An open label, phase 2 study of ibrutinib in combination with rituximab and lenalidomide in previously untreated subjects with follicular lymphoma and marginal zone lymphoma

Principal Investigator:

Loretta J. Nastoupil, MD

Assistant Professor

Department of Lymphoma and Myeloma

The University of Texas M.D. Anderson Cancer Center

1515 Holcombe Blvd, Unit 429

Houston, TX 77030

Email: lnastoupil@mdanderson.org

Tel: 713-745-4017

Fax: 713-794-5656

Co-Principal Investigator:

Nathan Fowler, MD

Associate Professor

Department of Lymphoma Myeloma

Email: nfowler@mdanderson.org

Protocol number: 2015-0361

IND Number: 127088

Investigational Drugs: Ibrutinib and lenalidomide

Source of Investigational Drug: Janssen Scientific Affairs, LLC is providing study drug ibrutinib and funding support;

MD Anderson Cancer Center is the Sponsor of the protocol

Celgene Corporation is providing study drug lenalidomide

Version: 4.0

Revised: 01/12/2017

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ANC	Absolute neutrophil count
AE	Adverse event
AESI	Adverse Events of Special Interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
C	Celsius
Cl	Chloride
CR	Complete remission (response)
CI	Confidence interval
CrCL	Creatinine clearance
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
ECG	electrocardiogram
EFS	Event free survival
F	Fahrenheit
FL	Follicular lymphoma
G-CSF	Granulocyte colony-stimulating factor
HR	Hazard ratio
ICF	Informed consent form
LDH	Lactate dehydrogenase
MRD	Minimal residual disease
N	Number

NHL	Non-Hodgkin lymphoma
OS	Overall survival
PR	Partial response
PS	Performance status
PET	Positron emission tomography
K	Potassium
PQC	Product Quality Complaint
PD	Progressive disease
PFS	Progression free survival
SPM	Second primary malignancy
SAE	Serious adverse event
Na	Sodium
TTNT	Time to next anti-lymphoma treatment
TNF-α	Tissue necrosis factor- alpha
VTE	venous thromboembolism

1. BACKGROUND

Follicular lymphoma (FL) is the most common indolent Non-Hodgkin lymphoma (NHL) and is characterized by high response rates to initial therapy coupled with relapse, and is considered incurable with standard treatment options. Prognosis has been associated with age, stage, disease burden, lactate dehydrogenase, hemoglobin, and presence of B-symptoms.[1, 2] The majority of patients with FL present with advanced stage disease and are often asymptomatic. In addition to clinical prognostic factors, biologic or immune signature prognostic factors have been reported.[2-4] FL is characterized by high incidence of BCL-2 deregulation, t(14:18) and forms the basis for PCR assessment of minimal residual disease (MRD) in FL.[5] Despite high response rates, most patients with FL will succumb to their disease and clinical outcomes remain heterogeneous.

Though a number of management strategies have been utilized for patients with previously untreated FL, it was not until incorporation of rituximab, a monoclonal antibody to CD20 antigen that improvement in overall survival was achieved.[6] Based on the Stanford experience, there was no significant change in the natural history of FL from the 1960's through the early 1990's, despite modifications of the chemotherapy regimens[7]. The most commonly prescribed frontline strategy for FL in the United States in the modern era is rituximab in combination with chemotherapy.[8] Despite high response rates[9, 10], and median PFS exceeding 5 years with the addition of maintenance rituximab[11], chemoimmunotherapy is not considered curative in FL, as patients continue to relapse. In addition, the side effect profile associated with cytotoxic therapy[12] raises the question, what is the optimal frontline strategy for FL?

Lenalidomide, a thalidomide derivative, is a second generation immunomodulatory drug, proposed to have multiple mechanisms of action, including beneficial effects on both tumor and microenvironment. Lenalidomide has been associated with TNF-α inhibitory, and T-cell costimulatory, and antiangiogenic activities.[13] The molecular action of lenalidomide, involves its binding to protein targets cereblon, Ikaros, and Aiolos[14-17], and subsequent effects on protein ubiquitination and degradation.[18] Lenalidomide as an immunomodulator is an interesting approach to the management of FL given the most successful therapy to date for FL has been incorporation of immune therapy (rituximab).

Most frequently reported adverse events reported during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, urinary tract infection, upper respiratory infection, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, cerebral vascular accident, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures.

The combination of lenalidomide plus rituximab has synergistic effects against lymphoma, as demonstrated in vitro and in animal models, by enhancing rituximab-induced apoptosis and rituximab-dependent NK cell-mediated cytotoxicity.[19-22] Based on the observed efficacy of lenalidomide combined with rituximab in relapsed/refractory indolent NHL[23], and the expectation of synergy between these agents, our group completed a phase 2, single arm study to evaluate the efficacy and safety of lenalidomide and rituximab in patients with untreated, advanced-stage indolent NHL, demonstrating efficacy and safety of the combination.[24] Overall response rate (ORR) in our study was 90% with a complete response rate of 63%, and 75% of patients remained in remission at 36 months. Of the evaluable patients with FL (N=46), 45 had an ORR, 98%. 40 patients with FL had a CR or unconfirmed CR (87%), and three-year PFS estimates were 78.5%.[24] Similar findings were demonstrated by a phase 2, multi-center study investigating the combination in previously untreated patients with indolent NHL.[25] Based on these findings, a phase 3, randomized international registration study comparing the efficacy of lenalidomide and rituximab versus chemoimmunotherapy for previously untreated FL patients (RELEVANCE; NCT01476787) has completed enrollment, results are eagerly awaited, but not anticipated for a few years.

Another compelling approach to management of indolent NHL is targeting a key cellular pathway or attribute specific to tumor cells. The B-cell receptor (BCR) is the unique molecular fingerprint of each B-cell and signals emanating from the BCR act through downstream pathways to direct development, proliferation, and survival of normal B cells. The BCR and downstream pathways are also frequently manipulated by B-cell malignancies. As a result, targeted agents inhibiting BCR-activated signaling pathways have been successfully translated into the clinical setting.[26, 27] Ibrutinib, an orally available, selective kinase inhibitor irreversibly binds Cys-481 residue on Bruton tyrosine kinase. In a phase 1 study of ibrutinib in relapsed/refractory B-cell malignancies, ibrutinib was well tolerated; the maximum tolerated dose was not reached.[28] Notable was an ORR of 60% in evaluable patients. These findings prompted multiple phase 2 studies [26, 29], demonstrating efficacy of ibrutinib and led to FDA approval in relapsed mantle cell lymphoma patients who have received at least one prior therapy, chronic lymphocytic leukemia or small lymphocytic lymphoma patients who have received at least one prior therapy, chronic lymphocytic leukemia or small lymphocytic lymphoma patients with deletion 17p, and Waldenstrom's macroglobulinemia. Ibrutinib is being studied for the treatment of several other illnesses and its use in this study is investigational.

Commented [CP[1]]: GCDO: align with current label – add Small Lymphatic Lymphoma.

