclonal antibody rituximab, although the response rates to these are poor and short lived.

In a single institution study, Hyper-CVXD regimen was used in 49 patients (31 patients with RT with a median interval to diagnosis of RT from CLL diagnosis of 52 months (range 0-112 months) and 19 patients with fludarabine-refractory CLL). Nine of 49 patients (19%) achieved a complete remission (CR) and 11 (22%) patients achieved a partial remission (PR) for an overall response rate of 41% and a median survival of 8.5 months. Nevertheless, patients with fludarabine-refractory CLL had a significantly higher survival rate compared with patients who had RT when a 2-month landmark analysis was performed (RT 12/25 deaths, CLL 1/11 deaths). Most currently available regimens have a high risk of a serious toxicity despite the use of multiple prophylactic and supportive agents, as evidenced by early treatment mortality of 18% and 4% during the first and second cycle of therapy, respectively (Tsimberidou 2003).

Another phase I/II study looking at a combination regimen of oxaliplatin, fludarabine, cytarabine, and rituximab (OFAR) showed overall response rate of 50% (10/20 patients responded) but a sixmonth overall survival of only 59% (Tsimberidou 2008). As expected, patients who achieve a CR or PR have a longer survival than patients whose disease fails to respond to therapy.

A recent single institution study reported the outcomes of 16 RT patients following progression after ibrutinib failure in patients participating on ibrutinib clinical trials: with a median follow-up of 16 months (<1-42months), 6 patients received no additional therapy and died within a month of transformation. The remaining 10 patients were treated with R-EPOCH, R-CHOP, R-ICE, or OFAR; the reported median survival from date off ibrutinib study was 120 days (Woyach 2014).

Given that CLL is considered a "disease of the elderly", a significant number of patients who develop RT are not able to tolerate intensive regimens and die without the ability to receive any salvage therapy. Furthermore, patients with RT continue to be excluded from clinical trials. RT patients have a reported median overall survival of 5 to 8 months (Tsimberidou 2005), even in younger patients that would be better fit to tolerate current multidrug chemotherapy regimens. It is clear that there is an unmet need to study the activity of the recently approved agents that are showing remarkable activity as monotherapy or in combination in CLL and NHL.

Kinase inhibitors affecting signaling of the B-cell antigen receptor (BCR) have shown significant promise in patients with CLL and NHL. Ibrutinib is an orally bioavailable, potent inhibitor that covalently binds to the cysteine-481 amino acid of the Bruton's tyrosine kinase (BTK) enzyme, leading to irreversible inhibition of activity (Honigberg 2010). In vitro studies

demonstrate BTK inhibition in CLL cells blocks BCR-related survival signals, thereby leading to apoptosis. Ibrutinib has demonstrated single-agent activity in a variety of relapsed or refractory B-cell malignancies with excellent tolerability (Advani 2013). A recent phase1b–2, open-label, multicenter study testing single agent ibrutinib in patients with relapsed CLL (including patients with high risk disease) showed an overall response rate, based on standard criteria of 71% in two different cohorts (420-mg QD and 840-mg QD cohort). In addition, 10 patients in the 420-mg QD cohort (20%) and 5 patients in the 840-mg QD cohort (15%) had a partial response with persistent lymphocytosis. Blood lymphocytosis peaked at a median of 4 weeks and then slowly declined. Lymphocytosis occurred concomitantly with a notable reduction in lymph node and spleen sizes, along with frequent improvement of baseline cytopenias in a time-dependent manner. Irrespective of dose, treatment with ibrutinib provided durable responses. The 26-month estimated rate of progression-free survival was 75%, and the rate of overall survival was 83% (Byrd 2013). As required by clinical trial protocols, patients with a diagnosis of RT were excluded from participation in these initial trials.

Obinutuzumab is an anti-CD20 monoclonal antibody (mAb) that differs from previous anti-CD20 mAbs in its glycoengineered Fc region and type 2 CD20-binding mode. Anti-CD20 antibodies have two main binding sites and downstream effects on target cells: type 1 binding results in the formation of lipid rafts containing the antibody bound target that cluster the target antigen on the cell surface; type 2 binding does not produce the same lipid-raft clustering but may transduce signals into the cell that add to the usual complement-mediated and antibody-dependent cell-mediated cytotoxicity and phagocytosis mechanisms. Glycoengineering increases the binding affinity of the Fc portion of obinutuzumab to Fcγ receptor III on innate immune effector cells (natural killer cells, macrophages, and neutrophils), which in turn leads to enhanced antibody-dependent cell-mediated cytotoxicity and antibody-dependent cellular phagocytosis. The consequence of type 2 CD20 binding (as compared with type 1 binding with the other available drugs, i.e. rituximab and ofatumumab) is mainly different B-cell signaling downstream of CD20 engagement, which leads to increased direct cell death (through a caspase-independent mechanism) and reduced internalization and degradation of monoclonal antibody–bound membrane CD20 molecules (Mössner 2010, Honeychurch 2012). The type 2 binding feature of obinutuzumab as well as its glycoengineered constant region of immunoglobulin has translated into an impressive improvement over other antibody therapies targeting CD20 (Goede 2014).

We propose the use of ibrutinib in combination with obinutuzumab with and without a commonly used chemotherapy regimen used in Richter's patients known as CHOP (i.e. cyclophosphamide, doxorubicin, vincristine, and prednisone). Given the outstanding responses from these recently approved agents (ibrutinib and obinutuzumab) reported in both CLL and NHL, we expect an improved clinical activity when these agents are used in patients that develop RT.

1.1.2. Role of BTK in Disease/Histology

1.2. Ibrutinib Background – Investigational Product Name and Description

Ibrutinib (IMBRUVICA®) 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, and 4) Waldenström's Macroglobulinemia. Ibrutinib is currently under investigation in various other 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 that comprise the antigen-binding portion of the B-cell receptor (BCR), which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways (Bishop 2003).

The process of B-cell maturation, including immunoglobulin variable (IGHV), diversity (IGHD) and joining (IGHJ) region gene rearrangement and somatic mutation, is tightly regulated. It is thought that B-cell lymphomas and CLL result from translocations and mutations, respectively, acquired during normal B-cell development (Shaffer 2002) or subsequently during germinal center reactions in secondary lymphoid tissues. 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. Although the selective effect of BTK mutations suggests that its primary functional role is in antigen receptor signaling in B-cells (Satterthwaite 2000), the enzyme also is critical for the function of other receptors such as the chemokine receptor, CXCR4.

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 post dose at dose levels ≥2.5 mg/kg. In Study PCYC-04753, the BTK occupancies 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 both 4 and 24 hours after drug administration.

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

1.3. Summary of Nonclinical Data

For the most comprehensive nonclinical information regarding ibrutinib, refer to the current version of the Investigator's Brochure.

1.3.1. Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of the Btk (Pan 2007). In vitro, ibrutinib is a potent inhibitor of Btk activity (IC_{50} = 0.39 nM). The irreversible binding of ibrutinib to cysteine-481 in the active site of Btk results in sustained inhibition of the catalytic activity of that Btk molecule 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 CD69 expression after anti-IgM stimulation (Herman 2011)

Ibrutinib arrested arrests cell growth and induces apoptosis in human B-cell lymphoma cell lines in vitro and inhibited tumor growth in vivo in xenograft models (Herman 2011) Ibrutinib also inhibits adhesion and migration of mantle cell lymphoma (MCL) cells in co-culture and reduces tumor burden in lymph node and bone marrow in a murine model of MCL dissemination and progression (Chang 2013a, Chang 2013b).

For more detailed and comprehensive information regarding nonclinical pharmacology, refer to the current Investigator's Brochure.

1.3.2. Toxicology

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 rat and dog including general toxicity studies up to 13 weeks duration, the greatest potential for human toxicity with ibrutinib is predicted to be in lymphoid tissues (lymphoid depletion) and the gastrointestinal tract (soft feces/diarrhea with or without inflammation). Additional toxicity findings seen in only one species with no observed human correlate in clinical studies to date include pancreatic acinar cell atrophy (rat), minimally decreased trabecular and cortical bone (rat) and corneal dystrophy (dog).

In 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) at ibrutinib doses that result in approximately 6 times and 14 times the exposure (AUC) in patients administered the dose of 560 mg daily, respectively.

1.3.2.1.Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ibrutinib.

Ibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay and was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells or in an in vivo bone marrow micronucleus assay in mice at doses up to 2000 mg/kg.

Fertility studies with ibrutinib have not been conducted in animals. In the general toxicology studies conducted in rats and dogs, orally administered ibrutinib did not result in adverse effects on reproductive organs.

1.4. Summary of Clinical Data

For the most comprehensive clinical information regarding ibrutinib, refer to the current version of the Investigator's Brochure.

1.4.1. Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging 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 9 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Taking into account the approximate doubling in mean systemic exposure when dosed with food and the favorable safety profile, ibrutinib can be dosed with or without food. Ibrutinib is extensively metabolized primarily by cytochrome P450 (CYP) 3A4. The on-target effects of metabolite PCI-45227 are not considered clinically relevant. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure. Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with creatinine clearance (CrCl) >30 mL/min. Patients with severe renal impairment or patients on dialysis have not been studied. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. A higher proportion of Grade 3 or higher adverse reactions were reported in patients with B-cell malignancies (CLL, MCL and WM) with mild hepatic impairment based on NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction compared to patients with normal hepatic function.

Evaluations of exposure/response using PK/PD modeling of data from 11 completed Phase 2 and 3 studies have been conducted from a total of 1,306 ibrutinib-treated subjects with B-cell malignancies or cGVHD. The results from these analyses are as follows:

- No meaningful relationship between tumor response (ORR) and systemic exposure to ibrutinib was observed for patients with CLL, MCL, MZL, or cGVHD.

- Similarly, there was no meaningful or consistent indication of any potential relationship between the safety-related endpoints of treatment-emergent atrial fibrillation, neutropenia, or liver function test abnormalities and ibrutinib systemic exposure.

- The integrated exposure-response exploration for the 9 studies in CLL/SLL and MCL combined suggested that the incidence of major hemorrhage events was minimally increased with increasing systemic ibrutinib exposure. A more detailed analysis by indication and approved clinical doses indicated that this effect was most evident among

subjects with MCL treated with the 560 mg/day dose. There was no apparent association of major hemorrhage events with ibrutinib exposure in subjects with CLL assigned the 420 mg/day dose.

1.5. Summary of Clinical Safety

For combination therapy studies:

Integrated safety data for a total of 422 subjects treated with B-cell malignancies from 4 combination therapy studies that have completed primary analysis or final analysis included in the CSR as of 31 July 2017, are briefly summarized below. Therapies used in combination with ibrutinib in these studies, included BR (bendamustine and rituximab), FCR (fludarabine, cyclophosphamide, and rituximab), ofatumumab, and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

The most frequently reported TEAEs in subjects receiving ibrutinib in combination therapy (N=422):

Most frequently reported TEAEs >10% [a]	Most frequently reported Grade 3 or 4 TEAEs >2% [a]	Most frequently reported Serious TEAEs >1% [b]
Neutropenia	Neutropenia	Febrile neutropenia
Diarrhea	Thrombocytopenia	Pneumonia
Nausea	Febrile neutropenia	Atrial fibrillation
Thrombocytopenia	Pneumonia	Pyrexia
Fatigue	Neutrophil count decreased	Cellulitis
Anemia	Anemia	Sepsis
Pyrexia	Fatigue	Neutropenia
Infusion related reaction	Diarrhea	Tumor lysis syndrome
Upper respiratory tract infection	Hypertension	Urinary tract infection
Constipation	Pyrexia	
Vomiting	Cellulitis	
Rash	Leukopenia	
Headache	Tumor lysis syndrome	
Cough	Atrial fibrillation	
Muscle spasms	Hyperuricaemia	
Pneumonia	Urinary tract infection	
Oedema peripheral	White blood cell count decreased	
Arthralgia		
Decreased appetite		
Contusion		
Insomnia		
Chills		
Peripheral sensory neuropathy		
Stomatitis		
Febrile neutropenia		

Abdominal pain
Back pain
Bronchitis

[a] Source is Table 7 of IB (v11), [b] Source is Table 8 of IB (v11)

1.5.1. Risks

1.5.2. Bleeding-related events

There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage and hematuria. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding.

Initially, subjects were excluded from participation in specific ibrutinib Phase 2 and 3 studies if they required warfarin or other vitamin K antagonists. Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib unless specified in the protocol. Supplements such as fish oil and vitamin E preparations should be avoided.

Subjects with congenital bleeding diathesis have not been studied. See section 6 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 6.4 for guidance on ibrutinib management with surgeries or procedures.

1.5.3. Atrial Fibrillation

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor subjects clinical for atrial fibrillation. Subjects who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset of dyspnea should be evaluated clinically, and if indicated, have an ECG performed. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines. Ventricular tachyarrhythmia has also been reported. Abnormal rapid and/or irregular heart rhythm that starts from the lower chambers (ventricles) of the heart (ventricular tachyarrhythmia).

1.5.4. Cytopenias

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

1.5.5. Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe and are generally managed with supportive therapies including antidiarrheals and antiemetics. Subjects should be monitored carefully for gastrointestinal AEs and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies such as *Clostridium difficile* or other infectious agents. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 5.2.1.3).

1.5.6. Infections

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

1.5.7. Non-Melanoma Skin Cancer

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

1.5.8. Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. In a randomized Phase 3 study (PCYC-1112-CA), rash occurred at a higher rate in the ibrutinib arm than in the control arm. Most rashes were mild to moderate in severity. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects should be monitored for signs and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events including erythema, urticaria, and angioedema have been reported.

1.5.9. Lymphocytosis and Leukostasis

There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes (>400,000/μL) may confer increased risk. Consider temporarily holding ibrutinib. Subjects should be closely monitored. Administer supportive care

including hydration and/or cytoreduction as indicated. For subject and ibrutinib management guidance, refer to Sections 5.2.1 and 6.4.

Upon initiation of treatment, a reversible increase in lymphocyte counts (i.e., ≥50% increase from baseline and an absolute count >5000/μL), often associated with reduction of lymphadenopathy, has been observed in most subjects with CLL/ small lymphocytic lymphoma (SLL) treated with ibrutinib. This effect has also been observed in some subjects with MCL treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first months of ibrutinib therapy and typically resolves within a median of 8.0 weeks in subjects with MCL and 14 weeks in subjects with CLL/SLL.

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

1.5.9.1. Tumor Lysis Syndrome

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

1.5.9.2. Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in patients treated with ibrutinib. Monitor patients for pulmonary symptoms indicative of ILD. Should symptoms develop, interrupt ibrutinib and manage ILD appropriately. If symptoms persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 5.2.1.3).

1.5.9.3 Inflammation

Inflammation of the fatty tissue underneath the skin (panniculitis).

1.5.9.4 Hypertension

Hypertension has been commonly reported in subjects treated with ibrutinib. Monitor subjects for new onset of hypertension or hypertension that is not adequately controlled after starting ibrutinib.

Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

1.6. Obinutuzumab Background

1.6.1. Structure and Mechanism of Action of Obinutuzumab

Obinutuzumab (GA101, RO5072759), is a glycoengineered, humanized, type II anti-CD20 monoclonal antibody (mAb). Obinutuzumab was derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering leading to the following characteristics (Beers et al. 2010; Mössner et al. 2010): high antibody-dependent cellular cytotoxicity (ADCC); high affinity binding to the CD20 antigen; low complement-dependent cytotoxicity (CDC) activity; and antibody dependent cellular phagocytosis (ADCP) through recruitment of FcγRIII positive immune effector cells such as natural killer (NK) cells, macrophages and monocytes; and high direct cell death induction. Given the direct cell death inducing properties of obinutuzumab and the significantly enhanced ADCC in preclinical assays, it is possible that obinutuzumab may have greater efficacy than the widely used anti-CD20-mAb rituximab (Rituxan®).

1.6.2. Clinical Experience with Obinutuzumab

For the most up-to-date information on obinutuzumab, please refer to the current version of the Investigator's Brochure.

1.6.2.1. Tolerability and Efficacy of Obinutuzumab in Chronic Lymphocytic Leukemia

Study BO20999 (GAUGUIN; NCT00517530) (Phase I)

BO20999 was an open-label, multicenter, Phase I/II study to explore obinutuzumab safety and activity in relapsed/refractory NHL and CLL. Thirteen CLL patients have received obinutuzumab at doses with a range of 400–2000 mg (given as a flat dose) across four cohorts (Morschhauser et al. 2009). There were no dose-limiting toxicities (DLTs) and no requirement for dose reductions. Infusion-related reactions (IRRs) occurred in all CLL patients and were characterized predominantly by National Cancer Institute Common Terminology Criteria (NCI-CTC) Grade 1–2 toxicities: chills, nausea, vomiting, fever, pyrexia, hypertension, hypotension, dyspnea, and dizziness. Two patients experienced four NCI-CTC Grade 3 toxicities: sweats, flushing, asthenia, and hepatic cytolysis.

Although the safety profile appears otherwise similar between NHL and CLL, there was an increase in NCI-CTC v3.0 Grade 3/4 neutropenia noted in CLL patients, which were observed in 9 patients across the four dose levels administered. Five patients experienced NCI-CTC Grade 4 neutropenia and 4 patients experienced NCI-CTC Grade 3 neutropenia as the maximum severity. Of the 9 patients, 7 had one NCI-CTC Grade 3/4 event and 2 patients experienced more than one event. Granulocyte colony-stimulating factor (G-CSF) support was administered to 6 of the 9 patients, and these patients responded quickly to G-CSF support. For the 3 patients who did not receive G-CSF, neutrophil counts normalized spontaneously. Furthermore, it is important to note that these neutropenia events did not appear to be accompanied by a higher incidence of infections. No deaths were reported in Phase I of this study for CLL.

As assessed by the International Workshop on CLL (IWCLL) criteria, the end-of-treatment response rate with obinutuzumab monotherapy was 62% (8 of 13 patients with partial response [PR]) (Morschhauser et al. 2009).

Study BO20999 (GAUGUIN; NCT00517530) (Phase II)

Twenty patients with relapsed/refractory CLL have received 1000 mg of obinutuzumab. The most commonly reported adverse event (AE) during the treatment period was IRR, reported in 19 (95%) of 20 patients. Fifteen patients experienced Grade 3/4 AEs of whom 14 patients had treatment-related Grade 3/4 AEs (investigator assessment). Treatment-related Grade 3/4 AEs were IRR (6 patients), neutropenia (4 patients), lymphopenia (2 patients), thrombocytopenia (2 patients), and anemia, pure red cell aplasia, pancytopenia, febrile neutropenia, herpes zoster, and interstitial lung disease (1 patient each). Eleven serious adverse events (SAEs) in 9 patients were reported during treatment, 9 of which were assessed by the investigator as related to obinutuzumab: IRR (4 patients) and febrile neutropenia, pancytopenia, pure red cell aplasia, interstitial lung disease and pyrexia (1 patient each). Three patients withdrew from further study treatment after the first infusion due to IRR. One death has been reported during follow-up from colon cancer. The most common AE in follow-up was nasopharyngitis, reported in 2 patients. End-of-treatment response assessment showed that four patients (20%) achieved a clinical response, with a best overall response rate (ORR) of 25% in evaluable patients (*Salles* et al. 2011).

Study BO21003 (GAUSS; NCT00576758) (Phase I)

BO21003 is an open-label, dose-escalating, multicenter Phase I/randomized Phase II study in patients with relapsed/refractory CD20+ malignant disease. In Study BO21003, 5 CLL patients have been administered obinutuzumab. The fifth patient withdrew at Cycle 1, Day 1 because of a Grade 4 IRR, which occurred minutes after the start of infusion in the setting of high tumor burden. Efficacy assessments are available for only the 4 patients who completed treatment (received 4 cycles of infusion). The end-of-treatment response in patients with CLL receiving obinutuzumab monotherapy in this study included 3 stable disease and 1 progressive disease patients (Sehn, et al. 2009).

Study GAO4768g / GAGE / NCT01414205 (Phase II)

GAO4768g is an open-label, randomized, multicenter, Phase II study evaluating the efficacy and safety of obinutuzumab administered at 1000 mg versus 2000 mg doses in patient with previously untreated CLL. The results of the GAGE study were recently presented at the 2014 annual meeting of the American Society of Clinical Oncology.

Eighty patients were randomized and stratified based on Rai stage and tumor mass.

For patients who received the 1000-mg doses, obinutuzumab was administered with three 1000-mg doses in the first 21-day cycle (the first 1000-mg dose was administered over 2 days: 100 mg administered on Day 1, 900 mg administered on Day 2; 1000 mg was administered on both Days 8 and 15). In the subsequent cycles (2 – 8), 1000 mg of obinutuzumab was administered on the first day of each cycle.

For patients who received the 2000-mg doses, obinutuzumab was administered as follows: 100 mg on Cycle 1, Day 1; 900 mg on Day 2; and 1000 mg on Day 3. On Days 8 and 15 of Cycle 1, 2000 mg was administered on each day. For Cycles 2 – 8, 2000 mg of obinutuzumab was administered on Day 1 of each cycle.

ORR was assessed at 2 months post-therapy according to the IWCLL criteria. The ORR for the 1000 mg and 2000 mg obinutuzumab treatment arms were 49% compared with 67%, respectively; 2-sided p = 0.0779. Complete response/complete remission with incomplete blood count recovery (CR/CRi) were achieved by 5% of patients (2/41) in the 1000-mg arm compared with 21% of patients (8/39) in the 2000-mg arm. In study GAO4768g in previously untreated patients with CLL, 44% and 46% of the patients achieved a PR in the 1000 mg and 2000 mg cohorts, respectively. The proportion achieving a CR/CRi was higher in high dose cohort (20.5% vs. 4.9%).

The most common Grade 3/4 AEs were IRRs (23% vs. 11%) and neutropenia (3% vs. 5%) for the 1000-mg and 2000-mg arms, respectively (Flynn et al. 2014).

Study GAO4779g (GALTON; NCT01300247) (Phase II)

GAO4779g is an open-label, non-randomized, multicenter, Phase II study. In the GALTON study, 41 patients with untreated CLL were treated with obinutuzumab 1000 mg (100 mg IV on Day 1, 900 mg on Day 2, and 1000 mg on Days 8 and 15 of Cycle 1; 1000 mg on Day 1 in Cycles 2 – 8) and either fludarabine + cyclophosphamide (G-FC; 25/250 mg/m^2 IV on Days 2 – 4 of Cycle 1, then on Days 1 – 3 of Cycles 2 – 6) or bendamustine G-B; 70 mg/m^2 IV on Days 2 – 3 of Cycle 1, then on Days 1 – 2 of Cycles 2 – 6). Each cycle was 28 days long.

The most common AEs (any grade) occurring in the G-FC arm were obinutuzumab-related IRRs (91%), nausea (76%), fatigue (57%), constipation (48%), and neutropenia (43%); in the G-B arm, they were obinutuzumab-related IRRs (90%), nausea (65%), neutropenia (55%), diarrhea (50%), and pyrexia (45%). The most common Grade 3/4 AEs were obinutuzumab-related IRRs (29%, 10%), neutropenia (43%, 55%), and infections (19%, 5%) for G-FC and G-B, respectively.

Fourteen patients experienced SAEs (G-FC, n = 6; G-B, n = 8), with events including febrile neutropenia (5 events); infections (4 events); IRRs (3 events); nausea, vomiting, pyrexia (2 events each); and diarrhea, fatigue, tachycardia, tumor lysis syndrome, syncope, mental status changes, neutropenia, face swelling, and hypertension (1 event each). Nine patients (G-FC, n = 7; G-B, n = 2) had AEs leading to treatment discontinuation, including Grade 3/4 neutropenia (3 patients in G-FC [1 of these 3 patients also had Grade 4 cellulitis] and 2 patients in G-B), Grade 3 thrombocytopenia (2 patients in G-FC), Grade 4 pancytopenia (1 patient in G-FC), and Grade 4 aspartate aminotransferase (AST)/Grade 3 alanine aminotransferase (ALT) elevation (1 patient in G-FC).

The ORR was 62% (CR, 2; CRi, 3; PR, 8) in patients who received G-FC and 90% (CR, 4; CRi, 5; PR, 9) in patients who received G-B, including 6 patients (G-FC, n = 4; G-B, n = 2) not evaluable due to inadequate response evaluation. Four patients in the G-FC arm (0 in G-B) had stable disease during and after therapy. No patient progressed during the study (Brown et al. 2013). Efficacy data of obinutuzumab administered in combination with chemotherapy are available from the Phase II study GAO4779g, from the updated Stage 1a (GClb vs. Clb) and primary Stage 2 (GClb vs. RClb) analyses of the randomized Phase III study BO21004, and from phase IIIb study subgroup analysis of Cohort 1 (G-Benda) MO28453. In study GAO4779g, 13/21 patients (62%) with previously untreated CLL treated with G-FC achieved a response (2

CR patients, 3 CRi, 8 PR) and 18/20 patients (90%) achieved a response with G-benda (4 CR patients, 5 CRi, and 9 PR).

In study GAO4779g, at the end of treatment 39/41 patients with a B-cell assessment were B-cell depleted and all 36 patients with an assessment at the 6-month follow-up visit remained B-cell depleted. At the 18-24 month assessment, 13/39 patients (33.3%) had B-cell recovery without PD and 6/39 patients (15.4%) remained B-cell depleted, at the 30-36 months follow-up assessment 14/39 patients (35.9%) had B-cell recovery without PD and 4/41 patients (10.3%) remained B-cell depleted. The median time to B-cell recovery in the G-FC arm was 542 days (range 1 to 1067 days; 95% CI for the median 395; not estimated) and 632 days (range 54 to 1079 days; 95% CI for the median: 460, not estimated) in the G-benda arm.

Study BO21004 (CLL11; NCT01010061) (Phase III)

This is an ongoing, open-label, multicenter, three-arm randomized, Phase III study to compare the efficacy and safety of obinutuzumab + chlorambucil (GClb), rituximab + GClb (RClb), or Clb alone in previously untreated CLL patients with comorbidities. BO21004 enrolled 781 patients and an additional 6 patients during a safety run-in period before randomization. An analysis based on data collected by the data cutoff date for these 6 patients accrued from December 2009 until February 2010 for the BO21004 safety run-in phase showed that all 6 patients completed 6 cycles of treatment but two patients had significant dosing delays. IRRs occurred in 5 patients, all were Grade 1 or 2, with no severe IRRs. All 6 patients experienced neutropenia, 5/6 patients reported Grade 3 – 4 afebrile neutropenia with no febrile neutropenia. All 6 reported thrombocytopenia with one case of Grade 3 – 4 thrombocytopenia. No patient died during the safety run-in period. Given that none of the pre-defined stopping criteria were met during this safety run-in period, Study BO21004 opened to randomization in April 2010 (Goede 2012).

Study BO21004 includes two separate stages evaluating efficacy and the primary endpoint is progression-free survival (PFS). Stage 1 evaluated obinutuzumab + chlorambucil compared with chlorambucil alone.

In the Stage 1 analysis, the safety and efficacy of obinutuzumab + chlorambucil or rituximab + chlorambucil was compared with chlorambucil alone. Compared with chlorambucil, both obinutuzumab + chlorambucil and rituximab + chlorambucil demonstrated statistically significant PFS benefit compared with chlorambucil alone. Median PFS of chlorambucil vs. obinutuzumab + chlorambucil was 11.1 vs. 23 months, respectively, (median observation time, 14.2 months; hazard ratio [HR], 0.16 [0.11 – 0.24]; $p< 0.0001$; stratified log-rank test) as assessed by independent review. The difference in PFS was smaller between chlorambucil and rituximab + chlorambucil; median PFS was 16.3 months with rituximab + chlorambucil vs. 11.1 months with chlorambucil alone; HR, 0.44; 95% CI, 0.34 – 0.57; $p < 0.001$).

In the Stage 2 analysis of this study, obinutuzumab + chlorambucil was compared with rituximab + chlorambucil. At the pre-planned interim analysis, the primary endpoint was met early and the results were released by the independent data monitoring board. Median PFS was 26.7 months vs. 15.2 months for obinutuzumab + chlorambucil vs. rituximab + chlorambucil, respectively. The ORR was 78% vs. 65%, and CR was 21% vs. 7%, respectively.

In the comparison of obinutuzumab + chlorambucil vs. chlorambucil alone, the most common AEs (all grades, Grades 3 – 4), respectively, were IRRs (69% vs. 0, 21% vs. 0), neutropenia (40% vs. 18%, 34% vs. 16%), thrombocytopenia (15% vs. 7%, 11% vs. 3%), anemia (12% vs. 10%, 4% vs. 5%), leukopenia (7% vs. 0, 5% vs. 0), pyrexia (10% vs. 7%, < 1% vs. 0), and cough (10% vs. 7%, 0 vs < 1%). Hematologic laboratory abnormalities (all grades, Grades 3 – 4) with obinutuzumab + chlorambucil vs. chlorambucil alone, respectively, were neutropenia (77% vs. 53%, 46% vs. 27%), lymphopenia (80% vs. 9%, 40% vs. 2%), leukopenia (84% vs. 12%, 36% vs. < 1%), and thrombocytopenia (47% vs. 50%, 14% vs. 11%).

Non-hematologic laboratory abnormalities (all grades, Grades 3 – 4) with obinutuzumab + chlorambucil vs. chlorambucil alone, respectively, were hypocalcemia (32% vs. 29%, 3% vs. < 1%), hyperkalemia (31% vs. 17%, 5% vs. 2%), hyponatremia (29% vs. 11%, 8% vs. 22%), AST (SGOT increased; 28% vs. 12%, < 1% vs. 0), creatinine increased (28% vs. 18%, < 1% vs. < 1%), ALT (SGPT increased; 25% vs. 14%, < 1% vs. 0), hypoalbuminemia (22% vs. 14%, < 1% vs. < 1%), alkaline phosphatase increased (16% vs. 11%, 0 vs. 0), and hypokalemia (13% vs. 4%, 1% vs. < 1%) (Goede et al. 2014; Obinutuzumab USPI).

Because Study BO21004 is a pivotal Phase III study in patients with CLL (median age: 73 years; 44% patients were ≥ 75 years), a sparse serum sampling scheme was implemented which involved pre- and post-infusion samples only on each infusion day. Due to this limited sampling schedule, derived PK parameters for obinutuzumab could not be obtained by NCA. Mean serum obinutuzumab pre (Ctrough) and post-infusion (Cmax) concentrations used in the population PK analysis are provided in Table 11 of Investigator's Brochure Version 11 (dated September 2016). The geometric mean post-infusion serum concentrations of obinutuzumab increased from 224 µg /mL (Cycle 1, Day 1) to 588 µg /mL (Cycle 1, Day 15). From Cycle 2 to Cycle 6, serum post-infusion levels remained constant during the course of treatment, ranging from 577 µg /mL on Cycle 2 to 529 µg /mL on Cycle 6. Pre-infusion serum concentrations remained constant from Cycle 3 (160 µg/mL) to Cycle 6 (182 µg /mL).

In the Phase III study BO21004, at the safety cutoff date of 04 July 2016, a total of 118 of the 212 patients with B-cell assessments (55.7%) in the GClb arm and 45 of the 74 patients with B-cell assessments (60.8%) in the RClb arm had B-cell recovery without PD within 48-54 months of follow-up. The median time to B-cell recovery in the GClb arm was 743 days (range 64 to 1673 days; 95% CI for median: 608, 763) compared with 393 days (range 85 to 1555 days; 95% CI for median: 385, 540) in the RClb arm.

For more information related to safety and efficacy in the CLL indication, please refer to the Obinutuzumab Investigator's Brochure or the Obinutuzumab USPI.

1.6.3. Overview of Safety of Obinutuzumab

Obinutuzumab has been administered to approximately 1310 patients with CD20-positive malignancies. Both in patients with NHL and with CLL, IRR was the most common AE in clinical

trials conducted to date. They were predominantly associated with the first infusion, generally occurring early during the infusion, shortly after, or in some cases up to 24 hours after the completion of the infusion with obinutuzumab. The incidence and intensity of IRRs decreased with subsequent infusions of obinutuzumab. In a few patients, concurrent signs of tumor lysis syndrome (TLS) were observed. Other frequently observed AEs include infections and neutropenia. These events appeared to be more common in patients with CLL compared to NHL.

In trials investigating the combination of obinutuzumab and CHOP, FC, chlorambucil or bendamustine, the incidence of AEs in the treatment arms with combined use was consistent with the known safety profiles of the individual study drugs. So far, no maximum tolerated dose, no dose-limiting toxicities, and no clear dose-related trends in the incidence of AEs have been determined.

A pooled analysis of safety data for obinutuzumab collected during the monotherapy studies BO20999 and BO21003 was conducted in patients with NHL (aggressive [aNHL] and indolent []iNHL]) or CLL who participated in those two studies (both Phase I and Phase II) and received monotherapy treatment with obinutuzumab and included a total 205 patients with NHL (49 aNHL and 156 iNHL patients) and 38 patients with CLL.

In the group of 38 patients with CLL treated with obinutuzumab monotherapy, the majority of patients (25 [66%]) were treated for ≥ 4 weeks to < 6 months. Eleven patients (29%) were exposed for 6 to < 12 months, and two patients (5%) were exposed for 12 months or longer. Eight of 38 patients (21%) with CLL were withdrawn during the treatment phase; 4 patients (11%) were withdrawn due to AEs, which indicates that AEs were mostly manageable. Almost all patients (37/38 [97%]) experienced an IRR. The number of patients with Grade 3□4 IRRs was 11/38 (29%). As is typical for patients with CLL, blood and lymphatic system disorders were among the most frequently reported AEs, in particular neutropenia (13/38 patients [34%]), febrile neutropenia (5/38 patients [13%]), and thrombocytopenia (7/38 patients [18%]).

Infections and infestations were common AEs, occurring in 21/38 patients (55%). Infections reported in more than one patient were nasopharyngitis (6 patients), bronchitis and sinusitis (4 patients each), influenza and lung infection (3 patients each), and herpes zoster and oral herpes (2 patients each).

Thirteen patients (34%) died, 8 of these due to disease progression. One patient died from an unspecified cause after withdrawal from the study for lack of response. This patient had received subsequent experimental therapies and had stable CLL at the time she died. For 4 additional patients, the cause of death was reported as colon cancer, lung adenocarcinoma, metastasis, and septic shock, and all were considered not to be related to treatment.

In the two studies investigating obinutuzumab as monotherapy, BO20999 and BO21003, patients with CLL appeared to be at a higher risk of experiencing an AE of special interest than patients with NHL. The largest difference in the incidences was seen for neutropenia (occurring

in 47% of patients with CLL [18/38] vs. 8% of patients with aNHL [4/49] and 8% of patients with iNHL [13/156]) and treatment-related AEs associated with the infusion (100% [38/38] vs. 80% (39/49) and 83% [129/156]).

To date, a very small number of patients have experienced TLS (six in total); four patients in the aNHL population (population including MCL) and one patient each in the CLL and iNHL populations.

Infections have been reported in 20/49 aNHL patients (41%), 74/156 iNHL patients (47%), and 21/38 CLL patients (55%). One iNHL patient was withdrawn from the study because of an infection. In addition, one CLL patient and one iNHL patient died from an infection (septic shock in both cases) during survival follow-up 671 days and 494 days after last dose of treatment, respectively.

Three CLL and 3 iNHL patients were withdrawn from treatment due to an AE of special interest, all for IRRs. An additional patient in the iNHL group discontinued treatment because of an infection. This indicates that these events were generally manageable.

In the Phase III Study BO21004 (CLL11), comparison of obinutuzumab + chlorambucil to chlorambucil alone showed that the most common AEs (all grades, Grades 3 – 4), respectively, were IRRs (69% vs. 0, 21% vs. 0), neutropenia (40% vs. 18%, 34% vs. 16%), thrombocytopenia (15% vs. 7%, 11% vs. 3%), anemia (12% vs. 10%, 4% vs. 5%), leukopenia (7% vs. 0, 5% vs. 0), pyrexia (10% vs. 7%, < 1 vs. 0), and cough (10% vs. 7%, 0 vs. < 1%).