With the evolving knowledge of the BCR pathway and tumor microenvironment, exploiting insights into the oncogenic pathways appears to be a promising approach. The combination of lenalidomide and ibrutinib has reported synergism in vitro.[14] In a cereblon-dependent fashion, lenalidomide downregulates IRF4 and SPIB, transcription factors that prevent interferon β production by repressing IRF7 and amplify NF-κB signaling by transactivating CARD11.[14] Blockade of BCR signaling using ibrutinib also downregulates IRF4 and synergizes with lenalidomide in killing activated B-cell like diffuse large B-cell lymphoma cell lines, suggesting an attractive therapeutic strategy.

A phase 1 study of ibrutinib in combination with rituximab and lenalidomide in previously untreated stage II-IV FL patients has been completed (NCT01829568). The primary objective was to determine the recommended phase 2doses of ibrutinib and lenalidomide for combination with rituximab in previously

untreated FL. Secondary objectives were to determine the pharmacokinetics of ibrutinib and its major metabolite (PCI-45227) when combined with lenalidomide and rituximab and to determine the pharmacodynamics of basophil activation and BTK occupancy in PBMCs over a 24-hour period of ibrutinib when given in combination with lenalidomide and rituximab. Treatment consisted of dose escalations of lenalidomide and ibrutinib and a fixed dose of rituximab (375 mg/m2). Once the maximum tolerated dose was reached, there was to be an expansion cohort of ten additional patients. These ten patients were to receive the fixed dose of rituximab, and the recommended phase 2 doses of ibrutinib and lenalidomide. Patients received lenalidomide PO on days 1-21 of a 28 day cycle for 18 cycles, and ibrutinib PO on days 1-28 until disease progression. Patients received rituximab by IV infusion on day 1, day 8, day 15, and day 22 of cycle 1. Four remaining doses of rituximab were to be given at week 13, week 21, week 29, and week 37.

22 subjects with FL were enrolled at different dose levels.

Dose Level	Ibrutinib (mg)	Lenalidomide (mg)	Rituximab (mg/m2)
-2	280	5	375
-1	420	10	375
0	420	15	375
1	560	15	375
2	560	20	375

The dose escalation schema was standard for a 3+3 design. If dose level 0 is shown to be too toxic (i.e. has > 1/6 DLTs), dose de-escalation was to be continued until finding a dose level with 0/3 or 1/6 DLT. If the dose level has 1/6 DLT this dose was to be selected as the MTD. If the dose level has 0/3 DLT, another 3 patients were to be added at this level. If the level has ≤ 1/6 DLT with the addition, of 3 patients, it will be selected as the MTD. If the dose level has > 1/6 DLTs, dose de-escalation was to continue. DLT was defined as any non-hematologic or hematologic toxicity listed below that occurs during the first cycle of treatment. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0. Patients were to be evaluated once per cycle for any adverse events.

Non-hematologic dose-limiting toxicity was defined as any of the following: any Grade 3 or 4 non-hematologic toxicity (excluding: Grade 3 rash that resolves to < Grade 2 within 10 days with systemic corticosteroid treatment, fatigue, anorexia, nausea, fever without neutropenia, tumor lysis syndrome); grade 3 rash that does not resolve to < Grade 2 within 10 days with corticosteroid treatment; any grade Stevens-Johnson syndrome or toxic epidermal necrolysis; grade 3-4 bullous dermatitis; failure of any Grade 3 or 4 non-hematologic toxicity (as defined above) to resolve or recover to baseline level after delaying the next dose by more than 2 weeks; AST or ALT ≥ 3 x ULN in combination with a total bilirubin ≥ 2 x ULN. Hematologic dose-limiting toxicity was defined as any of the following: any Grade 4 hematologic toxicity, except for grade 4 neutropenia ≤ 7 days; grade 4 neutropenia > 7 days; grade 3 or

4 neutropenia complicated by fever ≥ 38.5°C or infection; grade 4 thrombocytopenia (must be repeated same day by a separate peripheral blood draw to confirm toxicity); grade 2-3 thrombocytopenia complicated by hemorrhage.

The preliminary safety data that has not been reported or published suggests the combination is tolerable. Of 22 subjects, 8 developed a Grade 1 or 2 rash, and 8 subjects developed a Grade 3 rash; rash was not considered a DLT in this study unless the rash did not resolve to < Grade 2 within 10 days with corticosteroid treatment. In addition, rash was associated with allopurinol in several cases and with Bactrim (sulfamethoxazole and trimethoprim) in 1 case. No cytokine storm reactions were seen. As a result of this approach, in the CTEP/A051103 study, no DLTs were seen and no MTD was identified. The rashes were manageable with temporary holding of ibrutinib and lenalidomide, concomitant therapy with corticosteroids and/or antihistamines, and discontinuation of potential contributors such as allopurinol if applicable. The maximum dose of lenalidomide given was the highest planned dose of 20 mg.

In the phase 2 study of lenalidomide and rituximab in previously untreated FL [24], the most common hematologic adverse event was neutropenia (25% grade 3, 10% grade 4), however, febrile neutropenia was infrequent (<1%), upper respiratory infections were generally mild (21% grade 2, 2% grade 3). Common non-hematologic adverse events were fatigue (90% all grades, 5% grade ≥3), pain or myalgia (82% all grades, 9% grade 3), nausea or vomiting (61% all grades, 0 grade ≥3), rash (58% all grades, 7% grade 3), diarrhea (50% all grades, 0 grade≥3), and constipation (52% all grades, 0 grade ≥3). Less frequent non-hematologic grade 1 or 2 adverse events included cough (44%), dizziness (43%), edema (43%), peripheral neuropathy (36%), infusion reaction (13%), and thyroid test abnormalities (23%). Second malignancies were reported in 5 patients. No deaths occurred on study as a result of toxicity.

The MTD of ibrutinib in phase 1 studies has not been reached. [28] The most common (>20%) non-hematologic adverse events associated with ibrutinib have generally been mild (Grade 1 or 2) and include diarrhea (50%), fatigue (41%), nausea (31%), peripheral edema (28%), dyspnea (27%), constipation (25%), upper respiratory infection (23%), vomiting (23%), and decreased appetite (21%). Grade ≥ 3 hematologic toxicities include neutropenia (16%), thrombocytopenia (11%), and anemia (10%). [26] Four patients in the phase 2 study that led to the FDA indication for ibrutinib in relapsed/refractory mantle cell lymphoma had subdural hematomas (Grade 1 in 1 subject, Grade 2 in 1 subject, Grade 3 in 2 subjects); all were associated with falls, head trauma, or both. [26] Though infrequent, additional non-traumatic bleeding complications associated with ibrutinib have been reported including gastrointestinal bleeding and hematuria.

Marginal zone lymphoma is a less frequent indolent NHL and is most commonly managed similar to follicular lymphoma given limited prospective data to guide routine practice. We included untreated marginal zone and small lymphocytic lymphoma in the phase 2 study of rituximab in combination with lenalidomide.[30] We enrolled 30 subjects with untreated marginal zone lymphoma subjects, 67% achieved a CR and 22% a PR with an ORR of 89%. Median PFS was 53.8 months in the subjects with marginal zone lymphoma. The median PFS in follicular lymphoma had not been reached suggesting the

combination of lenalidomide and rituximab was most promising in follicular lymphoma, but still associated with favorable outcomes in marginal zone lymphoma.