The incidence of IRRs was 69% with the first infusion of obinutuzumab. The incidence of Grade 3 or 4 IRRs was 21%, with 8% of patients discontinuing therapy. The incidence of reactions with subsequent infusions was 3%, with the second 1000-mg dose and <1% thereafter. No Grade 3 or 4 IRRs were reported beyond the first 1000--mg infusion. Of the first 53 patients receiving obinutuzumab in the trial, 47 (89%) experienced an IRR. After this occurrence, study protocol modifications were made to require pre-medication with a corticosteroid, antihistamine, and acetaminophen. The first dose was also divided into two infusions (100 mg on Day 1 and 900 mg on Day 2). Of the 45 patients for whom these mitigation measures were implemented, 21 patients (47%) experienced a reaction with the first 1000-mg dose and <2% thereafter.

The incidence of neutropenia reported as an AE was 40% in the obinutuzumab-treated arm and 18% in the chlorambucil-alone arm, with the incidence of SAEs being 1% and 0%, respectively. Cases of late-onset neutropenia (occurring 28 days after completion of treatment or later) were 16% in the obinutuzumab-treated arm and 12% in the chlorambucil-alone arm.

The incidence of infections was similar between arms. Thirty-eight percent of patients in the obinutuzumab–treated arm experienced an infection, 9% were Grade 3 – 4, and none were fatal.

The incidence of thrombocytopenia reported as an AE was 15% in the obinutuzumab-treated arm and 7% in the chlorambucil-alone arm. Five percent of patients in the obinutuzumab-treated arm experienced acute thrombocytopenia (occurring within 24 hours after the obinutuzumab infusion).

The incidence of Grade 3 or 4 tumor lysis syndrome was 2% in the obinutuzumab-treated arm vs. 0% in the chlorambucil-alone arm.

AEs related to musculoskeletal disorders, including pain (System Organ Class), have been reported with obinutuzumab with higher incidence than with the comparator (17% vs. 13%, respectively) (Goede et al. 2013).

1.6.4. Risks Associated with Obinutuzumab Therapy

1.6.4.1. Hepatitis B Virus Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with anti-CD20 antibodies such as obinutuzumab. HBV reactivation has been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation has also occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive, and hepatitis B surface antibody [anti-HBs] positive). HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels and, in severe cases, increase in bilirubin levels, liver failure, and death.

All patients will be screened for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with obinutuzumab. For patients who show evidence of hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), physicians with expertise in managing hepatitis B will be consulted regarding monitoring, and initiation of HBV antiviral therapy will be considered.

Patients with evidence of current or prior HBV infection will be monitored for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following treatment with obinutuzumab. HBV reactivation has been reported for other CD20-directed cytolytic antibodies following completion of therapy.

In patients who develop reactivation of HBV while receiving obinutuzumab, immediately discontinue obinutuzumab and any concomitant chemotherapy, and institute appropriate treatment. Resumption of obinutuzumab in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming obinutuzumab in patients who develop HBV reactivation.

1.6.4.2. Progressive Multifocal Leukoencephalopathy

JC virus infection resulting in progressive multifocal leukoencephalopathy (PML), which can be fatal, was observed in patients treated with obinutuzumab. Consider the diagnosis of PML in any patient presenting with new onset or changes to pre-existing neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture. Discontinue obinutuzumab therapy and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

1.6.4.3. Infusion-Related Reactions

Obinutuzumab can cause severe and life-threatening IRRs. Two-thirds of patients experienced a reaction to the first 1000 mg of obinutuzumab infusion. IRRs can also occur with subsequent infusions. Symptoms may include hypotension, tachycardia, dyspnea, and respiratory symptoms (e.g., bronchospasm, larynx and throat irritation, wheezing, and laryngeal edema). Other common symptoms include nausea, vomiting, diarrhea, hypertension, flushing, headache, pyrexia, and chills.

Pre-medicate patients with acetaminophen, antihistamine, and a glucocorticoid. Institute medical management (e.g., glucocorticoids, epinephrine, bronchodilators, and/or oxygen) for IRRs as needed. Closely monitor patients during the entire infusion. IRRs within 24 hours of receiving obinutuzumab have occurred.

For patients with any Grade 4 IRRs, including but not limited to anaphylaxis, acute life-threatening respiratory symptoms, or other life-threatening infusion reaction, stop the obinutuzumab infusion. Permanently discontinue obinutuzumab therapy.

For patients with Grade 1, 2, or 3 IRRs, interrupt obinutuzumab for Grade 3 reactions until resolution of symptoms. Interrupt or reduce the rate of the infusion for Grade 1 or 2 reactions and manage symptoms.

For patients with pre-existing cardiac or pulmonary conditions, monitor more frequently throughout the infusion and the post-infusion period because these patients may be at greater risk of experiencing more severe reactions. Hypotension may occur as part of the obinutuzumab IRR. Consider withholding antihypertensive treatments for 12 hours prior to, during, and for the first hour after administration of each obinutuzumab infusion until blood pressure is stable. For patients at increased risk of hypertensive crisis, consider the benefits versus the risks of withholding their hypertensive medication as is suggested here.

1.6.4.4. Tumor Lysis Syndrome

Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, and/or hyperphosphatemia from TLS can occur within 12 – 24 hours after the first infusion. Patients with high tumor burden and/or high circulating lymphocyte count ($> 25 \times 10^9$/L) are at greater risk for TLS and should receive appropriate tumor lysis prophylaxis with anti-hyperuricemics (e.g.,

allopurinol) and hydration beginning 12 – 24 hours prior to the infusion of obinutuzumab. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

1.6.4.5. Infection

Serious bacterial, fungal, and new or reactivated viral infections can occur during and following obinutuzumab therapy. Do not administer obinutuzumab to patients with an active infection. Patients with a history of recurring or chronic infections may be at increased risk of infection.

1.6.4.6. Neutropenia

Obinutuzumab in combination with chlorambucil caused Grade 3 or 4 neutropenia in 34% of patients in clinical trials. Patients with Grade 3 to 4 neutropenia should be monitored frequently with regular laboratory tests until resolution. Anticipate, evaluate, and treat any symptoms or signs of developing infection. Neutropenia can also be of late onset (occurring more than 28 days after completion of treatment) and/or prolonged (lasting longer than 28 days).

Patients with neutropenia are strongly recommended to receive antimicrobial prophylaxis throughout the treatment period. Antiviral and antifungal prophylaxis should be considered.

1.6.4.7. Thrombocytopenia

Obinutuzumab in combination with chlorambucil caused Grade 3 or 4 thrombocytopenia in 12% of patients in clinical trials. In 5% of patients, obinutuzumab caused an acute thrombocytopenia occurring within 24 hours after the obinutuzumab infusion. In patients with Grade 3 or 4 thrombocytopenia, monitor platelet counts more frequently until resolution. Transfusion of blood products (i.e., platelet transfusion) may be necessary.

1.6.5. Summary of Pharmacokinetic and Pharmacodynamic Data for Obinutuzumab

A two-compartment model comprising a time-varying clearance pathway and a linear clearance pathway provides an adequate description of the pharmacokinetics of obinutuzumab following intravenous (IV) administration in Studies BO20999 and BO21003. Following the infusion of obinutuzumab, the elimination appears to be characterized by a clearance pathway that is dependent on time (i.e., starting at a typical value of 630 mL/day and then gradually decreasing to an asymptote of 60 mL/day at steady state) and a linear clearance pathway. Tumor burden may potentially contribute significantly to the clearance of obinutuzumab, especially at the beginning of treatment when CD20-positive tumor cells are most abundant. As tumor burden decreases, the clearance reaches an asymptote, which is believed to be primarily a function of the proteolytic metabolic clearance. Consequently, some patients with a high tumor burden may appear to clear the drug from the plasma faster than do patients with a low tumor burden because obinutuzumab binds to the CD20-positive tumor cells and is effectively removed from the plasma. Therefore, the clearance of the drug will vary with time, since repeated treatments with obinutuzumab will

reduce the quantity of CD20-positive tumor cells. Consequently, the number of obinutuzumab administrations during the first cycle of treatment may be expected to reduce the number of CD20-positive tumor cells, thus minimizing the impact of the time varying clearance pathway on obinutuzumab exposure.

Treatment with obinutuzumab resulted in extensive B-cell depletion, with all patients showing a reduction in cell count to absolute zero at some stage of their treatment cycle. Overall, there has been no notable increase in complement levels before and after infusion, but changes have been observed in the levels of interleukin (IL)-6 and IL-8 before and after infusion.

1.6.6 Worsening of Pre-existing Cardiac Conditions

In patients with underlying cardiac disease, arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure have occurred when treated with obinutuzumab. These events may occur as part of an IRR and can be fatal. Therefore patients with a history of cardiac disease should be monitored closely. In addition, these patients should be hydrated with caution in order to prevent a potential fluid overload.

1.7 Overview of Safety of CHOP

Risks and side effects related to Cyclophosphamide include:

Rev. 1/14, 6/14

(Table Version Date: May 28, 2013)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cyclophosphamide, more than 20 and up to 100 may have:
• Hair loss • Nausea, vomiting, loss of appetite • Sores in mouth • Infection, especially when white blood cell count is low • Absence of menstrual period which may decrease the ability to have children • Blood in urine

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cyclophosphamide, from 4 to 20 may have:
• Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions • Loss or absence of sperm which may lead to an inability to father children • Stuffy nose • Fluid around the heart

RARE, AND SERIOUS In 100 people receiving Cyclophosphamide, 3 or fewer may have:
• Severe skin rash with blisters and peeling which can involve mouth and other parts of the body • Damage to the heart or heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness • A new cancer including cancer of bone marrow (leukemia) caused by chemotherapy • Swelling of the body including the brain which may cause dizziness, confusion • Scarring of the lungs

Rev. 1/14, 6/14

Risks and side effects related to Doxorubicin include:

(Table Version Date: October 24, 2013)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Doxorubicin, more than 20 and up to 100 may have:
• Hair loss • Vomiting • Red colored urine, saliva, or sweat

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Doxorubicin, from 4 to 20 may have:
• Heart failure or heart attack which may cause shortness of breath, swelling of ankles, cough or tiredness which may occur years after the dose • Swelling of the body which may cause shortness of breath • Swelling and redness at the site of the medication injection or area of previous radiation • Belly pain • Sores in the mouth, throat or stomach • Nausea, diarrhea • Hepatitis which may cause yellow eyes and skin

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Doxorubicin, from 4 to 20 may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Cancer of the bone marrow (leukemia) caused by chemotherapy • Damage to organs which may cause infection, bleeding, may require transfusions • Darkening of the nail beds or skin or hands and feet • Loss of nails

RARE, AND SERIOUS In 100 people receiving Doxorubicin, 3 or fewer may have:
• Infection, especially when white blood cell count is low • Bruising, bleeding • Severe blood infection

Rev. 1/14, 6/14

Risks and side effects related to Vincristine include:

(Table Version Date: May 28, 2013)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Vincristine, more than 20 and up to 100 may have:
• Constipation • Hair loss • Pain or redness at the site of injection • Numbness and tingling of fingers or toes • Headache, jaw pain and/or muscle pain • Weakness and difficulty walking • Swelling of lower legs

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Vincristine, from 4 to 20 may have:
• Anemia which may cause tiredness, or may require transfusion • Drooping eyelids • Hoarseness

RARE, AND SERIOUS In 100 people receiving Vincristine, 3 or fewer may have:
• Seizure

Rev. 1/14, 6/14

Risks and side effects related to Prednisone include:

(Table Version Date: June 24, 2013)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Prednisone, more than 20 and up to 100 may have:
• In children and adolescents: decreased height • Loss of bone tissue • Mood swings • Skin changes, acne • Swelling of the body, tiredness, bruising • High blood pressure which may cause headaches, dizziness, blurred vision • Pain in belly • Increased appetite and weight gain • Weight gain in the belly, face, back and shoulders

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Prednisone, from 4 to 20 may have:
• Cloudiness of the eye, visual disturbances • Glaucoma • Infection • Non-healing wound • Diabetes • Damage to the bone which may cause joint pain and loss of motion • Kidney stones • Heartburn

RARE, AND SERIOUS In 100 people receiving Prednisone, 3 or fewer may have:
• Bleeding from sores in the stomach • Broken bones

REPRODUCTIVE RISKS:

You should not become pregnant or father a baby while on this study because the drugs in this study can affect a fetus. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. The long-term effects of lenalidomide and chemotherapy with

RCHOP on your ability to have children in the future are unknown. You should discuss fertility preservation strategies with your doctor.

1.8 Study Rationale

As discussed in section "1.1.1 Treatment Options", there are currently no standard of care management recommendations for patients that develop RT. Treatments of RT currently include the use of aggressive lymphoma combination regimens, but the response rates to these are poor and short lived. Given that CLL is considered a "disease of the elderly", a significant number of patients who develop RT are not able to tolerate intensive regimens and die without the ability to receive any salvage therapy.

Despite the advent of promising new drugs to clinical trials of patients with relapsed CLL and NHL over the last few years, patients with RT continue to be excluded from clinical trials. RT patients have dismal overall survival with a median ranging from five to eight months (Tsimberidou 2005), even in younger patients that would be better fit to tolerate current multidrug chemotherapy regimens. It is clear that there is an unmet need to study the novel investigational agents that are showing remarkable activity as monotherapy or in combination in CLL and NHL.

Two case reports of ibrutinib monotherapy in RT have been published to date showing clinical activity. The first report from Blood Cancer Journal noted Ibrutinib had activity highlighted two cases of Richter's Syndrome patients with activated-B-cell type (ABC) DLBCL. One case involved a 60-year old male with Rai stage IV CLL at diagnosis, with no chromosomal abnormalities who one month later developed rapidly progressive lymphadenopathy and was diagnosed with RS. The other case involved 59-year old male with Rai stage III CLL at diagnosis. His disease course was observed for eight years until he developed progressive lymphadenopathy, FISH showed trisomy 12 and deletion of p53 chromosomal abnormalities. Both patients were treated with chemotherapeutic regimens and neither were candidates for an allogeneic hematopoietic stem cell transplant. The first patient demonstrated 70% regression of his disease by CT scan one month after starting ibrutinib and 90% regression of disease after 3 months. The second patient was refractory to all treatments given prior to ibrutinib. Two months after beginning ibrutinib, CT scan showed 100% progression of neck adenopathy. Ibrutinib was discontinued after three months due to refractory response. Given the superior response of the first patient in contrast to that of the second patient, the data may suggest that ibrutinib is beneficial in RS patients with a certain genetic profile. A second report from the Mayo Clinic described the treatment of four patients with RS (Giri 2015) All patients experienced improvement in constitutional symptoms with two patients achieving a partial response, one patient achieving a complete response and one patient showing clinical activity as evidenced by a reduction in lymphadenopathy by physical exam (Wilson 2012).

A recent phase 1b, open-label, non-randomized study was conducted involving histologically confirmed CD20-positive B-cell non-Hodgkin lymphoma patients in six centers within the USA and France (Younes 2014). The treatment regimen consisted of Ibrutinib plus R-CHOP. Of the 33 patients enrolled, 32 completed treatment (one patient withdrew). 30 of the 32 remaining patients achieved an overall response. The maximum tolerated dose was not achieved

and the highest dose administered, 560mg per day of Ibrutinib, was recommended for phase 2 study. In this study, we will administer 560mg po daily of Ibrutinib as it has demonstrated clinical activity, safety, and tolerability in NHL patients in combination regimens.

We propose the use of ibrutinib in combination with obinutuzumab with and without CHOP, the chemotherapy regimen traditionally used to treat Richter's transformation.

The incorporation of the targeted agents ibrutinib and obinutuzumab in patients with a Richter's transformation may demonstrate improved responses and duration of responses, particularly given the outstanding responses from these drugs seen in both CLL and in NHL. This is a two-arm trial with two cohorts of patients based on their fitness to tolerate therapy.

2. STUDY OBJECTIVE

2.1. Primary Objective

To determine the efficacy of combining Ibrutinib with obinutuzumab (with or without CHOP) as measured by overall response rate (ORR).

2.2. Secondary Objectives

- To assess the safety of Ibrutinib in combination with obinutuzumab as measured by the incidence of prolonged hematologic toxicity in cycle 1 in subjects with a diagnosis of Richter's Transformation (RT), hematologic improvement, progression-free survival (PFS), overall survival (OS), and quality of life.
- Identify and correlate potential markers predictive of response to the combination therapy and associate pharmacogenetic findings to response and toxicity.

2.3.Exploratory Objective(s)

- To evaluate patient-reported outcome (PRO) of health-related quality of life by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACiT-Fatigue) scale
- **Exploratory Biomarker Assessments**

  The following biomarker samples will be collected
  • Serum
  • Plasma
  • Blood
  • Archival tumor tissue, when feasible
  • Leftover tissue from Bone marrow biopsies and/or aspirates (if obtained as part of clinical disease response assessments and tissue is remaining after clinical analysis, including pathology reports), when feasible

Requests for archival tissue and corresponding pathology report (i.e. samples obtained prior to study initiation) should be initiated at Cycle 1 Day 1.

- Correlative studies, to be performed depending on tissue availability. The following array will be performed for samples sent to Cancer Genetics or a local pathology laboratory and may be performed more than once. Whole exome sequencing will be done only once.
    - Selective array CGH for 15 distinct chromosomal regions, including **8q24 (MYC), 18q21 (BCL2), 17p13 (TP53), 9p21 (CDKN2A), and 13q14.**
    - Determination of B-cell clonality (by PCR)
    - Immunofluorescence and flow cytometry to characterize surface marker phenotype
    - Karyotyping
    - FISH:
        - 3q27 (BCL-6 breakpoint)
        - t(8;14) (MYC/IGH translocation)
        - t(14;18) (IGH translocation/BCL-2 translocation)
    - Immunohistochemistry:
        - Distinguish GCB versus non-GCB types of DLBCL
        - MYC
        - Ki-67
        - P53
        - Bcl-2
        - Bcl-6
        - CD30
        - EBER
    - Mutation analysis:
        - NOTCH1
        - SF3B1
        - TP53
        - MYD88

3. STUDY DESIGN AND TREATMENT

3.1. Overview of Study Design

This is a nonrandomized open-label Phase II study of Ibrutinib 560mg daily in combination with obinutuzumab on days 1, 2, 8, and 15 of cycle 1 and then on day 1 of cycles 2-6 in subjects with RT.