Gene expression profiling studies though limited by small number of samples have identified a set of markers with differential expression in nodal marginal zone lymphoma compared with follicular lymphoma. [31, 32] The nodal marginal zone lymphoma signature was associated with deregulated pathways including BCR signaling, interleukins (IL-2, IL-6, IL-10), integrin signaling (CD40), and cell survival pathways (MAPKs, tumor necrosis factor, transforming growth factor-β, and NF-κB), conferring a survival advantage in nodal marginal zone lymphoma. Inactivation of the A20 gene is also a common genetic aberration in marginal zone lymphoma which may contribute to lymphomagenesis via constitutive NF-κB signaling. [33] Alteration in lymphoma biology and signaling may explain the differences observed with therapeutic outcomes in follicular and marginal zone lymphoma. Targeting the BCR pathway may be even more atractive in marginal zone lymphoma. A phase II trial PCYC-1121 (NCT01980628) examined single agent ibrutinib in 63 patients with marginal zone lymphoma with at least one prior therapy. The results are eagerly awaited, but are anticipated to be favorable given a supplemental new drug application has been submitted to the FDA for use of ibrutinib as treatment for patients with marginal zone lymphoma. Therefore, extending the eligibility of this study to untreated marginal zone lymphoma is warranted to examine the safety and efficacy of rituximab, lenalidomide and ibrutinib in untreated marginal zone lymphoma.

With the prolonged natural history of FL, identifying optimal endpoints or surrogates for overall survival for frontline studies is an evolving field. In an analysis of the National LymphoCare Study, previously untreated patients with FL who experienced progressive disease within 2 years of initial treatment were identified as a high risk group, “early progressors”.[34] Early progression was dramatically associated with poor overall survival, hazard ratio (HR) =13.3 (95% confidence interval [CI] 7.94-22.4). After adjusting for FLIPI score, early progression was associated with an increased risk of death (HR=15.4, 95% CI 9.6-24.7). This suggests that a landmark progression-free survival at 2 years may predict for a high risk population and discern a difference in outcomes. Another proposed efficacy endpoint includes the complete response rate at 120 weeks or 30 months.[35] Both approaches serve as surrogate endpoints for overall survival.

We are proposing a novel frontline, open-label, phase 2 clinical trial for previously untreated patients with FL and marginal zone lymphoma, a non-cytotoxic approach based on sound scientific rationale with emerging clinical endpoints. The proposed study builds on our experience with frontline rituximab in combination with lenalidomide which has demonstrated similar efficacy in single-arm phase 2 studies with historical comparison to rituximab in combination with chemotherapy, with the addition of ibrutinib as a mechanism of targeting the BCR pathway in addition to the tumor and microenvironment. We aim to explore the efficacy and safety of the novel combination of rituximab, lenalidomide, and ibrutinib in previously untreated patients with FL and marginal zone lymphoma.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to evaluate the efficacy of ibrutinib combined with rituximab and lenalidomide in patients with previously untreated FL and marginal zone lymphoma (determined by PFS at 2 years).

2.2 Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy of ibrutinib combined with rituximab and lenalidomide in subjects with FL and marginal zone lymphoma as assessed by CR at 120 weeks, ORR, DOR, EFS, TTNT, and OS.
- To evaluate the safety and tolerability of ibrutinib combined with rituximab and lenalidomide in previously untreated subjects with FL and marginal zone lymphoma.

2.3 Exploratory Objective

The exploratory objectives are to evaluate prognostic and mechanistic biomarkers relative to treatment outcomes.

3. STUDY DESIGN

3.1 Description of Study

This is an open-label, Phase 2, single center study designed to assess the efficacy and safety of ibrutinib combined with rituximab and lenalidomide in previously untreated subjects with FL and marginal zone lymphoma. The study will include approximately 60 subjects in one treatment arm.

Once a patient provides written informed consent, the patient may enter the screening period, which is permitted to last up to 4 weeks. During the screening period, the patient will undergo safety and other assessments to determine eligibility for the study. The patient eligibility will be based on investigator assessment. The patient will enter the treatment period once the patient has fulfilled the required assessment in the screening period. The treatment period for each patient starts with study day 1 of cycle 1. The treatments will be given as described in Section 7. The patients will receive protocol-specified treatments, until:

1) Relapse or progression of disease
2) Withdrawal of consent,
3) Unacceptable toxicity, or
4) End of study.

Upon completion of the required treatments, the patient will enter the three-year follow-up period. During the follow-up period, patients will be followed for disease progression, next lymphoma treatment, and OS.

3.2 Endpoints

3.2.1 Primary Endpoint:

Progression-free survival (PFS) at 2 years as assessed by the investigator

3.2.2 Secondary Endpoints:

Efficacy:

- Complete response rate ([CR], based on Cheson, Lugano classification 2014) at 120 weeks as assessed by the investigator
- Overall response rate (CR + partial response [PR]) based on Cheson, Lugano 2014 as assessed by the investigator
- Duration of response (DOR)
- Event free survival (EFS)
- Time to next anti-lymphoma treatment (TTNT)
- Overall survival (OS)

Safety:

- Frequency, severity, and relatedness of treatment-emergent adverse events (AEs)
- Frequency of treatment-emergent AEs requiring discontinuation of study drug or dose reductions

3.2.3 Exploratory Endpoints:

- Immunophenotyping of PBMCs to determine alteration in immune cell subsets
- Identification of signaling pathways or biomarkers that predict sensitivity or resistance by gene expression profiling
- Determination of alteration of cytokines and chemokines

3.3 Safety Plan

This study will be monitored by the Principal Investigator and in accordance with all FDA safety reporting requirements. AEs and SAEs will be reviewed on an ongoing basis to identify potential safety concerns. The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy. Enrolled subjects will be evaluated clinically including vital signs and standard laboratory test assessment.

3.5 Statement of Compliance

The study will be conducted in compliance with this protocol, principles of International Conference on Harmonization (ICH), Good Clinical Practice (GCP), Declaration of Helsinki, and all applicable national and local regulations governing clinical studies.

4. SUBJECT SELECTION

4.1 Number of Subjects

The planned sample size is 60 subjects.

4.2 Inclusion Criteria

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

1. Histologically confirmed CD20+ follicular lymphoma, grade 1, 2, or 3a or marginal zone lymphoma.
2. Have had no prior systemic treatment for lymphoma
3. Bi-dimensionally measurable disease, with at least one mass lesion ≥ 2 cm in longest diameter by CT, PET/CT, and/or MRI.
4. In the opinion of the investigator would benefit from systemic therapy
5. Stage II, III, or IV disease
6. Must be ≥ 18 years of age
7. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
8. Adequate hematologic function within 28 days prior to signing informed consent, including:
    a. Absolute neutrophil count (ANC) ≥ 1,000/mm^3, independent of growth factor support
    b. Platelet counts ≥ 100,000/mm^3 or ≥ 50,000/mm^3 if bone marrow involvement with lymphoma, independent of transfusion support in either situation
9. Adequate organ function, including:
    a. Serum aspartate transaminase (AST) or alanine transaminase (ALT) < 3 x upper limit of normal (ULN)
    b. Creatinine clearance >30 ml/min calculated by modified Cockcroft-Gault formula.
    c. Bilirubin < 1.5 x ULN unless bilirubin is due to Gilbert's syndrome, documented liver involvement with lymphoma, or of non-hepatic origin, in which case bilirubin should not exceed 3g/dL.
    d Prothrombin time (PT)/international normalized ratio (INR) < 1.5 x ULN and partial thromboplastin time (PTT) < 1.5 x ULN
10. Must be able to adhere to the study visit schedule and other protocol requirements

11. Women of childbearing potential and men who are sexually active must be practicing a highly effective method of birth control during and after the study (females of childbearing potential: must either completely abstain from heterosexual sexual conduct or must use 2 methods of reliable contraception, 1 highly effective [intrauterine device, birth control pills, hormonal patches, injections, vaginal rings, or implants] and at least 1 additional method [condom, diaphragm, cervical cap] of birth control. Reliable contraceptive methods must be started at least 4 weeks before lenalidomide. Males who are sexually active must be practicing complete abstinence or agree to a condom during sexual contact with a pregnant female or female of child bearing potential. Men must agree to not donate sperm during and after the study. For females, these restrictions apply at least 4 weeks before study treatment, during the period of therapy and for 1 month after the last dose of study drug. For males, these restrictions apply during the period of therapy and for 3 months after the last dose of study drug.

12. Women of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [β-hCG]) pregnancy test at screening. Women who are pregnant or breastfeeding are ineligible for this study.

    a. Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.

13. Sign (or their legally-acceptable representatives must sign) an informed consent document indicating that they understand the purpose of and procedures required for the study, including biomarkers, and are willing to participate in the study.

14. All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the REMS® program.

4.3 Exclusion criteria

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

1. Known active central nervous system lymphoma or leptomeningeal disease, except subjects with a history of central nervous system lymphoma treated and in remission > 6 months.

2. Evidence of diffuse large B-cell transformation

3. Grade 3b FL

4. Any prior history of other malignancy besides FL or marginal zone lymphoma, unless the patient has been free of disease for ≥ 5 years and felt to be at low risk for recurrence by the treating physician, except:

   a. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.

   b. Adequately treated cervical carcinoma in situ without evidence of disease.

5 Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ibrutinib or lenalidomide capsules, or put the study outcomes at undue risk, including but not limited to:

   a. Moderate to severe hepatic impairment (Child-Pugh classes B and C)

6. Known history of human immunodeficiency virus (HIV), or active Hepatitis C Virus, or active Hepatitis B Virus infection, or any uncontrolled active systemic infection

   a. Patients with inactive hepatitis B infection must adhere to hepatitis B reactivation prophylaxis unless contraindicated.

7. Prior use of ibrutinib or other BTK inhibitors, rituximab or lenalidomide

8. Concurrent systemic immunosuppressant therapy (e.g., cyclosporine, tacrolimus, etc., or chronic administration glucocorticoid equivalent of >10mg/day of prednisone) within 28 days of the first dose of study drug

9. Known anaphylaxis or IgE-mediated hypersensitivity to murine proteins or to any component of rituximab

10. Requires anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon). If patients have been on warfarin or equivalent vitamin K antagonists in the past, they will not be eligible if administered within 30 days of the first dose of study drug.

11. Requires chronic treatment with strong CYP3A inhibitors, for a list of strong CYP3A inhibitors, see Section 6.1.2.1. If patients have been on a strong CYP3A inhibitor in the past, they will not be eligible if the CYP3A inhibitor was administered within 7 days of the first dose of study drug.

12. Requires chronic treatment with strong CYP3A inducers, for a list of strong CYP3A inducers, see Section 6.1.2.1. If patients have been on a strong CYP3A inducer in the past, they will not be eligible if the CYP3A inducer was administered within 7 days of the first dose of study drug.

13. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification.

14. Significant screening electrocardiogram (ECG) abnormalities including left bundle branch block, 2nd degree atrioventricular (AV) block, type II AV block, or 3rd degree block.

15. Known bleeding diathesis (e.g., von Willebrand's disease) or hemophilia

16. History of stroke or intracranial hemorrhage within 6 months prior to study entry.

17. Vaccinated with live, attenuated vaccines within 4 weeks of study entry

18. Lactating or pregnant subjects

19. Administration of any investigational agent within 28 days of first dose of study drug.

20. Patients who have undergone major surgery within 7 days or minor surgery within 3 days of first dose of study drug.

5. TREATMENT OF SUBJECTS

5.1 Enrollment and Blinding

This is an open-label, phase 2 study with one treatment arm. Subjects will not be blinded to study drug nor will they be randomized. Enrolled subjects will receive open-label capsules of ibrutinib and lenalidomide in combination with IV rituximab.

5.2 Formulation, Packaging and Storage

5.2.1 Ibrutinib

Ibrutinib capsules are provided as a hard gelatin capsule containing 140mg of ibrutinib. The ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottle with labels bearing the appropriate label text as required by governing regulatory agencies. Study drug will be dispensed in child-resistant packaging.

At the study site, all investigational study drugs will be stored at room temperature in a locked, safe area to prevent unauthorized access. Ibrutinib will be provided by Janssen Scientific Affairs, LLC to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Additional prescribing information can be found at www.imbruvica.com

5.2.2 Rituximab

Commercially available rituximab will be used. Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration. Rituximab is supplied at a concentration of 10mg/mL in either 100mg (10mL) or 500mg (50mL) single-use vials. The product is formulated for IV administration in 9.0mg/mL sodium chloride, 7.35mg/mL sodium citrate dehydrate, 0.7mg/mL polysorbate 80, and Sterile Water for Injection. The pH is adjusted to 6.5. Rituximab vials should be stored refrigerated between 2° to 8°C (36° to 46°F). Vials should be protected from the light. Additional prescribing information can be found at www.gene.com/download/pdf/rituxan_prescribing.pdf

5.2.3 Lenalidomide

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the Celgene Corporation's Revlimid REMS® program. Per standard Revlimid REMS® program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS® program.

Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site for IND studies. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

Lenalidomide is available in capsule doses of 2.5mg, 5mg, 10mg, 15mg, 20mg, and 25mg. Lenalidomide should be stored as directed on the respective package labels. Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold. Additional prescribing information can be found at www.revlimid.com/wp-content/uploads/2013/11/PI.pdf

5.3 Treatment Schedule

Patients will receive 12 cycles of lenalidomide, 15mg daily on days 1-21 of cycle 1, and 20mg daily on days 1-21 (± 2 days) of cycles 2 through 12. Cycles will be 28 days in length. Patients will receive rituximab, 375mg/m2 on days 1, 8 (± 2 days), 15 (± 2 days), and 22 (± 2 days) of cycle 1, and day 1 (± 2 days) of cycles 2 through 12. Patients will receive ibrutinib 560mg daily, starting on day 1 of cycle 1 and continued through 12 cycles. Therapy is continued for 12 cycles or until disease progression, unacceptable toxicity, or voluntary withdrawal.

5.3.1 Dosage and Administration

Below are specific administration instructions for drugs used within this study:

Ibrutinib

Ibrutinib 560mg (4 x 140mg capsules) is administered orally once daily with approximately 8 ounces (240mL) of water. Ibrutinib may be administered with or without food. For patients with mild liver impairment (Child-Pugh Class A), the recommended dose of ibrutinib is 140 mg daily (one capsule), see Table 1. Grapefruit or Seville oranges should be avoided due to CYP3A4/5 inhibition. Capsules should be swallowed intact and subjects should not attempt to open, break or chew the capsules or dissolve in water. Capsules should be taken at approximately the same time each day. No extra capsules should be taken to make up missed doses of ibrutinib. Ibrutinib dosing is continuous throughout the treatment phase. If a dose is missed, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. No extra capsules to make up the missed dose should be taken.