3.1.1 Study Schema and Design Overview

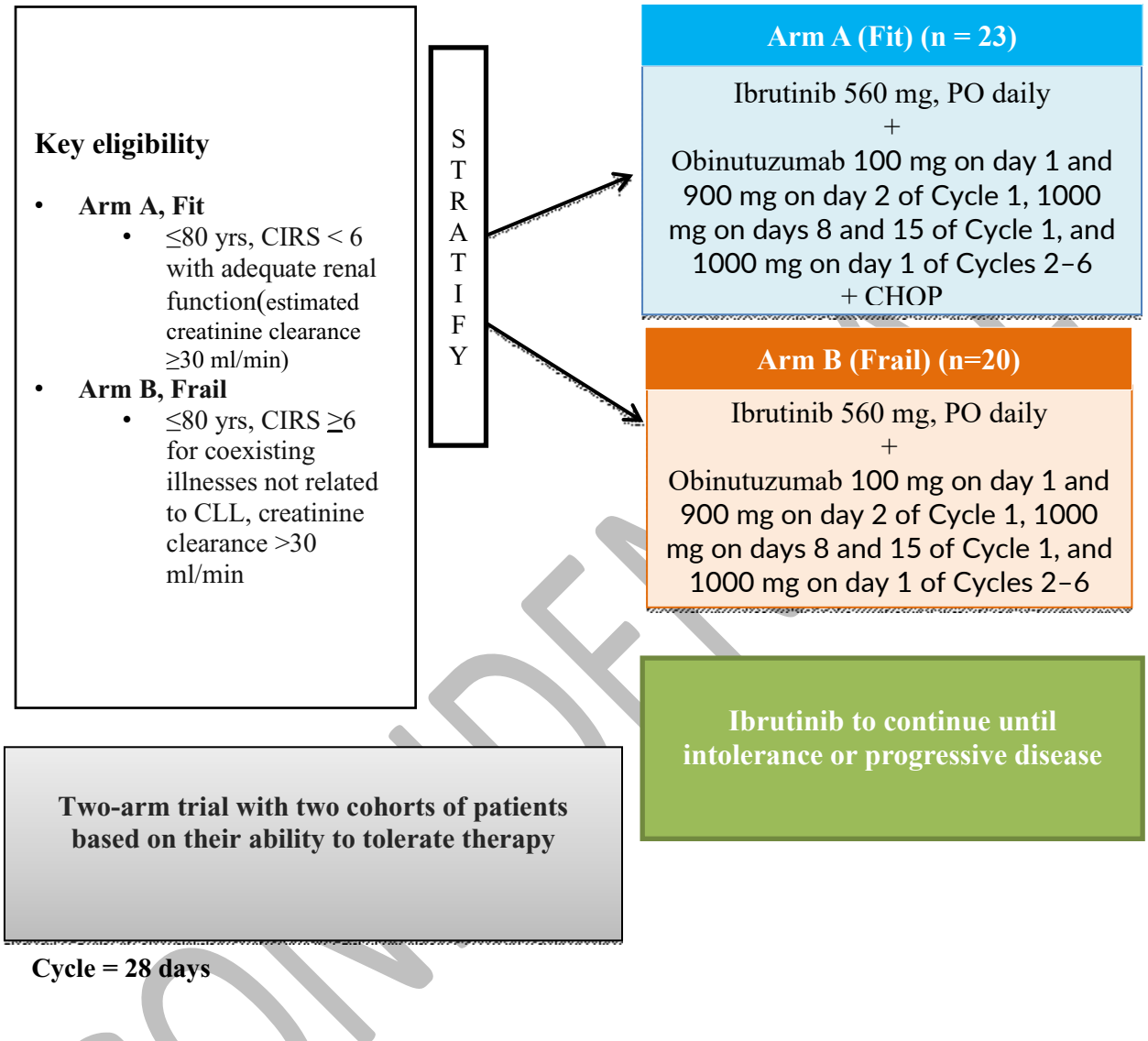

Figure 1. Study Design

3.2.Study Design Rationale

Study Design and Treatment

This is a nonrandomized open-label Phase II study of Ibrutinib 560mg po daily in combination with Obinutuzumab, 100 mg on day 1 and 900 mg on day 2 Cycle 1, 1000 mg on day 8 and 15 of Cycle 1, and 1000 mg on day 1 of Cycles 2–6in subjects with RT. We propose a design to evaluate two study arms: fit and frail.

Up to 50 subjects will be screened in the combination treatment groups: up to 20 patients will receive the combination ibrutinib and obinutuzumab alone (frail patients) and up to 23 patients will receive ibrutinib and obinutuzumab in combination with the CHOP regimen (fit patients). Each group will follow an independent but parallel design and will receive up to 6 cycles of infusion therapy.

The primary objective of the study is to determine the efficacy of combining Ibrutinib with obinutuzumab (with or without "CHOP" chemotherapy regimen) as measured by overall response rate (ORR), defined as CR PR, or SD. We plan to estimate the response rate and generate a 95% confidence interval (CI). Further development will proceed if the 95% CI will include 50%.

Secondary objectives include assessment of the safety of Ibrutinib in combination with obinutuzumab and determination of progression-free survival (PFS) and overall survival (OS). Exploratory analysis will evaluate patient-reported outcome (PRO) health-related quality of life by FACiT-Fatigue scores.

Patients who have no evidence of progressive disease after cycle 3 will be treated for up to 3 additional 28 day cycles of the infusion regimen based on tolerability and lack of evidence of progressive disease. Ibrutinib will be continued indefinitely until progression of disease or toxicity.

All patients will be treated with ibrutinib at a dose of 560 mg orally continuously with standard doses of 1000mg obinutuzumab as per package insert guidelines to be given for up to six cycles. Obinutuzumab [and CHOP treatment ("G-CHOP") if in the fit cohort] will be stopped sooner than 6 cycles in subjects with unacceptable toxicity, disease progression, or achievement of complete remission with no evidence of minimal residual disease. Ibrutinib will be held in subjects with unacceptable toxicity.

If investigator feels the toxicity is from chemoimmunotherapy rather than ibrutinib, patient will be allowed to continue on ibrutinib monotherapy while the toxicity from the other agents resolves or improves to a grade 1 toxicity. Concomitant chemoimmunotherapy regimen (G-CHOP) or immunotherapy (G) can be dose delayed if the toxicity occurs without interruption of ibrutinib administration if the investigator considers that ibrutinib is not contributing to or is not a direct cause of the toxicity.

After treatment with obinutuzumab, or G-CHOP, is completed or stopped, patients achieving good response with tolerable side effects will continue on ibrutinib until progression of disease or undue toxicities.

Toxicities will be scored using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All adverse clinical experiences will be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. To monitor for tumor lysis syndrome and cytopenia(s), the subjects will have blood drawn on days 1 through 3 of the first cycle of therapy, then days 8, 15, and 28 during the first cycle of therapy. Subjects will also have blood drawn on Day 1 and Day 15 during subsequent cycles of therapy. All subjects will receive prophylactic medications (allopurinol, acyclovir, bactrim, diflucan, levaquin) as clinically indicated.

4. SUBJECT SELECTION

4.1. Inclusion Criteria

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

- Subjects ≥ 18 and ≤80 years of age
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤2
- Histologically confirmed Richter's transformation in treatment-naive and previously treated CLL/SLL patients
- Regimen-specific inclusions:

  Fit Group: Patients with prior BTK agent exposure (including Ibrutinib) may be included on the FIT arm.

  Frail Group: Patients who have had prior BTK inhibitors (including Ibrutinib) should not be included on the Frail arm.

Patients may have had prior exposure to alternative B-cell signaling receptor agents including prior exposure to a Phosphoinositide 3-Kinase Delta (PI3Kd) inhibitor, and a Spleen tyrosine kinase (SYK) inhibitor.

- Prior exposure to anti-CD20 monoclonal antibody
- Willing and able to participate in all required evaluations and procedures in this study protocol
- Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations)
- Adequate hematologic function defined as:
  - Absolute neutrophil count ≥1000cells/mm^3 (1.0 x 10^9/L).
  - Platelet count ≥50,000 cells/mm^3 (50 X 10^9/L).
  - Hemoglobin >8.0 g/dL.
- Adequate hepatic and renal function defined as:
  - Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 2.5 x upper limit of normal (ULN).
  - Estimated Creatinine Clearance ≥30 ml/min (Cockcroft-Gault)
  - Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
- PT/INR <1.5 x ULN and PTT (aPTT) <1.5 x ULN, unless patient has lupus anticoagulant or liver impairment due to lymphoma infiltration.
- Documentation of CD20+ status (for B cell malignancies)

- Female subjects who are of non-reproductive potential (i.e., post-menopausal by history - no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR

history of bilateral oophorectomy). Female subjects of childbearing potential must have a negative serum pregnancy test upon study entry.

- Male and female subjects who agree to use highly effective methods of birth control (e.g., implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence, or sterilized partner) and a barrier method (e.g., condoms, vaginal ring, sponge etc.) during the period of therapy and for 30 days after the last dose of study drug

4.2. Exclusion Criteria

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

Regimen-specific exclusions:

- ARM A: **Fit Group:** known hypersensitivity to any of the agents in the combination regimen or having a comorbidity that may affect patient's ability to tolerate therapy at the investigator's discretion. Patients with prior BTK agent exposure (including Ibrutinib) may be included on the FIT arm.
- ARM B: **Frail Group:** Known grade 4 hypersensitivity to a monoclonal antibody. Patients who have had prior BTK inhibitors (including Ibrutinib) should not be included on the Frail arm.
- Chemotherapy ≤21 days prior to first administration of study treatment
- Biologic immunotherapy ≤10 days prior to days prior to first administration of study treatment
- BCR inhibitors ≤24 hours days prior to first administration of study treatment
- Major surgery, excluding diagnostic tissue biopsies, within 4 weeks of first dose
- Any of the following laboratory abnormalities:
  - Absolute neutrophil count (ANC) < 1000 cells/mm3 (1.0 x 109/L)
  - Platelet count <50,000/mm3 (<50 x 10^9/L)
  - Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) >2.5 x upper limit of normal (ULN)
  - Estimated Creatinine Clearance ≤30 ml/min (Cockcroft-Gault)
  - Bilirubin >1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
- 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.
- History of other malignancies, except:
  - Malignancy treated with curative intent and with no known active disease present for ≥2 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician.
  - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.

- Adequately treated carcinoma in situ without evidence of disease.

- Concurrent systemic immunosuppressant therapy (e.g., cyclosporine A, tacrolimus, etc., or chronic administration [>14 days] of >20 mg/day of prednisone) within 28 days of the first dose of study drug.
- Recent infection requiring systemic treatment that was completed ≤14 days before the first dose of study drug.
- Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 4), grade ≤1, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia.
- Known bleeding disorders (e.g., von Willebrand's disease) or hemophilia.
- History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
- Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). *Subjects who are positive for hepatitis B core antibody or hepatitis B surface antigen or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.*
- Any uncontrolled active systemic infection.
- Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization.
- Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.
- Concomitant use of warfarin or other Vitamin K antagonists.
- Subjects who received a strong cytochrome P450 (CYP) 3A4 inhibitor within 7 days prior to the first dose of ibrutinib or subjects who require continuous treatment with a strong CYP3A inhibitor. (see Appendix 3)
- Known active bacterial, viral, fungal, mycobacterial, or other infection (excluding fungal infections of nail beds) or any major episode of infection requiring treatment with IV antibiotics or hospitalization (related to the completion of the course of antibiotics) within 4 weeks before the start of Cycle 1
- Known infection with human immunodeficiency virus (HIV) or human T-cell leukemia virus 1 (HTLV-1) seropositive status
- Women who are pregnant or lactating
- Fertile men or women of childbearing potential unless 1) surgically sterile or 2) using an adequate measure of contraception such as oral contraceptives, intrauterine device, or barrier method of contraception in conjunction with spermicidal jelly.
- Effective contraception is required while receiving obinutuzumab. For women, effective contraception is required to continue for ≥ 12 months after the last dose of obinutuzumab. For men, effective contraception is required to continue for 3 months after the last dose of obinutuzumab treatment.

- Currently active, clinically significant hepatic impairment Child-Pugh class C according to the Child Pugh classification (see Appendix 4)
- Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug

5. TREATMENT OF SUBJECTS

5.1.Study treatment

This is a nonrandomized open-label Phase II study of Ibrutinib 560mg daily in combination with obinutuzumab 100 mg on day 1 and 900 mg on day 2 Cycle 1, 1000 mg on day 8 and 15 of Cycle 1, and 1000 mg on day 1 of Cycles 2–6 in subjects with RT. Each cycle will consist of 28 days.

For those subjects accrued to the fit arm (ARM A), they will also receive cyclophosphamide (IV) at 750 mg/m² on day 1 of cycles 1-6, hydroxydaunorubicin (IV) at 50 mg/m² on day 1 of cycles 1-6, oncovin (vincristine) (IV) at 1.4 mg/m² (max. 2 mg) on day1 of cycles 1-6, and prednisone or equivalent (PO) at a flat dose of 100mg flat dose per day, or dosage as investigator sees fit on days 1-5 of cycles 1-6. Up to 50 subjects will be screened for enrollment in the combination treatment groups: up to 20 patients will receive the combination ibrutinib and obinutuzumab alone (frail patients) and up to 23 patients will receive ibrutinib and obinutuzumab in combination with the CHOP regimen (fit patients).

All patients will be treated with ibrutinib at a dose of 560 mg orally daily with standard doses of 1000mg obinutuzumab as per package insert guidelines to be given for up to six cycles. Obinutuzumab [and CHOP treatment ("G-CHOP") if in the fit cohort] will be stopped sooner than six cycles in subjects with unacceptable toxicity, disease progression, or achievement of complete remission with no evidence of minimal residual disease. Ibrutinib will be held in subjects with unacceptable toxicity. After treatment with obinutuzumab or G-CHOP is completed or stopped, patients achieving good response with tolerable side effects will continue on Ibrutinib until progression of disease or undue toxicities.

5.2.Study Medication

5.2.1. Ibrutinib

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

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

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

Study drug labels will contain information to meet the applicable regulatory requirements.

5.2.1.1. Dose and Administration

Ibrutinib 560 mg (4 x 140-mg capsules) is administered orally once daily. The capsules are to be taken around the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study (Appendix 3).

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

The first dose will be delivered in the clinic on Day 1, after which subsequent dosing is typically on an outpatient basis. Ibrutinib will be dispensed to subjects in bottles at each visit. Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records updated at each visit. Returned capsules must not be re-dispensed to anyone.

5.2.1.2. Overdose

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

Refer to Section 11.4 for further information regarding AE reporting.

5.2.1.3. Dose Modification for Adverse Reactions

If investigator feels adverse reactions are related to chemoimmunotherapy rather than ibrutinib, patient will be allowed to continue on ibrutinib monotherapy while the toxicity from the other agents resolves. Concomitant chemoimmunotherapy regimen (G-CHOP) or immunotherapy (G) can be dose delayed if the toxicity occurs without interruption of ibrutinib administration if the investigator considers that ibrutinib is not contributing to or is not a direct cause of the toxicity.

The dose of the ibrutinib study drug should be modified according to the dose modification guidelines in Table 1 if any of the following toxicities occur:

- 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[9]
- 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) or for subjects with baseline thrombocytopenia, 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 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 6.2.4).

Table 1. Ibrutinib Dose Modifications

Occurrence	Action to be Taken
First	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at original dose level
Second	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (420 mg per day for 560 mg /day dose)
Third	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (280 mg per day for 560 mg /day dose)
Fourth	Discontinue study drug

A high number of circulating malignant cells (>400000/mcL) may confer increased risk of leukostasis; these subjects should be closely monitored. Administer supportive care such as hydration and/or leukophoresis as indicated. Ibrutinib may be temporarily held, and medical monitor should be contacted.

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

Dose Modification for Hepatic Impaired Subjects

Subjects who develop acute hepatic toxicity with liver enzymes Grade 3 or higher while on study should be managed per standard dose modification guidelines in **Section 5.2.1.3**. Ibrutinib is metabolized in the liver and therefore subjects with clinically significant hepatic impairment at the time of screening (Child- Pugh class C) are excluded from study participation. Concomitant use of strong CYP inhibitors is not permitted in subjects with chronic hepatic impairment. Refer

to Appendix 6 for Child-Pugh classification. Please refer to Table 2 for dose modification due to hepatic impairment.

Table 2. Dose Modification Guidance for Hepatic Impaired Subjects

	Child Pugh class A (Mild hepatic impairment)*		**Child Pugh Class B (Moderate hepatic impairment)****		**Child Pugh class C (Severe hepatic impairment)**
	Ongoing at time of enrollment	Develops during study	Ongoing at time of enrollment	Develops during study	Develops during study
Ibrutinib Dose (daily)	280 mg	280mg	140 mg	140 mg	Hold until improves to moderate [Class B] or better)

* If further reduction is needed due to non-hepatic toxicity, dose may be reduced to 140 mg. In the event that additional reduction is needed, ibrutinib should be held for non-hepatic toxicity until resolution.
** If further reduction is needed due to non-hepatic toxicity, ibrutinib should be held until resolution.

5.2.2. *Obinutuzumab*

5.2.3. Obinutuzumab

5.2.3.1. Formulation

Obinutuzumab is provided as a single-use vial. Each vial contains a sterile liquid formulation in a 50-mL pharmaceutical-grade glass vial containing a nominal dose of 1000 mg of obinutuzumab (G3 material). The formulated drug product consists of 25 mg/mL drug substance formulated in histidine/histidine-HCl, trehalose, and poloxamer 188. The vial contains 41 mL (with 2.5% overfill).