Table 1. Ibrutinib Dose Adjustment for Patients with Hepatic Impairment

Category	Hepatic Impairment (Child-Pugh)	Dose
Mild hepatic impairment	Class A	140mg (1 capsule) daily

Ibrutinib will be dispensed to subjects in bottles. Unused ibrutinib capsules dispensed during the previous visits should be returned and accountability records must be updated. Unused capsules should not be re-distributed to anyone. Subjects should return all used bottles to the site when they receive new study drug. Unused study drug will be destroyed as per our institution guidelines.

Treatment will continue until disease progression, end of study, or other reason for treatment discontinuation outlined in section 8. Dose modifications for toxicity are outlined in section 5.4.

Rituximab

Rituximab is given as 375mg/m2 IV infusion once weekly for 4 doses starting on day 1 of cycle 1 (± 2 days). For cycles 2 through 12, rituximab is given as 375mg/m2, one dose on day 1 (± 2 days) of each cycle. The costs for administering rituximab are to be covered by the individual subject's insurance. Pre medications for rituximab will be administered per institutional guidelines.

First infusion:

Rituximab should be administered intravenously per institutional guidelines. The final concentration of rituximab is 1mg/mL. Rituximab will be administered at an initial rate of 50mL/hr. The infusion rate may be escalated in 50mL/hr increments every 30 minutes to a maximum of 400mL/hr as tolerated. If hypersensitivity or an infusion reaction develops, the infusion should be interrupted until symptoms resolve or improve. For management of infusion reaction, please refer to the institution's

hypersensitivity reaction order sheet. The infusion can continue at one-half the previous rate upon improvement in symptoms, and the escalation of 50mL/hr increments every 30 minutes resumes to a maximum rate of 400mL/hr.

Subsequent infusions:

If subjects tolerated the first infusion well, the subsequent infusions can start at an initial rate of 100mL/hr as per institution guidelines and increase by 100mL/hr increments every 30 minutes to a maximum of 400mL/hr as tolerated. If subjects did not tolerate the first infusion well, follow the guidelines for the first infusion.

Lenalidomide

Patients with CrCl >60 mL/min will receive 15mg of lenalidomide days 1 through 21 of cycle 1, and 20mg of lenalidomide days 1 (± 2 days) through 21 every 28 day days for cycles 2 through 12 for a total of 12 cycles. Dosing will be based on patient's creatinine clearance (CrCL) as calculated by modified Cockcroft-Gault (Appendix 13.3), Table 2. See below for further instruction on dose adjustment for subjects with renal impairment.

Lenalidomide should be taken orally at about the same time each day, either with or without food. Lenalidomide capsules should be swallowed whole with water, and should not be opened, broken, or chewed. If a dose is missed, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. No extra capsules to make up the missed dose should be taken. Females of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves. Unused lenalidomide capsules dispensed during the previous visits should be returned and accountability records must be updated. Unused capsules should not be re-distributed to anyone. Subjects should return all used bottles to the site when they receive new study drug. Unused study drug will be destroyed as per our institution guidelines.

Lenalidomide Dose Adjustment for Renal Impairment

Subjects with renal impairment (CrCl ≤ 60 ml/min) will be dosed based on Table 2. CrCL assessment will occur on: Day 1, 8, 15, and 22 for cycle 1; Day 1 and 15 for cycle 2; Day 1 of cycles 3-12. However, if a subject has a creatinine obtained at any time during the Treatment Phase because it was clinically indicated, a dose reduction based on CrCL and Table 2 should be performed. For cycle 1, subjects with renal impairment, CrCL of 30-60mL/min, will initiate 15mg of lenalidomide every 48 hours. Subjects with renal impairment, CrCL of <30 mL/min prior to cycle 1, will initiate 10mg of lenalidomide every 48 hours. For subjects with renal impairment (CrCl ≤ 60 ml/min) necessitating dose adjustment on Day 1 of a cycle according to Table 2, but then stably improves, a dose increase based on CrCL will not occur until day 1 of the next cycle. For subjects with CrCl ≤ 60 ml/min at study initiation, but then stably improves to > 60 ml/min, proceed to lenalidomide 20 mg once daily with Cycle 2. At any point, should a patient

require dose reduction due to reduced CrCl, and the CrCl then stably improves, dose escalation will not occur until day 1 of the next cycle.

Table 2. Lenalidomide Dose Adjustment for Patients with Renal Impairment

Category	Renal Function (modified Cockcroft-Gault)	Cycle 1	Cycle 2 onward
Mild or no renal Impairment	CrCl > 60 mL/min	15 mg once daily	20 mg once daily
Moderate renal impairment	CrCl 30-60 mL/min	15 mg every 48 hours	10mg every 24 hours *
Severe renal impairment	CrCl <30mL/min (not requiring dialysis)	10 mg every 48 hours	15mg every 48 hours *

* If CrCl is ≤ 60 ml/min at study initiation but then stably improves to >60 mL/min, proceed to lenalidomide 20 mg once daily with Cycle 2.

5.4 Dose Reduction, Delay and Discontinuation

Toxicity necessitating dose modification or delay is based on NCI CTCAE v 4.03 Toxicity Grade. The Principal Investigator will assess whether each AE is related or not to each of the study drugs. Events that are judged definitely, probably or possibly related are considered related AEs. Events that are considered unlikely or definitely not related are considered not related AEs. Factors to be taken into consideration include the temporal relationship between administration of study drug and the onset of the AE, other potential causes of the AE including the subject's underlying medical condition and concomitant medications, whether the AE is consistent with known AEs previously attributed to a study drug, whether the AE decreases or resolves upon withholding or reducing the dose of the study drug, or whether the AE recurs upon reintroduction of the study drug. AEs defined below (Sections 5.4.1), unless the Principal Investigator considers the event clearly unrelated to study drug, will be considered a toxicity that necessitates dose modification or delay.

5.4.1 Toxicities Necessitating Dose Modification or Delay

Toxicities necessitating dose modification or delay will be defined as any non-hematologic or hematologic toxicity listed below. Study treatment should be discontinued in the event of a toxicity lasting more than 28 days despite appropriate medical management, unless reviewed and approved by the Principal Investigator. The action in Table 3 should be taken for the following toxicities:

Non-hematologic toxicity will be defined as any of the following:

- Any unmanageable Grade 3 or 4 non-hematologic toxicity with failure to improve (< Grade 2) or recover to baseline within 14 days of withholding drug
- Grade 3 or 4 non-blistering rash that does not resolve to < Grade 2 within 14 days
- Any desquamating (blistering) rash
- Any grade Stevens-Johnson syndrome or toxic epidermal necrolysis
- Grade 3 or 4 thrombosis/embolism
- Grade 3 or 4 peripheral neuropathy which began or worsened while on study

Hematologic toxicity will be defined as any of the following:

- Grade 3 neutropenia with infection or fever (single temperature of > 38.3 ºC, or with a sustained temperature of ≥ 38 º C lasting > 1 hour).
- Grade 4 neutropenia (ANC<500/µL) lasting > 7 days.
- Grade 4 thrombocytopenia (<25,000/µL)

The following action should be taken for any unmanageable toxicity that is consistent with the rules outlined above:

Table 3. Dose modification for toxicity

Toxicity Grade	Action to be Taken
Grade 3 neutropenia associated with fever (single temperature of > 38.3 ºC, or with a sustained temperature of ≥ 38 º C lasting > 1 hour) OR Grade 4 neutropenia lasting > 7 days.	•Hold lenalidomide and ibrutinib. •Follow CBC weekly. •If neutropenia has resolved to < Grade 2 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level, (see Table 5) and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. •Withhold ibrutinib until recovery to < Grade 2 or baseline; may restart at original dose level for the first occurrence. For subsequent occurrence, please refer to Table 4 for next lower dose level. •Withhold rituximab until recovery to < Grade 2 or baseline. •Omitted doses are not made up. •G-CSF may be used
≥ Grade 4 thrombocytopenia	• Hold lenalidomide and ibrutinib dose. • Follow CBC weekly. • If thrombocytopenia resolves to < Grade 2 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose

	level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. • Withhold ibrutinib until recovery to < Grade 2 or baseline; may restart at original dose level for the first occurrence. For subsequent occurrence, please refer to Table 4 for next lower dose level. • Withhold rituximab until recovery to < Grade 2 or baseline. • Omitted doses are not made up. • Hold prophylactic anti-coagulation including aspirin, if applicable. • Restart prophylactic anti-coagulation and/or aspirin when platelet count is ≥ 50,000/mm^3.
Non-blistering rash Grade ≥ 3	• If Grade ≥3, hold lenalidomide and ibrutinib dose. Follow weekly. If the toxicity resolves to < Grade 2 prior to Day 21 of the current cycle, restart lenalidomide at original dose level (for first occurrence) and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle. • Omitted doses are not made up. • For the second occurrence of Grade ≥3, hold lenalidomide, and follow weekly. If the toxicity resolves to ≤ Grade 2 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. • Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level for the first occurrence. For subsequent occurrence, please refer to Table 4 for next lower dose level. • Treatment with 10mg of prednisone or equivalent for 10 days (with or without taper) and/ or antihistamines PO daily is recommended. •If Grade ≥3 rash has not improved to at least Grade 1 within 14 days of drug being withheld and administration of 10mg of steroids and/or antihistamines daily, the subject will discontinue study treatment.
Desquamating (blistering) rash Any grade	• Discontinue study drugs. Remove patient from study. • Start supportive care: daily antihistamine, 10mg or higher of prednisone or corticosteroid equivalent as clinically indicated

≥ Grade 3 thrombosis/embolism	•Hold lenalidomide and start therapeutic anticoagulation with low molecular weight heparin, if appropriate. Warfarin anticoagulation is not allowed. •Restart lenalidomide at investigator's discretion (maintain dose level) after anticoagulation is initiated. •See anticoagulation considerations, Section 6.1.2.2.
Peripheral neuropathy Grade 3 Grade 4	•If Grade 3, hold lenalidomide dose. Follow at least weekly. •If the toxicity resolves to ≤ grade 1 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. •If Grade 4, discontinue lenalidomide. Remove patient from study.
Other non-hematologic toxicity ≥ Grade 3	• Hold lenalidomide and ibrutinib dose. Follow at least weekly. • If the toxicity resolves to < Grade 2 prior to Day 21 of the current cycle, restart lenalidomide and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle. Omitted doses are not made up. For toxicity attributed to lenalidomide, reduce the lenalidomide dose by 1 dose level when restarting lenalidomide. • Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level for the first occurrence. For subsequent occurrence, please refer to Table 4 for next lower dose level. • Withhold rituximab until recovery to < Grade 2 or baseline.

5.4.2 Ibrutinib

The ibrutinib dose should be held for any unmanageable toxicity that is consistent with the rules outlined in Section 5.4.1. Dose should be modified according to the dose modification guidelines in Table 3. See Table 4 for dose reduction levels for ibrutinib.

Please see Sections 10.2.2.1 and 10.2.2.2 for reporting of major hemorrhage and intracranial hemorrhage.

Table 4. Dose Reduction Levels for Ibrutinib.

Dose Level	Ibrutinib Dose
Level -1	420 mg per day

Level -2	280 mg per day
Level -3	140 mg per day
Level -4	Discontinue ibrutinib

The dose of ibrutinib may be reduced successively by one level from starting dose, Table 4. Once a patient's dose has been reduced, no dose re-escalation is permitted. Patients who cannot tolerate the lowest applicable dose level are to be discontinued from the Treatment Phase. Patients with mild hepatic impairment will be starting at 140mg per day as outlined in Table 1. If these subjects have toxicity that result in dose modification of ibrutinib as outlined above, they will be discontinued from the Treatment Phase as they are starting at the lowest applicable dose level and cannot tolerate therapy.

Please see Section 6.1.2.1 for guidelines for management of ibrutinib in subjects who require treatment with a strong CYP3A4/5 inhibitor.

5.4.3 Rituximab

The rituximab dose should be held for any unmanageable toxicity that is consistent with the rules outlined in Table 3. A missed dose of rituximab on the weekly schedule for any reason will not be made up (the visit window for this visit and Day 1 of Cycles 2 -12 is ±2 days).

5.4.4 Lenalidomide

The lenalidomide dose should be held for any unmanageable toxicity that is consistent with the rules outlined in Table 3.

The dose of lenalidomide may be reduced successively by one level from starting dose, Table 5. Once a patient's dose has been reduced, no dose re-escalation is permitted. Patients who cannot tolerate the lowest applicable dose level are to be discontinued from the Treatment Phase. Dose modification should also meet the specifications outlined for those subjects with renal insufficiency as outlined in Table 2. If patients with renal impairment are currently receiving 10mg every 24 hours and need a dose modification, they will then be dose reduced to 15mg every 48 hours. If they need further dose reduction due to toxicity, they will be discontinued due to being unable to tolerate the lowest applicable dose. Similarly, patients starting at 15mg every 48 hours who need further dose reduction will be discontinued due to being unable to tolerate the lowest applicable dose.

Table 5. Dose Reduction Levels for Lenalidomide

Dose Level	Lenalidomide 15 mg starting dose	Lenalidomide 20 mg starting dose
Level -1	10mg daily on Days 1-21, every 28 days	15mg daily on Days 1-21, every 28 days

Level -2	5mg daily on Days 1-21, every 28 days	10mg daily on Days 1-21, every 28 days
Level -3	Discontinue lenalidomide	5mg daily on Days 1-21, every 28 days

5.5 Overdose Instructions

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any SAE criterion must be reported as an SAE in the appropriate time frame and documented as clinical sequelae of an overdose. In the event of an overdose, subjects should be closely monitored and given appropriate supportive treatment.

5.6 Criteria for Permanent Discontinuation of Study Drug

Investigators are encouraged to keep a subject who is experiencing a clinical benefit on study unless significant toxicity puts the subject at risk or routine noncompliance puts the study outcomes at risk. If a subject meets any of the following criteria, then withdrawal from the study treatment is mandatory:

- Subject has confirmed progressive disease (PD)
- Subject has an intercurrent illness or AE that prevents further treatment administration beyond 28 days
- Subject decides to withdraw from study
- Subject becomes pregnant
- Subject is routinely noncompliant with study procedures and/or scheduled evaluations
- Subject requires a prohibited concomitant medication
- Investigator considers withdrawal to be in the best interest of the subject.