5.2.3.2. Storage

The recommended storage conditions for the obinutuzumab drug product are between 2°C and 8°C, protected from light. Chemical and physical in-use stability for obinutuzumab dilutions in 0.9% sodium chloride (NaCl) at concentrations of 0.2 – 20 mg/mL have been demonstrated for 24 hours at 2°C – 8°C and an additional 24 hours at ambient temperature and ambient room lighting. The prepared diluted product should generally be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C unless reconstitution/dilution has taken place in controlled and validated aseptic conditions. Obinutuzumab should not be frozen

or shaken. Mix gently. All transfer procedures require strict adherence to aseptic techniques. Do not use an additional in line filter because of potential adsorption.

Preparation

Obinutuzumab drug product intended for IV infusion is prepared by dilution of the drug product into an infusion bag containing 0.9% NaCl.

One vial may be used to prepare both the 100-mg dose (equals 4 mL) and 900-mg dose (equals 36 mL) following the directions below. If both bags are prepared at the same time, the reconstitution/dilution has to take place in controlled and validated aseptic conditions. Subsequently store the 900-mg bag for a maximum of 24 hours at 2°C – 8°C and administer the next day.

To prepare a 100-mg dose: The final drug concentration of a 100-mg dose should be in the range of 0.4 mg/mL to 4.0 mg/mL. Using a 250-mL infusion bag containing 0.9% NaCl, withdraw and discard 4 mL of the sodium chloride. Withdraw 4 mL of obinutuzumab from a single glass vial and inject it into the infusion bag (discard any unused portion of obinutuzumab left in the vial unless reconstitution/dilution has taken place in controlled and validated aseptic conditions). Gently invert the infusion bag to mix the solution. Do not shake.

To prepare a 900-mg dose: The final drug concentration of a 900-mg dose should be in the range of 0.4 mg/mL to 4.0 mg/mL. Using a 250-mL infusion bag containing 0.9% NaCl, withdraw and discard 36 mL of the sodium chloride. Withdraw 36 mL of obinutuzumab from a single glass vial and inject it into the infusion bag (discard any unused portion of obinutuzumab left in the vial unless reconstitution/dilution has taken place in controlled and validated aseptic conditions). Gently invert the infusion bag to mix the solution. Do not shake.

To prepare a 1000-mg dose: The final drug concentration of a 1000-mg dose should be 4 mg/mL. Using a 250-mL infusion bag containing 0.9% NaCl, withdraw and discard 40 mL of the NaCl. Withdraw 40 mL of obinutuzumab from a single glass vial and inject it into the infusion bag (discard any unused portion of obinutuzumab left in the vial). Gently invert the infusion bag to mix the solution. Do not shake.

Administration sets with polyvinyl chloride, polyurethane, or polyethylene as product contact surface and IV bags with polyolefin, polypropylene, polyvinyl chloride, or polyethylene as product contact surface are compatible and may be used. Use of a port or peripherally inserted central catheter line is acceptable.

Do not use obinutuzumab beyond the expiration date stamped on the carton.

5.2.4. Dosage and Administration

Obinutuzumab administered by IV infusion for up to 6 cycles (28-day cycles):

- On Cycle 1, Day 1, 100 mg obinutuzumab will be administered
- On Cycle 1, Day 2, 900 mg of obinutuzumab will be administered

- On Cycle 1, Days 8 and 15, 1000 mg of obinutuzumab will be administered.
- On Cycles 2 – 6, Day 1, 1000 mg of obinutuzumab will be administered (see Table 2)

Obinutuzumab must be administered in a clinical setting (inpatient or outpatient). Full emergency resuscitation facilities should be immediately available, and patients should be under close supervision by the investigator at all times. Obinutuzumab should be given as a slow IV infusion through a dedicated line. IV infusion pumps (such as Braun Infusomat Space) should be used to control the infusion rate of obinutuzumab. Do not administer as an IV push or bolus. After the end of the first infusion, the IV line should remain in place for at least 2 hours in order to be able to administer IV drugs if necessary. If no AEs occur after 2 hours, the IV line may be removed. For subsequent infusions, the IV line should remain in place for at least 1 hour from the end of infusion; if no AEs occur after 1 hour, the IV line may be removed.

If the subject has an infusion-related reaction, the obinutuzumab infusion could be given at a later date during the cycle. If the subject doesn't tolerate the dose of obinutuzumab on Cycle 1, Day 2 or in the event that the duration of the infusion will last longer than the outpatient facility operating hours, the patient may be admitted to the hospital for completion of the infusion without this being considered an SAE.

5.2.4.1. Premedication Requirements

Infusion-Related Reactions

Since some patients may develop hypersensitivity or other IRRs to obinutuzumab, pre-medication is recommended to reduce the risk of infusion reactions as outlined below:

- Cycle 1, Days 1 and 2, all patients require pre-medication with:
  - IV glucocorticoid: dexamethasone (20 mg) or methylprednisolone (80 mg) administered at least one hour prior to obinutuzumab infusion. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.
  - An oral acetaminophen (1000 mg) and an antihistamine such as diphenhydramine (50 mg) administered at least 30 minutes before starting each obinutuzumab infusion.
- Cycle 1, Days 8 and 15 and Cycles 2-6, Day 1:
  - All patients require pre-medication with oral acetaminophen (1000 mg) administered at least 30 minutes before starting each obinutuzumab infusion.
  - Patients who experience an IRR (Grade 1 or more) with the previous infusion will require pre-medication with an antihistamine such as diphenhydramine (50 mg) administered at least 30 minutes before starting each subsequent obinutuzumab infusion.
  - Patients who experience a Grade 3 IRR with the previous infusion or who have lymphocyte counts of $\geq 25 \times 10^9$/L prior to the next treatment will require pre medication with IV glucocorticoid: dexamethasone (20 mg) or methylprednisolone (80 mg) administered at least one hour prior to obinutuzumab infusion. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.

Hypotension may be expected to occur during obinutuzumab infusions. Withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their hypertensive medication.

For TLS prophylaxis, see Section 5.3.1.1.

5.2.4.2. *Obinutuzumab* Dosing

The first 1000 mg of obinutuzumab will be administered *over 2 days. During Cycle 1, Day 1, 100 mg will be administered. On the following day (Cycle 1, Day 2), 900 mg will be administered* (see Table 2).

Table 2 Obinutuzumab Dosing Schedule

Cycle and Day of Administration		Dose of Obinutuzumab	Rate of Infusion (in the Absence of Infusion Reactions/ Hypersensitivity during Previous Infusions)
Cycle 1	Day 1	100 mg	Administer at 25 mg/hour over 4 hours. Do not increase the infusion rate.
	Day 2	900 mg	Administer at 50 mg/hour. The rate of the infusion can be escalated in increments of 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour.
	Day 8	1000 mg	Infusions can be started at a rate of 100 mg/hour and increased by 100 mg/hour increments every 30 minutes to a maximum of 400 mg/hour.
	Day 15	1000 mg	
Cycles 2–6	Day 1	1000 mg	

If a patient experiences any grade infusion reaction during infusion, adjust the infusion as outlined below:

- Grade 4 (life threatening): Stop infusion and discontinue therapy.
- Grade 3 (severe): Temporarily interrupt infusion and treat symptoms. Upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the infusion reaction occurred) and, if patient does not experience any infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose.
- Grade 1 – 2 (mild to moderate): Reduce infusion rate and treat symptoms. Upon resolution of symptoms, continue infusion and, if patient does not experience any infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose.

5.2.5. Dosage Modification/Toxicity Management

If a patient experiences an IRR of any grade during infusion, adjust the infusion as follows:

- Grade 4 (life-threatening): Stop infusion immediately and permanently discontinue obinutuzumab therapy.
- Grade 3 (severe): Interrupt infusion and manage symptoms. Upon resolution of symptoms, consider restarting obinutuzumab infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred) and, if the patient does not experience any further infusion-reaction symptoms, the infusion rate escalation may resume at the increments and intervals appropriate for the treatment cycle dose. Permanently discontinue treatment if a patient experiences a Grade 3 infusion-related symptom at re-challenge.
- Grade 1 – 2 (mild to moderate): Reduce the infusion rate or interrupt infusion and treat symptoms. Upon resolution of symptoms, continue or resume infusion and, if the patient does not experience any further infusion-reaction symptoms, infusion rate escalation may resume at the increments and intervals appropriate for the treatment cycle dose.

5.2.5.1. Assessment of Hematologic Toxicities

The evaluation of potential treatment-induced toxicity in patients with advanced CLL may be quite difficult and requires careful consideration of both the manifestations of the underlying disease, as well as adverse reactions to the therapy under study. Some of the conventional criteria for toxicity are not applicable, especially under circumstances of progressive bone marrow failure from the CLL itself.

Dose modifications for hematologic toxicity in patients with CLL must be made with consideration of the increased frequency of hematologic compromise at the initiation of therapy. Therefore, the standard criteria used for solid tumors are difficult to be applied directly; many patients would be considered to have Grade 2 – 4 hematologic toxicity at presentation.

As a consequence, dose modification decisions for patients with cytopenia (below the lower limit of the normal range) at baseline will be based on the NCI sponsored Working Group (NCI-WG) grading scale for hematologic toxicity in CLL studies (Hallek et al. 2008). For patients with a normal neutrophil count, platelet count, and/or hemoglobin value at baseline, the NCI CTCAE, v4.0, will be used.

5.2.5.2. Dosage Modifications

Consider treatment interruption if a patient experiences an infection, Grade 3 or 4 cytopenia, or a ≥Grade 2 non-hematologic toxicity.

5.2.5.3. Administration of Granulocyte Colony-Stimulating Factor

G-CSF may be administered as primary prophylaxis in each cycle of therapy, as per the American Society of Clinical Oncology (ASCO) guidelines or each site's institutional standards.

5.2.5.4. Hepatitis B Virus Reactivation

Positive serology for Hepatitis B is defined as positivity for Hepatitis B surface antigen (HBsAg) or Hepatitis B core antibody (anti-HBc). Patients who are positive for anti-HBc may be considered for inclusion in the study by the Medical Monitor on a case-by-case basis if they are Hepatitis B viral DNA negative and are willing to undergo ongoing HBV DNA testing by real-time PCR. Patients with positive serology may be referred to a hepatologist or gastroenterologist for appropriate monitoring and management.

For the subset of patients who are Hepatitis B viral DNA negative and anti-HBc positive and have undetectable Hepatitis B viral DNA levels at screening, Hepatitis B viral DNA levels must be followed approximately every 4 weeks. Guidelines for the management of hepatitis B reactivation are outlined in Table 3.

Table 3 Management of Hepatitis B Reactivation

Hepatitis B Viral DNA Level by Real-Time PCR	Guideline
> 100 IU/mL	• Hold obinutuzumab • Begin anti-viral medication and treat for at least 1 year after the last dose of obinutuzumab. • Immediately refer the patient to a gastroenterologist or hepatologist for management. • Resume obinutuzumab once Hepatitis B viral DNA levels decrease to undetectable levels.
> 100 IU/mL while on anti-viral medication	Discontinue obinutuzumab.
29–100 IU/mL	Retest within 2 weeks. If still hepatitis B viral DNA positive: • Hold obinutuzumab • Begin anti-viral medication and treat for at least 1 year after the last dose of obinutuzumab. • Immediately refer the patient to a gastroenterologist or hepatologist for management • Resume obinutuzumab once Hepatitis B viral DNA levels decrease to undetectable levels

5.2.5.5. Management of Infusion-Related Reactions and Anaphylaxis

Please refer to Section 5.3.1 for information relating to permitted concomitant medications. Medications (including subcutaneous epinephrine, corticosteroids, and intravenous diphenhydramine) and resuscitation equipment should be available for immediate use.

Life-Threatening Infusion-Related Reactions and Anaphylaxis

In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or IgE-mediated anaphylactic reaction, obinutuzumab should be discontinued and no additional obinutuzumab should be administered. Patients who experience any of these reactions should receive aggressive treatment of symptoms and will be discontinued from study treatment.

Tumor Lysis Syndrome

For patients with evidence of TLS, obinutuzumab should be discontinued and the patient treated as clinically indicated. Following the complete resolution of TLS complications, obinutuzumab may be re administered at the full dose during the next infusion in conjunction with prophylactic therapy.

5.3. Concomitant and Excluded Therapies

5.3.1. Concomitant Therapy

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 14 days preceding the study entry evaluation and the early study treatment termination visit/study treatment completion visit. All concomitant medications should be reported to the investigator and recorded on the appropriate electronic Case Report Form (eCRF).

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. Effective contraception is required while receiving obinutuzumab. For women, effective contraception is required to continue for ≥ 12 months after the last dose of obinutuzumab. For men, effective contraception is required to continue for ≥ 3 months after the last dose of obinutuzumab.

5.3.1.1. Prophylaxis for Tumor Lysis Syndrome

All patients with peripheral blood lymphocyte counts of $\geq 25 \times 10^9$/L or bulky lymphadenopathy must receive prophylaxis for TLS prior to the initiation of study treatment. This includes appropriate hydration consisting of a fluid intake of approximately 3 L/day starting 1 to 2 days prior to the first dose of obinutuzumab and administration of allopurinol (300 mg/day orally) or a suitable alternative treatment starting prior to the first infusion of obinutuzumab (Cycle 1, Day 1). All patients should then be carefully monitored during the initial weeks of treatment. Patients still considered at risk for TLS because of persistently high tumor burden (i.e., peripheral blood lymphocyte counts $\geq 25 \times 10^9$/L) before the second and subsequent infusions of obinutuzumab should continue TLS prophylaxis with allopurinol and adequate hydration until the risk is abated, as determined by the investigator.

5.3.1.2. Infections Prophylaxis

Pneumocystis jirovecii pneumonia prophylaxis (160 mg trimethoprim/800 mg sulfamethoxazole orally twice daily or suitable alternative according to each site's institutional standards) and anti-

herpetic viral prophylaxis are recommended for patients with CLL during treatment and for up to 12 months following treatment as appropriate.

It is strongly recommended that patients with neutropenia receive antimicrobial prophylaxis throughout the treatment period. Antiviral and antifungal prophylaxis should be considered.

5.3.1.3. Other Concomitant Medications

Necessary supportive measures for optimal medical care will be given throughout the study according to each site's institutional standards, including the use of growth factors (e.g., erythropoietin) if clinically indicated. G-CSF may be administered as primary prophylaxis in each cycle of therapy according to the American Society of Clinical Oncology (ASCO) guidelines (Smith et al. 2006) or each site's institutional standards.

The use of live viral vaccines is contraindicated. Responses to inactivated vaccines, recombinant vaccines, and cell-wall vaccines are unreliable and suboptimal in CLL patients.

5.4. Criteria for Permanent Discontinuation of Study Drug

5.5. Obinutuzumab-Specific Criteria

Patients who meet the following criteria should be discontinued from the study:

- Active HBV infection or hepatitis
- Severe or life-threatening anaphylaxis or hypersensitivity reaction

Patients who are carriers of hepatitis B at the time of discontinuation from study treatment will continue to be followed for clinical and laboratory signs of active HBV infection and for signs of hepatitis.

5.6. General Criteria

- Inability of patient to comply with study requirements
- Determination by the investigator that it is no longer safe for the patient to continue therapy

6. CONCOMITANT MEDICATIONS/PROCEDURES

6.1. Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is permitted per institutional policy and in accordance with the ASCO guidelines (Smith 2006). Transfusions may be given in accordance with institutional policy.

Short courses (≤14 days) of steroid treatment for non-cancer related medical reasons (e.g., joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 100mg per day of prednisone or equivalent are permitted.

The following may be considered: localized hormonal or bone sparing treatment for non-B-cell malignancies, and localized radiotherapy for medical conditions other than the underlying B-cell malignancies.

Treatment for autoimmune cytopenias are permitted for <14 days at doses that do not exceed 100 mg per day of prednisone or equivalent.

6.2. Medications to be Used with Caution

6.2.1. CYP3A- Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A. Concomitant use of ibrutinib with drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure. Dose adjustment of ibrutinib due to concomitant use of CYP3A inhibitors should follow Table 4.

Table 4. Dose Modification Guidance for CYP3A Inhibitors/Inducers

Patient Population	Co-administered Drug	Recommended Ibrutinib Dose for the Duration of the Inhibitor Use[a]
B-Cell Malignancies	Mild CYP3A inhibitors	420 mg or 560 mg once daily per indication. No dose adjustment required.
	Moderate CYP3A inhibitors	280 mg once daily.
	Voriconazole Posaconazole at doses less than or equal to suspension 200 mg BID	140 mg once daily.
	Other strong CYP3A inhibitors Posaconazole at higher doses[b]	Avoid concomitant use and consider alternative with less CYP3A inhibitory potential. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib. If the benefit outweighs the risk, and long-term dosing with a CYP3A inhibitor is required (more than seven days), reduce ibrutinib dose to 140 mg once daily for the duration of the inhibitor use.
Chronic Graft versus Host Disease	Mild CYP3A inhibitors	420 mg once daily. No dose adjustment required.
	Moderate CYP3A inhibitors	420 mg once daily. No dose adjustment required.
	Voriconazole Posaconazole at doses less than or equal to suspension 200 mg BID	280 mg once daily.
	Posaconazole at higher doses[b]	140 mg once daily.
	Other strong CYP3A inhibitors	Avoid concomitant use and consider alternative with less CYP3A inhibitory potential. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib. If the benefit outweighs the risk and long-term dosing is required (more than seven days), reduce ibrutinib dose to 140 mg once daily for the duration of the inhibitor use.

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

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

After discontinuation of a CYP3A inhibitor, resume previous dose of ibrutinib.

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

A list of common CYP3A inhibitors and inducers is provided in Appendix 3. A comprehensive list of inhibitors, inducers, and substrates may be found at → http://medicine.iupui.edu/clinpharm/ddis/main-table/

This website is continually revised and should be checked frequently for updates.

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

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp), nor other major transporters, except OCT2, but is a mild inhibitor (with an IC_{50} of 2.15 μg/mL) of P-gp and breast cancer resistance protein (BCRP). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There are no clinical data available; therefore, to avoid a potential interaction in the GI tract, narrow therapeutic range P-gp or BCRP substrates such as digoxin, should be taken at least 6 hours before or after ibrutinib. Ibrutinib may also inhibit BCRP systemically and increase the exposure of drugs that undergo BCRP-mediated hepatic efflux, such as rosuvastatin.

Based on preliminary data from the combination studies of ibrutinib and venetoclax, venetoclax exposure (area under the concentration-time curve [AUC]) at 400 mg QD appears to be approximately 1.6-fold higher with 420 mg ibrutinib (chronic lymphocytic leukemia [CLL], N=32) and approximately 2-fold higher with 560 mg ibrutinib (mantle cell lymphoma [MCL], N=6) compared with venetoclax single agent exposure.

Within the same dataset, ibrutinib exposures when dosed in combination with venetoclax were comparable to those observed at the respective therapeutic dose levels of ibrutinib single agent. To date, no new safety signals have been identified in the ongoing combination studies. Patients should be closely monitored for signs of toxicity.

6.2.3. QT Prolonging Agents

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

6.2.4. Antiplatelet Agents and Anticoagulants

Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. Supplements such as fish oil and vitamin E preparations should be avoided. Bleeding events of any grade, including bruising and petechiae, occurred in subjects treated with ibrutinib. Ibrutinib should be held at least three to seven days pre- and post-surgery depending upon the type of surgery and the risk of bleeding (see Section 6.4) Subjects with congenital bleeding diathesis have not been studied.

6.3.Prohibited Concomitant Medications

Any non-study protocol related chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy are prohibited while the subject is receiving ibrutinib treatment.

Corticosteroids for the treatment of the underlying malignancy are prohibited. Corticosteroids for the treatment of non-cancer related reasons for longer than 14 days and/or at doses >100mg of prednisone or its equivalent are prohibited.

Erythropoietic growth factors (e.g., erythropoietin) and neutrophil growth factors (e.g., filgrastim and peg-filgrastim) are also prohibited (e.g., initial treatment, DLT assessment period).

6.4. Guidelines for Ibrutinib Management with Surgeries or Procedure

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:

6.4.1. Minor Surgical Procedures

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.

6.4.2. Major Surgical Procedures

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

6.4.3. Emergency Procedures

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

7. STUDY EVALUATIONS

7.1. Screening/Administrative

All screening clinical and laboratory assessments must be performed within 30 days of first dose of study drug and prior to randomization.

7.1.1. Informed Consent

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

7.1.2. Confirm Eligibility

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

The subject's complete history through review of medical records and by interview will be collected and recorded. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis and list of all prior anticancer treatments, dates administered, and responses and duration of response to these treatments, also will be recorded.

7.1.3. Prior and Concomitant Medications

All medications from the time of signed consent through 30 days after the last dose of study drug will be documented. After a subject discontinues study treatment, receipt of all subsequent anticancer therapies will be collected until death, subject withdrawal of full consent, loss to follow-up, or study termination by Sponsor, whichever comes first.

7.1.4. Adverse Events

The accepted regulatory definition for an adverse event is provided in Section 11. All medical occurrences that meet the adverse event definition must be recorded from the time the ICF is signed until 30 days after the last dose of ibrutinib. Laboratory abnormalities designated clinically significant by the Investigator will also be recorded as adverse events. Additional

important requirements for adverse event and serious adverse event reporting are explained in Section 11.3.4.

7.1.5. Physical Examination

The Screening, Week 1, Suspected PD, End-of-Treatment and Follow-Up physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

A limited symptom-directed physical examination will be required after Week 1 at time points specified in the Schedule of Assessments (Appendix 1).

7.1.6. ECOG

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

7.1.7. Vital Signs

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

7.2. Clinical Laboratory Assessments

7.2.1. Hematology

Hematology will be evaluated and will include a complete blood count (CBC) with differential: white blood cells, red blood cells, hemoglobin, hematocrit, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils and bands (if reported).

7.2.2. Chemistry (Serum)

Serum chemistry will be evaluated and include sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), phosphate, uric acid, magnesium and bicarbonate.

7.2.3. Coagulation Studies

Measurement of prothrombin time (PT)/INR, and activated partial thromboplastin time (aPTT) will be performed at Screening, Week 17 and at the End-Of-Treatment visit using a central laboratory.

7.2.4. Hepatitis Serologies

Hepatitis serologies include hepatitis C antibody, hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody and will be evaluated by local laboratory. PCR must be confirmed negative prior to randomization for subjects who are hepatitis B core antibody positive, hepatitis B surface antigen positive or hepatitis C antibody positive.

7.2.5. β2 -microglobulin

Samples will be collected at Screening.

7.2.6. Pregnancy Test

Serum pregnancy tests are required at Screening by local laboratory only for women of childbearing potential. If positive, pregnancy must be ruled out by ultrasound to be eligible. This test may be performed more frequently if required by local regulatory authorities.

7.2.7. Flow cytometry surface membrane phenotype

To determine the phenotype of malignant cells in patients, blood samples will be collected at screening, C1D1, C1D15, C1D28, day 1 of C3-C12. Samples will also be collected at a suspected CR visit or at disease progression or discontinuation of treatment. From these samples, peripheral blood mononuclear cells (PBMC) will be separated, collected and frozen as viable cells that will be analyzed at a future date by flow cytometry, for expression of cell surface markers including CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD11c, CD14, CD16, CD19, CD20, CD22, CD25, CD36, CD38, CD56, IgG, IgM, Kappa, Lambda, and CXCR4.

7.2.8. IGHVDJ Rearrangement DNA Sequencing

Peripheral blood and/or tissue samples (lymph node, bone marrow) will be collected and sorted for surface markers indicating B lymphocytes. DNA and RNA will be extracted from these cells, amplified by PCR and subjected to DNA sequencing. These samples will be collected at screening and at disease progression, should that occur.

7.3. Diagnostics/Procedures

7.3.1. ECG

12-lead ECG will be taken in triplicate (≥1 minute apart) at Screening. Subjects should be in supine position and resting for at least 10 minutes prior to the triplicate ECG measurements. The calculated QTcF average of the 3 ECGs must be <470 msec for eligibility.

The ECGs should be performed prior to any blood samples being collected. Any clinically significant abnormalities noted at Screening should be included in the medical history.

In addition, a single ECG may be performed, if clinically indicated, at any time during the study.

7.3.2. Pathological Diagnosis and Bone Marrow Sampling

Inclusion of the subject in the trial will be based on pathological assessment and histologic confirmation of Richter's transformation in treatment-naive and previously treated CLL/SLL patients (including other indolent lymphomas). When feasible, a portion of the BM aspirate will be viably cryopreserved for correlative studies.

7.4. Biomarkers

7.4.1. Genetic and Molecular Prognostic Markers

Up to four cores of Richter's Transformed lymph node tissue will be procured at screening or pre-dose C1D1. Half the cores will be snap frozen and the other half will be processed as FFPE.

Blood samples will be collected if lymphocytosis present, at pre-therapy, on days 15, 28, and 56 of therapy. One of the ACD tubes will undergo CD19+ enrichment and half of the enriched cells will be stored in RLT buffer and the other half will be viably cryopreserved. The other ACD tube will have the plasma and PBMC isolated and stored. From the sodium heparin tube a portion of the blood will undergo CLL and immune cell subset FACS testing. The remaining blood will have the plasma and PBMC isolated and stored.

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

Samples collected may be used for pharmacodynamic and biomarker assessments including BTK and other kinase activity and signaling, expression analysis, sequencing, and secreted protein analyses C8D1, Suspected PD, and End of Treatment visits.

7.4.4. **Correlative studies**

Peripheral blood, lymph node and/or bone marrow samples (depending on the site of disease activity) will be obtained pre-therapy. In addition, peripheral blood and possibly lymph node and bone marrow samples (depending on the site of disease activity) will be obtained on C1D15, D1D28, and C2D28 of therapy and at the end of the study or at the time of disease progression.

Recent studies have sub-categorized DLBCL arising in the context of a pre-existing CLL as either: (1) DLBCL that is "clonally related" to CLL (representing ~80% of cases) or (2) development of DLBCL that is "clonally unrelated" to the underlying CLL (remaining 20% cases) based on the *IGHVDJ* rearrangement (Mao 2007). We plan to determine the DNA sequence of the *IGHVDJ* rearrangement at the site of the RT and compare it with the original

CLL clone from peripheral blood or bone marrow collected before the diagnosis of RT. This will determine if the new lymphoma arose from the same clone or whether this is a *de novo* clone unrelated to the pre-existing CLL. This information will be correlated with safety/toxicity, response to therapy, and outcomes. As routine clinical practice, the CLL clones from all our patients are analyzed for *IGHV-D-J* DNA sequence and *IGHV* mutation status (UM-CLL and M-CLL) at the time of the CLL diagnosis or first visit to our clinics. Ibrutinib has shown clinical activity in both UM-CLL and M-CLL as a single agent and in combination regimens (Byrd 2013, Burger 2013, Brown 2013).

Furthermore, 90-95% of RT in patients with CLL is of the more aggressive activated B-cell (ABC) subtype (Mao 2007). We will determine ABC subtypes by gene expression profiling or immunohistochemistry (when tissue is available) to correlate disease outcomes and identify specific genes associated with overall survival. A recent phase 2 multicenter study of ibrutinib was performed in patients with relapsed/refractory DLBCL. The objectives were to assess whether ibrutinib had differential activity in ABC DLBCL and its role on overall response rate. Seventy patients were enrolled with a median age of 64 years and 3 (range 1-7) prior regimens. Overall, there were 29 ABC, 20 GCB, and 21 unclassified/unknown patients. Ibrutinib monotherapy showed clinical activity in ABC subtype (with a response rate of 41%), however, it did not have clinical activity in GCB DLBCL subtype, supporting the role of BCR signaling in ABC but not in GCB DLBCL (Mao 2007).

Since additional and possibly different mutations may be needed to generate Richter's in a patient with CLL, especially those that are clonally related to the CLL and those that are not, next generation whole exome deep sequencing at the time of RT diagnosis will be carried out to identify new mutations that might be mechanistically involved in the evolution from CLL to RT. This approach is currently in use in Dr. Chiorazzi's lab. Our aim is to determine if new mutations are generated, if they are derived from the same precursor, or if the Richter's comes from the same CLL clone.

To evaluate the mechanisms whereby new genomic aberrations occur (particularly point mutations and gene segment deletion, we will examine the expression of Activation Induced Deaminase (AID) and the related apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC) group of cytidine deaminases in the RT sample and in the preceeding CLL clone. mRNA expression will be documented by PCR and protein synthesis also by immunofluorescence using flow cytometry for single cells and immunohistochemistry for tissues. In addition, we will examine the next generation deep sequencing data for mutation signatures of AID/APOBEC, which may arise during transformation and/or development of resistance. Dr. Chiorazzi's group has recently published on AID protein expression in CLL cells and documented its ability to lead to IGHV-D-J mutations and isotype class switching (Patten 2012). AID/APOBEC mutagenic signatures have recently been described in many cancers (Alexandrov 2013) and implicated in the evolution of aggressive disease. To our knowledge, this has not been studied in RT.

Additional correlative data will be obtained by measuring changes in cell surface phenotype, surface membrane immunoglobulin density, cytokine/chemokine receptors, and ratios of proliferative to resting compartments in peripheral blood and in lymph node and bone marrow by flow cytometry. We plan to measure changes in constitutive and induced phosphorylation, pre- and post-therapy, and correlate this with changes in lymph node size and circulating absolute lymphocyte count and eventually to ibrutinib in combination with obinutuzumab with or without chemotherapy.

7.5. Efficacy Evaluations

Efficacy evaluations will be conducted as outlined in the Schedule of Assessments (Appendix 1). Response assessments will be performed using Cheson assessment criteria.

Nodal and extranodal disease should be evaluated based on the revised criteria for malignant lymphoma described in the revised International Working Group for NHL (Cheson 2007). The spleen is considered nodal disease.

Efficacy evaluation will include the following components:

7.5.1. Radiographic Imaging

Pre-treatment tumor assessment will be performed up to 28 days before the first dose of study drug. Lesions that have been irradiated cannot be included in the tumor assessment unless unequivocal tumor progression has been documented in these lesions after radiation therapy.

A MRI or PET/CT or CT scans (with contrast, unless contraindicated) of the neck, chest, abdomen, and pelvis must be performed. Information on extranodal involvement will also be recorded.

In the case where CT with contrast is contraindicated, an alternative would be MRI of the abdomen and pelvis and CT of the chest without contrast.

The same imaging method should be used for a given subject throughout the study, when feasible. The same equipment should be utilized for all scans whenever possible.

7.5.1.1. Radiographic Assessment

Nodal and extranodal disease should be evaluated based on the revised criteria for malignant lymphoma described in the revised International Working Group for NHL (Cheson 2007). The spleen is considered nodal disease.

7.6. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in source documents for transcription to the eCRF or laboratory requisition form. Refer to the Schedule of Assessments (Appendix 1) for the timing and frequency of all sample collections.

8. STUDY PROCEDURES

8.1. Screening Phase

Screening procedures will be performed up to 30 days prior to Day 1 of Week 1, unless otherwise specified. All subjects must first read, understand, and sign the IRB -approved informed consent form before any study-specific screening procedures are performed.

8.1.1. Screening Visit

A description of all required screening assessments is outlined in Appendix 1 (Schedule of Assessments). This will include blood sample collection for correlative studies, including analysis of genetic and molecular prognostic markers – TP53, NOTCH1, ZAP-70, MYD88, and SF3B1 mutation analysis as well as GCB vs. non-GCB subtyping.

8.2. Treatment Phase

Following completion of the Screening Visit and once eligibility has been confirmed, subjects will be assigned to ARM A (FIT) vs. ARM B (FRAIL).

Study drug treatment should be continued until disease progression, unacceptable treatment-related toxicity, or other reasons outlined in Section 9.

Refer to the Schedule of Assessments (**Appendix 1**) for a complete list of procedures to be performed at each scheduled study visit.

8.2.1. Cycle 1 Day 1

Subjects who are deemed eligible will return to the clinic on Day 1. The following procedures will be performed:

Confirmation of eligibility

FACiT-Fatigue

Physical Exam, including weight

Assessment of disease-related symptoms

ECOG performance status

Vitals signs including blood pressure, heart rate, respiratory rate, and body temperature

Clinical Laboratory Assessments (ideally on Day 1, or up to 7 days preceding Day 1)

- Hematology to include CBC with differential and platelets (review prior to dosing)
- Serum chemistry panel to include magnesium and phosphorous
- Predictive/resistance biomarkers
- Flow cytometry blood assays
- Serum Ig and β_2-microglobulin

Review of AEs and concomitant medications

Dosing and Post-Dose

Dispense study drug (Ibrutinib)

Administration of study drug

Administration of obinutuzumab +/- CHOP

Review of AEs and concomitant medications

8.2.2. Cycle 1 Day2

Administration of study drug and obinutuzumab

Serum chemistry panel to include magnesium, phosphorous

Review of AEs and concomitant medications

8.2.3. Cycle 1 Day 3

Serum chemistry panel to include magnesium, phosphorous

Review of AEs and concomitant medications

8.2.4. Cycle 1 Day 8

Administration of study drug and obinutuzumab

Physical Exam, including weight

ECOG performance status

Vitals signs including blood pressure, heart rate, respiratory rate, and body temperature

Hematology to include CBC with differential and platelets

Serum chemistry panel to include magnesium, phosphorous

Review of AEs and concomitant medications

8.2.5. Cycle 1 Day 15

FACiT-Fatigue

Physical Exam, including assessment of disease-related symptoms

ECOG performance status

Vitals signs including blood pressure, heart rate, respiratory rate, and body temperature

Collect blood samples for the laboratory tests

- Hematology to include CBC with differential and platelets
- Serum chemistry panel to include magnesium, phosphorous
- CD20+ status (for B-cell malignancies)
- Correlative studies
- Predictive/resistance biomarkers
- Flow cytometry surface membrane phenotype

Review of AEs and concomitant medications

8.2.6. Cycle 1 Day 28

Physical Exam, including weight

Assessment of disease-related symptoms

ECOG performance status

Vitals signs including blood pressure, heart rate, respiratory rate, and body temperature

Collect blood samples for the laboratory tests

- Hematology to include CBC with differential and platelets
- Serum chemistry panel to include magnesium, phosphorous
- Correlative studies
- Predictive/resistance biomarkers
- Flow cytometry surface membrane phenotype

Review of AEs and concomitant medications

8.2.7. Cycle 2 Day 1

Administration of study drug and obinutuzumab

Drug accountability

Physical Exam, including weight

Assessment of disease-related symptoms

ECOG performance status

Vitals signs including blood pressure, heart rate, respiratory rate, and body temperature

Hematology to include CBC with differential and platelets

Serum chemistry panel to include magnesium, phosphorous

Review of AEs and concomitant medications

8.2.8. Cycle 2 Day 28

Administration of study drug

FACiT-Fatigue

Overall Response Assessment

- Neck, Chest, Abdomen/Pelvis CT scans or Whole Body MRI or Whole Body PET/CT scan
- Assessment of disease-related symptoms
- Bone marrow aspirate or biopsy, if applicable

Collect blood samples for the laboratory tests

- Correlative Studies

8.2.9. Cycles 3 – 6, Day 1

Administration of study drug and obinutuzumab

8.2.10. Cycles 3-7, Day 1 (±3days)

Drug accountability

FACiT-Fatigue

Physical Exam

ECOG performance status

Vitals signs including blood pressure, heart rate, respiratory rate, and body temperature

Collect blood samples for the following laboratory tests:

- Hematology to include CBC with differential and platelets
- Serum chemistry panel to include magnesium, phosphorous
- Predictive/resistance biomarkers
- Flow cytometry surface membrane phenotype
- Serum Ig and β_2-microglobulin

Overall Response Assessment: Cycle 4, Day 1 and Cycle 6 Day 1

- Neck, Chest, Abdomen/Pelvis CT scans or Whole Body MRI or Whole Body PET/CT scan
- Assessment of disease-related symptoms

Review of AEs and concomitant medications

8.2.11. Cycles 3-7, Day 15 (±3days)

Collect blood samples for the following laboratory tests:

- Hematology to include CBC with differential and platelets
- Serum chemistry panel to include magnesium, phosphorous