A safety follow up visit is required for all subjects except those who have withdrawn full consent.

6. CONCOMITANT MEDICATIONS/PROCEDURES

6.1 Concomitant Medications

6.1.1 Permitted Concomitant Medications

Supportive medications (such as for emesis, diarrhea, constipation, etc.) should be delivered in accordance with standard practice. Tumor lysis prophylaxis should be administered during cycle 1 as clinically indicated in accordance with standard practice. Of note, aprepritant is a moderate CYP3A4/5 inhibitor and should be used with caution as outlined below in Section 6.1.2.1. Use of neutrophil growth factors (granulocyte colony-stimulating factor [G-CSF] such as filgrastim or pegfilgrastim) is permitted for management of neutropenia in accordance with the American Society of Clinical Oncology (ASCO) guidelines. Preemptive or prophylactic G-CSF during cycle 1 is not required. Transfusions may be given in accordance with institutional policy.

Short courses of corticosteroids (<14 days) for treatment of non-lymphoma related medical reasons (e.g. rash, arthritis, asthma) or for tumor flare at doses that do not exceed 10mg per day of prednisone or equivalent are permitted, See Section 6.1.3. However, if clinically indicated, higher doses of corticosteroids (>10mg per day) are permissible.

6.1.2 Concomitant Medications to be used with Caution

6.1.2.1 Concomitant use of CYP3A4/5 Inhibitors/Inducers

Ibrutinib is metabolized primary by CYP3A4/5. Due to the potential increase in ibrutinib exposure, concomitant use of strong CYP3A4/5 inhibitors (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithyromycin, telithromycin, itraconazole, and nefazadone) should be avoided while the subject is receiving treatment.

If use of a strong CYP3A4/5 inhibitor is necessary, selection of an alternate concomitant medication with less potent enzyme inhibition potential is strongly recommended. If concomitant use of ibrutinib with a strong CYP3A4/5 inhibitor is unavoidable, ibrutinib should be discontinued. After completing treatment with the strong CYP3A4/5 inhibitor, wait at least 7 days before resuming ibrutinib.

Subjects should avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A4/5. In addition, moderate CYP3A4/5 inhibitors commonly used include aprepitant, diltiazem, verapamil, erythromycin, and fluconazole. These moderate CYP3A4/5 inhibitors should be avoided, but if necessary are permissible and should be used with caution.

Co-administration of ibrutinib with strong CYP3A4/5 inducers (e.g., carbamazepine and rifampin) may decrease ibrutinib plasma concentrations and should be avoided.

A comprehensive list of inhibitors, inducers, and substrates may be found at www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#cypEnzymes

or

http://medicine.iupui.edu/clinpharm/ddis/table.aspx. These websites are revised continually and should be checked for updates.

6.1.2.2 Thromboembolism Prophylaxis

Aspirin and Heparin

It is recommended that patients who are at high risk for a thromboembolic event (history of a thromboembolic event, taking concomitant medications associated with an increased risk for a thromboembolic event, a known hypercoagulable state regardless of thromboembolic history) receive prophylactic aspirin (81mg) daily unless contraindicated. If aspirin is contraindicated, the patient must

be monitored closely and prophylactic measures must be taken in high-risk situations. For patients who are deemed very high-risk for venous thromboembolism, the treating physician should strongly consider prophylactic doses of low molecular weight heparin (i.e. enoxaparin 40 mg subcutaneously daily). All patients who develop a deep venous thromboembolism in any location must be treated appropriately with low molecular weight heparin. Heparin should continue for at least 3 months, however treating physician discretion is allowed. Study treatment is to continue during heparin use. For subjects in whom low molecular weight heparin is contraindicated (i.e., renal impairment), a non-vitamin K antagonist anti-coagulant can be used instead where medically appropriate.

Warfarin and Other Vitamin K Antagonists

Warfarin and similar vitamin K antagonists are not permitted during this trial. They should not be given within 30 days prior to initiation of ibrutinib.

6.1.2.3 Antiplatelet and Anticoagulation

VTE prophylaxis is discussed in Section 6.1.2.2. Warfarin or similar vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E should be avoided. Fatal bleeding events have occurred in patients treated with ibrutinib. Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half of patients treated with ibrutinib. The mechanism for the bleeding events is not well understood. Ibrutinib may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies. Recommend holding ibrutinib for at least 7 days pre and post major surgery and at least 3 days pre and post minor surgery.

6.1.2.4 QT prolongation

Any medications known to cause QT prolongation (Appendix 13.5) should be used with caution; periodic ECG and electrolyte monitoring should be considered. For an up to date list of drugs that cause QT prolongation, please refer to the following website: www.QTdrugs.org

6.1.3 Prohibited Concomitant Therapy

Chemotherapy, anti-cancer immunotherapy, corticosteroids for lymphoma treatment (at doses >10mg of prednisone or equivalent), experimental therapy, or radiotherapy are prohibited during the Treatment phase.

6.1.3.1 Concomitant use of Systemic Corticosteroids

Systemic corticosteroid use at doses above 10mg/day (prednisone or equivalent) is prohibited during the Treatment Phase. Systemic corticosteroid doses above 10mg/day (prednisone equivalent) are allowed for tumor flare reaction treatment (<14 days), ≥ grade 3 rash where clinically indicated, or rituximab cytokine release syndrome prophylaxis and treatment of infusion related reactions at any

time. For patients receiving systemic corticosteroids at doses > 10mg/day (prednisone equivalent), a 28 day washout period prior to Cycle 1 Day 1 is required.

6.2 Guidelines for Perioperative management of Ibrutinib

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

- For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguinous drainage.
- For minor procedures (such as central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.
- For emergency procedures, ibrutinib should be held at least for 7 days after the procedure and until the surgical site is reasonably healed.

7. STUDY PROCEDURES

Before study entry (Screening Phase), throughout the Treatment Phase, and during Follow-up, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these measurements is to ensure adequate safety and tolerability. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedule of Assessments is provided in Appendix 1.

7.1 Screening Phase

Screening procedures will be performed up to 28 days before Cycle 1 Day 1, unless otherwise specified. All subjects must first read, understand, and sign the IRB-approved informed consent form (ICF) before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to signing the ICF and are considered standard of care may be used as screening assessments if they fall within the 28 day screening window.