8.2.12. Cycles 8-12, Day 1 (±3days)

Drug accountability

FACiT-Fatigue

Physical Exam, including weight

ECOG performance status

Vitals signs including blood pressure, heart rate, respiratory rate, and body temperature

Hematology to include CBC with differential and platelets

Serum chemistry panel to include magnesium, phosphorous

Cycle 8, Day 1 only – Genetic and molecular prognostic markers – TP53, NOTCH1, ZAP-70, MYD88, and SF3B1 mutation analysis as well as GCB vs. non-GCB subtyping

Overall Response Assessment: Cycle 8, Day 1; Cycle 10 Day 1; and Cycle 12 Day 1

- Neck, Chest, Abdomen/Pelvis CT scans or Whole Body MRI or Whole Body PET/CT scan
- Assessment of disease-related symptoms

8.2.13. Suspected PD Visit

The Suspected PD visit should be performed at any time during the study, if, based on clinical and/or laboratory evaluation, the Investigator suspects progressive disease (PD), or if the subject discontinues treatment for any other reason. If possible, the visit should be performed within 24 hours after the subject's previous dose. The following procedures will be performed:

Complete physical exam, including weight

ECOG performance status

Vitals signs (including blood pressure, heart rate, respiratory rate, and body temperature)

Collect blood samples for the following laboratory tests:

- Hematology
- Serum chemistry

- Correlative studies

Tissue and/or bone marrow aspirate or biopsy, if applicable

Overall Response Assessment: Cycle 4, Day 1 and Cycle 6 Day 1

- Neck, Chest, Abdomen/Pelvis CT scans or Whole Body MRI or Whole Body PET/CT scan
- Assessment of disease-related symptoms

Review of AEs and concomitant medications

8.2.13.1. End-of-Treatment Visit

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

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

Complete physical exam, including weight

ECOG performance status

Vitals signs (including blood pressure, heart rate, respiratory rate, and body temperature)

Collect blood samples for the following laboratory tests:

- Hematology to include CBC with differential and platelets
- Serum chemistry panel to include magnesium, phosphorous
- Correlative studies

Review of AEs and concomitant medications

Bone marrow aspirate or biopsy, if applicable

Overall Response Assessment: Cycle 4, Day 1 and Cycle 6 Day 1

- Neck, Chest, Abdomen/Pelvis CT scans or Whole Body MRI or Whole Body PET/CT scan
- Assessment of disease-related symptoms

Drug accountability

8.3.Follow-up Phase

8.3.1 Pre-PD Follow Up

Physical Exam, including weight

ECOG performance status

Vitals signs including blood pressure, heart rate, respiratory rate, and body temperature

Assessment of disease-related symptoms

9. SUBJECT WITHDRAWAL FROM TREATMENT OR STUDY

9.1. Withdrawal from Study Treatment

All study participants may be discontinued from study drug for any of the following reasons:

- ☐ Any subject has the right to discontinue study drug at any time.
- ☐ Any subject who has objective evidence based on progression of disease will discontinue study drug.
- ☐ Any subject unable to tolerate a second re-challenge with protocol-described, dose-modified ibrutinib at Dose Level –2 (see Section 5.2.1.3) should discontinue study drug.
- ☐ Any subject who becomes pregnant or begins breastfeeding should discontinue study drug.
- ☐ Any subject who becomes significantly noncompliant with study drug administration, study procedures, or study requirements should discontinue study drug.
- ☐ Any subject who chooses to receive an allogeneic hematopoietic stem cell transplant.
- ☐ The investigator may discontinue the study drug if it is not in the subject's best interest to continue.

9.2.Withdrawal from Study

Subject study participants will be withdrawn from study due to any of the following reasons:

- ☐ Adverse event.
- ☐ Disease progression.
- ☐ Withdrawal of consent.
    - Withdrawal of consent is the primary reason for study termination only if a patient refuses any further contact or follow-up.
- ☐ Significant subject noncompliance with study drug administration, study procedures, or study requirements.
- ☐ Initiation of any additional anticancer therapies (other than corticosteroids) including chemotherapy, radiation, antibody therapy, immunotherapy, or other experimental treatment.
- ☐ Physician's decision to remove the subject from the study.
- ☐ The subject is lost to follow-up.
- ☐ Death.

When a patient withdraws before completing the study, the reason for withdrawal must be recorded in the source documents.

10. STATISTICAL METHODS AND ANALYSIS

A general description of the statistical methods for the analysis of the efficacy and safety data is outlined below.

10.1. General Consideration

All analyses will be performed based on data up to the timepoint of clinical cutoff. Long-term follow-up data will be summarized separately when the entire study has completed. Statistical inferences will be based on a two-sided Type I rate of 0.1 unless otherwise specified.

All analyses will be carried out separately for each of the two arms (fit and frail). The fit group will be treated with the combination chemotherapy regimen using Ibrutinib (I) with Obinutuzumab (G) and CHOP, "IG-CHOP" regimen. The frail group will use Ibrutinib (I) with Obinutuzumab (G), "IG."

10.2. Subject Information - Assignment to ARM A vs. ARM B

Subjects on the frail or unfit cohort will be ≤80 years of age have an estimated creatinine clearance of less than 60 ml per minute, and have a score on the Cumulative Illness Rating Scale (CIRS) of ≥6 for coexisting illnesses not related to CLL and will be treated with ibrutinib (I) and obinutuzumab (G), i.e. "IG".

Subjects on the fit cohort will have adequate renal function (estimated Creatinine Clearance ≥30 ml/min), and have a CIRS score of <6 and will be treated with the combination of ibrutinib, obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone; i.e. "IG-CHOP".

10.3. Endpoints

10.3.1. Primary Endpoint

- The primary endpoint of the study is Overall Response Rate, as assessed by Cheson 2007 criteria: ORR is defined as the proportion of patients who achieve complete response (CR) or partial response (PR) per Cheson 2007 criteria over the course of the study

- To determine the efficacy of combining Ibrutinib with obinutuzumab (with or without "CHOP" chemotherapy regimen) as measured by overall response rate (ORR), separately for the fit and the frail Richter's Syndrome patients.

Statistical Methods for the Primary Objective:

For each of the two Richter's groups-fit group (using the IG-CHOP regimen) and frail group (using the IG regimen), we will estimate the overall response rate (ORR) using standard methods for binomial proportions; corresponding 95% exact confidence intervals will be calculated.

1.8.1 Secondary Endpoints

1. To assess the safety of Ibrutinib in combination with obinutuzumab as measured by the incidence of prolonged hematologic toxicity in cycle 1 in subjects with a diagnosis of Richter's Transformation (RT), hematologic improvement, progression-free survival (PFS), overall survival (OS), and health-related quality of life (HRQL) measures.
2. To identify and correlate potential markers predictive of response to the combination therapy and associate pharmacogenetic findings to response and toxicity.

Statistical Methods for the Secondary Objectives:
The following analyses will be carried out for the outcomes in the secondary objectives:

1. For each of the two groups, fit and frail, we will estimate the rates of prolonged hematologic toxicity in cycle 1, and the rates of hematologic improvement, using standard methods for binomial proportions; corresponding 95% exact confidence intervals will be calculated.

2. Kaplan-Meier (Product-Limit Method) analysis will be used to estimate the overall survival (OS) and progression-free survival (PFS) in each of the fit and frail groups. OS and PFS will be estimated from the start of treatment. Subjects who are alive as of the last follow-up will be considered censored for survival. Subjects who have not progressed as of the last follow-up will be considered censored for disease progression.

3. For each of the two groups, fit and frail, we will examine patient reported outcome of health-related quality of life as measured by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACiT-Fatigue).

4. For each of the two groups, fit and frail, biomarkers measured from samples collected in patient serum, plasma, blood, tumor tissue, bone marrow biopsies/aspirates as well as data from pathology reports and genetic studies will be examined to determine which biomarkers are associated with certain genetic characteristics, pathologic features and pharmacogenetic findings. The analyses will be exploratory and descriptive in nature and may involve the use of t-tests, chi-square tests, Mann-Whitney/Kruskal-Wallis tests or Fisher's exact tests, as appropriate.

5. If feasible, Cox (proportional hazards) regression will be used to examine factors that might be associated with overall survival or progression-free survival. These factors will potentially include biomarkers, genetic characteristics, pathologic features and pharmacogenetic findings deemed important from a univariable analysis.

6. For each of the two groups, fit and frail, correlations between biomarker levels measured over time will also be examined using analysis of covariance methods (Bland and

Altman, 1995). This will allow for the computation of within-subjects correlations where the pairs of outcome variables are collected as repeated measures.

10.3.2. Exploratory Endpoints

- Patient-reported outcomes (PRO) measured by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACiT-Fatigue)
- Genetic and molecular characteristics as well as GCB vs. non-GCB subtyping to determine which, if any, factors influence ORR to study treatment.

10.4. Sample Size Determination

Simon's two-stage design (Simon, 1989) will be used for each of the two study groups (fit and frail groups).

For the frail group, the study will be designed to test the ORR at 55% (the alternative hypothesis) against the estimated true response rate of 30% (the null hypothesis). In the first stage, 8 patients will be accrued. If there are 2 or fewer responses in these 8 patients, the study will be stopped. Otherwise, 12 additional patients will be accrued for a total of 20. The null hypothesis will be rejected if 9 or more responses are observed in 20 patients. This design yields a type I error rate of alpha=0.1 and power of 80% when the true response rate is 55%.

For the fit group, the study will be designed to test the ORR at 60% (the alternative hypothesis) against the estimated true response rate of 35% (the null hypothesis). In the first stage, 10 patients will be accrued. If there are 4 or fewer responses in these 10 patients, the study will be stopped. Otherwise, 13 additional patients will be accrued for a total of 23. The null hypothesis will be rejected if 11 or more responses are observed in 23 patients. This design yields a type I error rate of alpha=0.1 and power of 80% when the true response rate is 60%.

For the frail (fit) group, the null hypothesis will be rejected if there are 9 (11) or more responses in the 20 (23) patients, 9/20=45% (11/23=48%). Therefore, the study will require a total of 20+23=43 patients (fit and frail groups).

10.5. Safety Analysis

Safety summaries will include tabulations in the form of tables and listings. The safety analysis will be divided between the two treatment cohorts. Patients will be analyzed according to the actual treatment received.
Study drug exposure including duration and dosage as well as dose modifications of study drug including dose reduction, dose delay, missed doses, and dose interruption will be summarized.

11. DATA AND SAFETY MONITORING PLAN (DSMP)

In accordance with federal guidelines, this study requires a DSMP. The PI will identify an independent Safety Officer/Medical Monitor with expertise in Richter's Syndrome who does not have any scientific, financial, or other conflict of interest related to the study and who is not responsible for patient care at any of the participating sites. Safety will be formerly monitored once yearly by the study team and the Safety Office/Medical Monitor throughout the duration of the study. The clinical research team will prepare a safety report for these regular reviews comprised of anticipated safety events and actions taken. The PI will contact the Safety Officer/Medical Monitor for ad hoc reviews of any unanticipated safety events. The study protocol will be carried out in accordance with OHRP/FDA/NIH guidelines and requirements. In the event of a serious adverse event during the study protocol, it will be reported immediately to the PI, the co-investigators, and the Safety Officer/Medical Monitor. It will also be reported to the Northwell Health IRB, Pharmacyclics Drug Safety group and to all members of the research team. With the approval of the participants and families, the information will be provided to other care providers as directed.

Data will be recorded in RedCap.

11.1. Risk Assessment

This study involves a minor/major increase above minimal risk to the subjects. The primary concern is the risk of development of tumor lysis syndrome, diarrhea, cytopenias, infections, atrial fibrillation, non-melanoma skin cancer, rash, lymphocytosis and leukostasis, and bleeding-related events from ibrutinib and risk of development of tumor lysis syndrome and HBV infection from obinutuzumab.

11.2. Ibrutinib Risk Assessment

- Monitoring: subjects will be monitored for overall risk assessment at screening visit and throughout study with laboratory assessments, EKGs, and study visits.

- Actions: The research team will keep record of adverse events. Table 1 "Ibrutinib Dose Modifications" and section 5.2.1.3 define the dose modifications for adverse reactions that will incur a dosage change in ibrutinib administered to subjects. Additional therapy may administered, as needed.

11.3. Obinutuzumab Risk Assessment

- Monitoring: subjects will be monitored at screening and each study visit

- Actions: Subjects will be tested for HBV at screening. Table 3 "Management of Hepatitis B Reactivation" describes guidelines for holding and discontinuing

obinutuzumab. Section 5.2.5.5 describes management of infusion-related reactions and anaphylaxis. Additional therapy may administered, as needed.

12. 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. Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

12.1. Definitions

12.1.1. Adverse Events

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

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

Adverse events may include, but are not limited to:

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

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with Richter's Transformation that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

The following are NOT considered AEs:

- **Pre-existing condition:** A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period. A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

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

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

- **Asymptomatic Treatment Related Lymphocytosis:** This event should also not be considered an AE. Subjects with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.

- Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical

procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- *Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions*
- *Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or*

Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

12.1.2. Serious Adverse Events

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

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

12.1.3. Severity Criteria (Grade 1-5)

Definitions found in the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) will be used for grading the severity (intensity) of *non-hematologic* AEs. *Refer*

to for the grading of hematologic AEs. The CTCAE v4.0 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 v4.0, the following grading system should be used to assess severity:

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

12.1.4. Causality (Attribution)

The Investigator is to assess the causal relation (i.e., whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

12.1.4.1 Yes

There is a plausible temporal relationship between the onset of the AE and administration of the obinutuzumab or ibrutinib, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the ibrutinib or obinutuzumab; and/or the AE abates or resolves upon discontinuation of the ibrutinib or obinutuzumab or dose reduction and, if applicable, reappears upon re-challenge.

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.

12.1.4.2 No

Evidence exists that the AE has an etiology other than the {study drug} (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to {study drug} administration (e.g., cancer diagnosed 2 days after first dose of study drug).

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.

12.2. Expected and Unexpected Adverse Events

"Expected" AEs are those AEs that are listed or characterized in the current Investigator's Brochure or package insert.

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.

12.3. Procedures for Eliciting, Documenting and Reporting of Adverse Events and Serious Adverse Events by Investigators

12.3.1. Eliciting Adverse Events

A consistent methodology for eliciting AEs at all evaluation timepoints should be adopted. Examples of non-directive questions include:

- *"How have you felt since your last clinical visit?"*
- *"Have you had any new or changed health problems since you were last here?"*

12.3.2. Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

12.3.2.1. Diagnosis versus Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

12.3.3. Assessment of Adverse Events

Investigators will assess the occurrence of adverse events and serious adverse events at all subject evaluation time points during the study. All adverse events and serious adverse events whether volunteered by the subject, discovered by study personnel during questioning, detected through physical examination, clinically significant laboratory test, or other means, will be recorded. Each recorded adverse event or serious adverse event will be described by its duration (i.e., start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to the investigational product, and any actions taken.

12.3.4. Adverse Event Reporting

Any SAE must be reported to the IRB as soon as possible but no later than 5 business days. The IRB requires a SAE report to be submitted electronically to Northwell Health IRB at irb@northwell.edu and through the electronic IRB portal. The report should be filled out entirely and include the following information:

Principal Investigator
Name: Jacqueline Barrientos, MD
Dept/Div: Medicine
Affiliation: Northwell Health Cancer Institute
Phone #: 516-470-4050
Fax #: 516-470-4250
E-mail: jbarrientos@northwell.edu

The principal investigator's or sub-investigator's signature and the date it was signed are required on the completed serious adverse event report.

12.3.5. Adverse Event Reporting Period

All AEs whether serious or non-serious, will be captured from the time signed and dated ICF is obtained and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

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

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

All adverse events, 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").

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. All deaths that occur during the protocol-specified AE reporting period (see Section 11.3.3.), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

If a death occurs within 30 days after the last dose of study drug, the death must be reported as a serious adverse event.

12.3.6. Pregnancy

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

A female subject must immediately inform the Investigator if she becomes pregnant from the time of consent to 30 days after the last dose of study drug. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of consent to 3 months after the last dose of study drug. Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 30 days (or 90 days for male partners) after the last dose of study drug must be reported. Any occurrence of pregnancy must be reported to Pharmacyclics Drug Safety, or designee, and Northwell Health HRPP per SAE reporting timelines. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. Pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing will need to be reported to Pharmacyclics per SAE reporting timelines. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the obinutuzumab or ibrutinib should be reported as an SAE.

12.3.7. Other Malignancies

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

12.3.8. Eye-Related Adverse Events

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

12.3.9. Adverse Events of Special Interest (AESI)

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

The following AEs are considered of special interest and must be reported to the Sponsor expeditiously irrespective of regulatory seriousness criteria:

- Tumor Lysis Syndrome (serious and non- serious events)

Please note that from Feb/2015, only non-serious TLS is an AESI.

The following events can be reported as AESI only when considered SERIOUS by the investigator:

- Serious neutropenia
- Serious infection
- Serious Infusion Related Reaction (IRR)

Selected events (in clinical trials, these are events for which additional data collection or analyses will be performed; no special case handling or follow-up is required):

- IRRs
- infections (including PML)
- neutropenia (including late onset neutropenia - defined as neutrophil count < 1000 cells/mm3, occurring 28 days or more after obinutuzumab treatment has been completed or stopped; prolonged neutropenia - defined as neutrophil count < 1000 cells/mm3, which does not resolve after 28 days (without obinutuzumab treatment),
- thrombocytopenia (including acute thrombocytopenia - events occurring during and within 24 hours post obinutuzumab infusion)
- TLS
- Hepatitis B reactivation
- cardiac events
- second malignancies
- GI perforation.

12.3.9.1. Major Hemorrhage- Ibrutinib Adverse Event of Special Interest

Major hemorrhage is defined as any of the following:

Any treatment-emergent hemorrhagic adverse events of Grade 3 or higher*

Any treatment-emergent serious adverse events of bleeding of any grade

Any treatment-emergent central nervous system hemorrhage/hematoma of any grade

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

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 11.3.7 above.

12.3.10. Reporting Requirements for Serious Adverse Events

All serious adverse events and AESIs (initial and follow-up information) will be reported on FDA Medwatch (Form 3500A) or Suspect Adverse Event Report (CIOMS Form 1) IRB Reporting Form and sent via email (AEintakeCT@pcyc.com) or fax (408) 215-

3500) to Pharmacyclics Drug Safety, or designee, within 24 hours of the event. Pharmacyclics may request follow-up and other additional information from the Sponsor Investigator.

Reporting to Regulatory Agencies:

Serious adverse events will be forwarded to FDA by the Sponsor according to 21 CFR 312.32.

It is the responsibility of the Investigator and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices (GCP), the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Methods and Timing for Assessing AND Recording Safety variables:

The investigator is responsible for ensuring that all AEs and SAEs, that are observed or reported during the study, are collected and reported to the U.S. Food and Drug Administration (FDA), appropriate Institutional Review Board (IRBs), in accordance with CFR 312.32 (IND Safety Reports).

MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (item 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the AE to each investigational product and suspect medication

Follow-Up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e., D.O.B. initial, patient number), protocol description and number, if assigned, brief AE description, and notation that additional or follow-up information is being submitted (The

patient identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm

12.4. Safety Reporting Requirements for IND Exempt Studies

As this is an investigator-sponsored IND exempt study, the investigator will submit safety reports in accordance with the reporting requirements set forth in **21 CFR 314.80**.

13. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

13.1. Protocol Amendments

Per the IST Agreement, any amendments to the Protocol or Informed Consent Form must be sent to Pharmacyclics for review and approval prior to submission to the IRB. Written verification of IRB approval will be obtained before any amendment is implemented.

13.2. Publication of Study Results

Per the IST Agreement, the Investigator is required to submit to Pharmacyclics a copy of a planned publication (abstract, poster, oral presentation or manuscript) prior to the submission thereof for publication or disclosure. Pharmacyclics may provide scientific comments and suggestions understanding that the Investigator has sole editorial responsibility, and retains the authority to make the final determination on whether or not to incorporate Pharmacyclics comments or requests for additional information.

13.3. Study Discontinuation

Per the IST Contract, the Investigator reserves the right to terminate the study at any time. Should this be necessary, both the Investigator will arrange discontinuation procedures in partnership with Pharmacyclics LLC. In terminating the study, the Investigator will assure that adequate consideration is given to the protection of the subjects' interests. Pharmacyclics may terminate the study for reasons including, but not limited to: evidence that the PI or an involved investigator is unqualified to conduct research or fulfill sponsor responsibilities (e.g., is listed on a debarment or ineligible investigator list); failure to meet timelines or achieve agreed upon milestones; a known or perceived risk to patient well-being is identified; or breach of contract. Additional grounds for termination are outlined in the IST Agreement.

14. RETENTION OF RECORDS

U.S. FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

For studies conducted outside the U.S. under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the U.S. FDA IND regulations and the relevant national and local health authorities, whichever is longer.

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16. APPENDICES

Appendix 1. Schedule of Assessments

Study Visits	Screening Phase	Treatment Phase (1 cycle = 28 days)										Suspected PD	End-of-Treatment	Pre-PD FU
		Cycle 1					Cycle 2		Cycles 3–7		Cycles 8–12			
		D1 (baseline)[a]	D2	D3	D8	D15	D1	D15	D1	D15	D1	Any time	Within 30 Days after treatment end[df]	q 4 mos, then q 6 mos[k]
Study Visit Windows	-28 days						Visits are ± 3 days Radiology procedures are ± 7 days					Any time	+ 7 days	± 7 days
Informed consent	x													
Medical history & Demographics (including date of birth) & Pregnancy Test	x													
Confirm eligibility and enroll		x												
FACiT Fatigue		x					x		x		x		x	
Concomitant medications	x	x			x	x	x		x		x		x	
Adverse events[b]	x	x	x	x	x	x	x		x		x		x	
Height	x													
Physical exam, vital signs, weight, ECOG	x	x			x	x	x		x		x	x	x	x
CIRS (Cumulative Illness Rating Scale) Score	x													
Disease assessment: [d]														
CT/MRI scan	x[e]								x[c]		x[c]	x	x	
PET/CT scan	x								x[c]		x[c]	x	x	
Bone marrow biopsy/aspirate[l]	x											x	x	
Disease-related symptoms[i]	x	x				x			x		x	x	x	x
Overall response assessment									x[c]		x	x	x	x
Hematology	x	x			x	x	x	x	x	x	x	x	x	x
Serum chemistry [j]	x	x[j]	x[j]	x[j]	x	x	x[j]	x[j]	x[j]	x[j]	x		x[j]	
EBV PCR	x													

Study Visits	Screening Phase	Treatment Phase (1 cycle = 28 days)										Suspected PD	End-of-Treatment	Pre-PD FU
		Cycle 1					Cycle 2		Cycles 3–7		Cycles 8–12			
		D1 (baseline)[a]	D2	D3	D8	D15	D1	D15	D1	D15	D1	Any time	Within 30 Days after treatment end[df]	q 4 mos, then q 6 mos[k]
Creatinine clearance (Cockcroft-Gault)	x													
Correlatives: Peripheral Blood, lymph node, and bone marrow [n]	x					x x		x				x	x	
IGHV mutation at site of RT; compare to original CLL clone from peripheral blood or bone marrow [d]	x											x		
Hepatitis serologies [m]	x													
Coagulation panel	x													
Predictive/resistance biomarkers[o]	x											x	x[k]	
Flow cytometry surface membrane phenotype (including CD20+ marker)	x												x[k]	
Serum Ig and β_2-microglobulin	x	x							x		x[i]	x	x[k]	
Genetic/molecular prognostic factors[p]	x											x	x	
12-lead ECG[g]	x		If clinically indicated (e.g., subjects with palpitations, lightheadedness)											
Any new anticancer therapy														x[k]
		Study Drug Administration and Dispensation												

Study Visits		Screening Phase	Treatment Phase (1 cycle = 28 days)										Suspected PD	End-of-Treatment	Pre-PD FU
			Cycle 1					Cycle 2		Cycles 3–7		Cycles 8–12			
			D1 (baseline)[a]	D2	D3	D8	D15	D1	D15	D1	D15	D1	Any time	Within 30 Days after treatment end[df]	q 4 mos, then q 6 mos[k]
ARM A	IBR 560 mg PO[h] + 1000 mg Obinutuzumab + CHOP		**Ibrutinib** is administered daily until PD. **Obinutuzumab** is administered: C1D1 100mg, C1D2 900mg, C1D8 and C1D15 1000mg, and then 1000mg on day 1 of cycles 2-6 **CHOP** dose cyclophosphamide D1 of C1-C6 750 mg/m², hydroxydaunorubicin D1 of C1-C6 50 mg/m² , oncovin (vincristine) D1 C1-C6 1.4 mg/m² (max. 2 mg) , and prednisone or equivalent D1 thruD5 of C1-C6 (100mg flat dose per day, or dosage as investigator sees fit) (FIT population n=23)										
ARM B	IBR 560 mg PO[h] + 1000 mg Obinutuzumab		**Ibrutinib** is administered daily until PD. **Obinutuzumab** is administered: C1D1 100mg, C1D2 900mg, C1D8 and C1D15 1000mg and then 1000mg on day 1 of cycles 2-6 (FRAIL population n=20)												

D = day; Term = treatment termination; d/c = discontinuation; PD = progressive disease; FU = follow-up; (x) = not all visits or all subjects

[a] To be collected pre-dose, unless otherwise specified

[b] AEs are reported from the time the patient signs the Informed Consent Form until 30 days following last dose of study drug. In addition to all routine AE reporting, all new malignant tumors including solid tumors, skin malignancies and hematologic malignancies are to be reported as adverse events for the duration of the study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

[c] At 2 months (ORR, DOR, TTP, PFS); if no evidence or PD at 2 months, give three additional 28 day cycles of Obinutuzumab; Ibrutinib continued indefinitely until PD or toxicity. Radiographic assessments (Neck, Chest, Abdomen/Pelvis CT scans **OR** MRI **OR** PET/CT scan) will be performed at C2D28, C5D1, C7D1, C9D1, C11D1.

[d] If a patient chooses to undergo an hematopoietic stem cell or bone marrow transplant patients will be censored at that time for statistical analysis of PFS.

[e] Baseline CT scan can be performed up to 28 days prior to C1D1. PET/CT or CT w/contrast (unless contraindicated) of neck/check/abdomen/pelvis or MRI should be performed at C2D28, C5D1, C7D1 then every six months.

[f] May be sooner if patient is scheduled to start a new anticancer treatment

[g] ECG's may be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea.

[h] Day 1 dose of Cycle 1 of ibrutinib should be administered at the investigational site. Subsequent daily doses may be self-administered at home

[i] Disease-related symptoms include weight loss, fatigue, fever, night sweats, abdominal pain/discomfort due to splenomegaly including early satiety, and anorexia.

[j] To monitor for tumor lysis syndrome and cytopenia(s), the subjects will have chemistries resulted on days 2 and 3 of the first cycle of therapy, every week during the first cycle of therapy and day 1 and day 15 during subsequent cycles of therapy.

[k] Every 4 months for 1 year, then every 6 months thereafter until 2 years.

[l] Bone marrow biopsy and/or aspirate should be performed at Screening or up to 90 days before the first dose of study drug, and as needed to confirm complete remission/response (CR) or evaluate cytopenia. Marrow collected to confirm CR should have minimal residual disease (MRD) assessed by flow cytometry on the aspirate; patients confirmed as MRD-negative in the marrow should be followed every 3 months for MRD by peripheral blood flow cytometry (see Section 7.2.7).

[m] PCR must be confirmed negative prior for subjects who are hepatitis B core antibody positive, hepatitis B surface antigen positive or hepatitis C antibody positive.
[n] When clinically indicated and feasible, peripheral blood should be collected for each correlative studies. When feasible, bone marrow and lymph node samples should be collected for analysis of correlative studies as well.
[o] Predictive/resistance biomarkers include those for BTK mutations, other kinases activity and signaling, expression analysis, sequencing, flow cytometry and secreted protein analyses.
[p] Genetic/molecular prognostic factors include TP53, NOTCH1, ZAP-70, MYD88, and SF3B1 mutation analysis as well as GCB vs. non-GCB subtyping. Performed at screening and suspected PD or End of Treatment visit, if feasible and/or clinically indicated.

Appendix 2. ECOG Status Scores

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

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

Available at: http://www.ecog.org/general/perf_stat.html.

Appendix 3. 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 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
SUBOXONE	Pioglitazone
TELITHROMYCIN	Rifabutin
Moderate inhibitors:	Rifampin
Aprepitant	St. John's Wort
Erythromycin	Troglitazone
diltiazem	
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 4. 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, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; ≥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).

**Reference: Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. Journal of Clinical Oncology 2007;25:579-586.

Appendix 5: Correlative Studies

Test	Collection Timepoint	Site / PI	Sample type	Collected sample	Processing/Banking	Site of Analysis
IGHVDJ rearrangement	Screening and Suspected PD visits, if clinically indicated and feasible					Site/s of RT disease
ABC subtyping	Screening, if clinically indicated and feasible					Site/s of RT disease
mRNA expression of Activation Induced Deaminase (**AID**) and apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (**APOBEC**)	*Screening ***Suspected PD** visit, if clinically indicated and feasible					Next generation clonal evolution analysis at site/s of RT disease PCR Protein synthesis analysis by immunofluorescence using flow cytometry for single cells & immunohistochemistry
AID and **APOBEC** mutation analysis	*Screening ***Suspected PD,** visit if clinically indicated and feasible				whole exome deep sequencing	

Appendix 6. Child-Pugh Score

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

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

Sources:

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

Appendix 7. Cumulative Illness Rating Score (CIRS)

Each system is rated as follows:		
Score	**Severity**	Findings
0=	**NONE:**	No impairment to that organ/system.
1=	**MILD:**	Impairment does not interfere with normal activity; treatment may or may not be required; prognosis is excellent. Easy to control. (Examples could be skin lesions, hernias, or hemorrhoids)
2=	**MODERATE:**	Impairment interferes with normal activity; treatment is needed; prognosis is good. Manageable. Requiring daily treatment or first-line therapy (Examples could be gallstones, diabetes, or fractures)
3=	**SEVERE:**	Impairment is disabling; treatment is urgently needed; prognosis is guarded. Hard to control. Requiring second-line therapy or multiple medications. (Examples could be carcinoma, pulmonary emphysema, or congestive heart failure)
4=	**EXTREMELY SEVERE:**	Impairment is life threatening; treatment is urgent or of an avail; prognosis is grave. Poorly manageable. Requiring urgent intervention or resistant to therapy. (Examples could be myocardial infarction, cerebrovascular accident, gastrointestinal bleeding, or embolus)

The CIRS used in this protocol is designed to provide an assessment of recurrent or ongoing chronic comorbid conditions, classified by 14 organ systems. Using the drop-down lists of organ-specific diagnoses, please select any conditions present in the study subject. If the subject has a recurrent or ongoing chronic conditions that are not described in the list for a given organ system, please indicate the name of the conditions under "other chronic condition" for that organ system. Please take into account that CLL-induced discomfort, symptoms, or disability should not be considered. If additional explanation would be helpful, text comments may be inserted.

Organ System Diagnosis Comment	**Organ System Diagnosis Comment**	**Organ System Diagnosis Comment**
Cardiac	Chronic heart failure Angina pectoris Medically relevant arrhythmia Valve dysfunction Congenital heart disease Cardiomyopathy Myocarditis Chronic pericarditis Endocarditis Other chronic cardiac condition: Other chronic cardiac condition	
Vascular	Hypertension Thrombosis Peripheral diabetic microvascular disease Peripheral artery disease Aortic aneurysm Aortitis Raynaud disease Vasculitis Other chronic vascular condition: Other chronic vascular condition	

Hematological/ Immunological	Sickle cell anemia Hemoglobinopathy Polycythemia Thrombocythemia Hemophilia Paroxysmal nocturnal hemoglobinuria Thrombotic thrombocytopenic purpura Dysfibrinogenemia HIV Other chronic hematological or immunological condition: Other chronic hematological or immunological condition	
Respiratory	Asthma Chronic obstructive pulmonary disease Cystic fibrosis Emphysema Chronic bronchitis Chronic pleural effusions Pulmonary fibrosis Sarcoidosis Pulmonary embolism Pulmonary arterial hypertension Lung cancer Other chronic respiratory condition: Other chronic respiratory condition	
Ophthalmological/ otolaryngological	Loss of vision Glaucoma Cataract Macular degeneration Diabetic retinopathy Loss of hearing Otitis/chronic otitis Vestibular impairment Vertigo Temporomandibular disorder Sialolithiasis Chronic sinusitis Laryngeal/pharyngeal disorders Other chronic ophthalmological or otolaryngological condition:	
Upper Gastrointestinal	Chronic esophagitis Dysphagia Achalasia Gastroduodenal ulceration Celiac disease Irritable bowel syndrome Short bowel syndrome Malnutrition Malabsorption Small bowel obstruction	

	Hernia Pseudomyxoma peritonei Upper gastrointestinal cancer Other chronic upper gastrointestinal condition: Other chronic upper gastrointestinal condition	
Lower Gastrointestinal	Diverticulitis Inflammatory bowel disease Volvulus Colon cancer Other chronic lower gastrointestinal condition: Other chronic lower gastrointestinal condition	
Hepatic/ Pancreatic	Chronic hepatitis or hepatic cirrhosis Biliary obstructive disorders Pancreatitis Hepatic, biliary, or pancreatic cancer Other chronic hepatic or pancreatic condition Other chronic hepatic or pancreatic condition	
Renal	Chronic kidney disease Diabetic nephropathy Pyelonephritis Renal cancer Other chronic renal condition: Other chronic renal condition	
Gynecological/ Urological	Recurrent/chronic urinary tract infection Nephrolithiasis Bladder dysfunction Vaginal/vulvar disease Uterine/ovarian disease Prostatitis Bladder, uterine, ovarian, prostate, or other cancer Prostate hypertrophy Other chronic gynecological or urological condition: Other chronic gynecological or urological condition	
Dermatologic/ musculoskeletal	Dermatitis Dermatomyositis Myopathy Gout Psoriasis Keratosis Urticaria Scleroderma Basal cell carcinoma Squamous cell carcinoma Melanoma Osteomyelitis Osteoarthritis	

	Rheumatoid arthritis Spondyloarthritis Temporal arteritis/polymyalgia rheumatica Polychondritis Fibromyalgia Osteoporosis Systemic lupus erythematosus Dermatomyositis Sjögren syndrome Other chronic dermatological or musculoskeletal condition: Other chronic dermatological or musculoskeletal condition	
Neurological	Cerebrovascular disease (transient ischemic attack/stroke/hemorrhage) Dementia Parkinson disease Non-Parkinsonian movement disorder (eg, ataxia/chorea) Leukodystrophic disorders Amyotrophic lateral sclerosis Multiple sclerosis Demyelinating disease Guillain-Barré syndrome Paralysis (eg, paraplegia/quadriplegia/hemiplegia) Myelopathy Cranial nerve disorder Degenerative disk disease with nerve root compression Migraine headaches Seizure disorder Secondary neuropathy (e.g., diabetic/alcoholic/autoimmune) Neurofibromatosis/tuberous sclerosis Benign or malignant central nervous system tumor Other chronic neurological condition: Other chronic neurological condition	
Endocrine/ Metabolic	Diabetes Adrenal disorder Thyroid disorder Parathyroid disorder Pheochromocytoma Pituitary disorder Hemochromatosis Porphyria Paget's disease Endocrine or neuroendocrine tumor	

	Other chronic endocrine or metabolic condition: Other chronic endocrine or metabolic condition	
	Depression Anxiety Bipolar disorder Paranoia Schizophrenia Neurosis Personality disorder Substance addiction/abuse Posttraumatic stress disorder Chronic fatigue syndrome Other chronic psychiatric condition: Other chronic psychiatric condition:	

Appendix 8. FACIT-Fatigue

FACIT Fatigue Scale (Version 4)

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

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4

An16	I have to limit my social activity because I am tired	0	1	2	3	4