The following procedures will be performed during the Screening Phase:

- Informed consent
- Review of eligibility criteria
- Medical history and demographics
- Record the Follicular Lymphoma International Prognostic Index (FLIPI) score
- Record tumor burden (GELF criteria)
- Review of AEs and concomitant medications

- Complete physical exam
- ECOG performance status
- Vital signs, weight, and height
- 12 lead ECG
- Imaging by CT/PET/or MRI
- Unilateral bone marrow aspirate and biopsy (can be done within 90 days of study entry)
- Clinical laboratory tests for:
    - Hematology (CBC with differential)
    - Serum chemistry (electrolytes [Na, K, Cl, bicarbonate, Ca], glucose, blood urea nitrogen [BUN], creatinine, alkaline phosphatase, AST, ALT, total protein, albumin, total bilirubin, lactate dehydrogenase [LDH], β2-microglobulin), uric acid
    - Coagulation (PT/INR, aPTT)
    - Serum pregnancy test (for women of childbearing potential only) will be performed 10-14 days prior to writing an initial prescription for lenalidomide and again 24 hours prior to writing an initial prescription for lenalidomide.
    - Hepatitis serologies (hepatitis B surface antigen [HBsAg], hepatitis B core antibody [anti-HBc, hepatitis C antibody])
    - HIV 1 and 2 antibody
    - TSH
    - Determination of creatinine clearance (modified Cockcroft-Gault estimate) utilizing actual body weight
- Optional research tumor sample collection, fresh (for patients undergoing a biopsy as part of standard clinical practice for patients who provide consent) or archival (paraffin embedded).

7.2 Treatment Phase

7.2.1 Cycle 1/Day 1

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

Pre-Dose

- Confirmation of eligibility
- Complete physical exam
- ECOG performance status
- Vital signs and weight
- Clinical laboratory tests for:
    - Hematology
    - Serum chemistry
    - Determination of creatinine clearance (modified Cockcroft-Gault estimate) utilizing actual body weight
- Research laboratory blood sample collected pre-dose for:

- Biomarkers
- Review of AEs and concomitant medications
- Dispense ibrutinib and lenalidomide

Dosing and Post-Dose

- In-clinic administration of ibrutinib
- In-clinic administration of rituximab
- In-clinic administration of lenalidomide

7.2.2 Cycle 1/Day 8

The following procedures will be performed on Cycle 1, Day 8 (±2 days)

Pre-Dose

- Complete physical exam
- ECOG performance status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
  - Determination of creatinine clearance (modified Cockcroft-Gault estimate) utilizing actual body weight
- Review of AEs and concomitant medications

Dosing

- In-clinic administration of rituximab

7.2.3 Cycle 1/Day 15

The following procedures will be performed on Cycle 1, Day 15 (±2 days)

Pre-Dose

- Complete physical exam
- ECOG performance status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
  - Determination of creatinine clearance (modified Cockcroft-Gault estimate) utilizing actual body weight
- Review of AEs and concomitant medications
- Research laboratory blood sample collected for:
  - Biomarkers
-

Dosing

- In-clinic administration of rituximab

7.2.4 Cycle 1/Day 22

The following procedures will be performed on Cycle 1, Day 22 (±2 days)

Pre-Dose

- Complete physical exam
- ECOG performance status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
  - Determination of creatinine clearance (modified Cockcroft-Gault estimate) utilizing actual body weight
- Review of AEs and concomitant medications

Dosing

- In-clinic administration of rituximab

7.2.5 Cycle 2/Day 1

The following procedures will be performed on Cycle 2, Day 1 (±2 days)

- Complete physical exam
- ECOG performance status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
  - Determination of creatinine clearance (modified Cockcroft-Gault estimate) utilizing actual body weight
- Review of AEs and concomitant medications
- Drug accountability
- Dispense ibrutinib and lenalidomide
- Research laboratory blood draw
  - Biomarkers

Dosing

- In-clinic administration of rituximab

7.2.6 Cycle 2/Day 15

The following procedures will be performed on Cycle 2, Day 15 (±2 days)

- Complete physical exam
- ECOG performance status
- Vital signs and weight
- Clinical laboratory tests for:
    - Hematology
    - Serum chemistry
    - Determination of creatinine clearance (modified Cockcroft-Gault estimate) utilizing actual body weight
- Review of AEs and concomitant medications

7.2.7 Cycle 3/Day 1 and every 4 weeks until Treatment Termination

Visits will be performed every 4 weeks (± 2 days) starting at Cycle 3, Day1. Visit windows are relative to Day 1 visit date. The following procedures will be performed:

- Complete physical exam
- ECOG performance status
- Vital signs and weight
- Clinical laboratory tests for:
    - Hematology
    - Serum chemistry
    - Determination of creatinine clearance (modified Cockcroft-Gault estimate) utilizing actual body weight
- Review of AEs and concomitant medications
- Drug accountability
- Dispense ibrutinib and lenalidomide
- CT/PET/or MRI on Cycle 4/Day 1 (± 7 days) and Cycle 7/Day 1 (± 7 days) only
- Research laboratory blood draw (Cycle 7/Day 1 only)
    - Biomarkers

<u>Dosing</u>

- In-clinic administration of rituximab

7.2.8 Early Treatment Termination Visit

The early treatment termination visit should be performed at any time during the study (± 14 days), if based on the clinical evaluation, the investigator suspects PD, or if the subject discontinues treatment for any other reason outlined in Section 5.6. If the subject comes in for a regular study visit and the investigator wants to discontinue treatment at that time, the regular visit will become the termination visit. Any additional procedures that would be performed for the regular study visit should be performed for the treatment termination visit. Adverse events and hospitalizations will be recorded up to 30 days after the last dose of study drugs.

The following procedures will be performed:

- Complete physical exam
- ECOG performance status
- Vital signs and weight
- Clinical laboratory tests for:
    - Hematology
    - Serum chemistry
    - TSH
- Research laboratory tests for:
    - Biomarkers
- Review of AEs and concomitant medications
- Drug accountability
- CT/PET/or MRI
- Optional tumor tissue biopsy to document PD (Research biomarker assessment)

7.2.9 End of Treatment Visit

The end of treatment visit will occur approximately 4 weeks (±14 days) from last dose of study drugs (end of cycle 12) for patients who complete the planned study treatment. Adverse events and hospitalizations will be recorded up to 30 days after the last dose of study drugs.

The following procedures will be performed:

- Complete physical exam
- ECOG performance status
- Vital signs and weight
- Clinical laboratory tests for:
    - Hematology
    - Serum chemistry
    - TSH
- Research laboratory tests for:
    - Biomarkers
- Review of AEs and concomitant medications
- Drug accountability
- CT/PET/or MRI

7.2.10 Response Evaluations

Response Evaluation visits will be performed at the following timepoints:

- At approximately Cycle 4, Day 1 and cycle 7, Day 1 (±7 days).
- At the End of treatment visit or at the early treatment termination visit (±2 weeks).
- Every 12 weeks (±2 weeks) during the follow up phase for the first 4 assessments and then every 24 weeks until the subject exhibits disease progression (± 4 weeks).
- The following procedures will be performed in conjunction with standard visits as follows:
    - Radiologic exam by CT, PET/CT, or MRI scan

- Bone marrow biopsy and/or aspirate with assessment of MRD, to be done once to confirm CR if marrow was involved with lymphoma at screening
- Overall response assessment
- Research laboratory blood samples (when subject achieved CR and/or at PD)

7.3 Follow-up Phase

The follow up period will start at the end of treatment visit (after cycle 12) Patients will be followed every 12 weeks (± 2 weeks) for the first year and then every 24 weeks (± 4 weeks) up to the end of the follow up period, 3 years after the last subject's last study drug dose.

For patients who have completed treatment the follow up assessments will include:

- Physical exam including vital signs and ECOG PS
- Clinical laboratory tests for hematology and serum chemistry
- Second primary malignancy (SPM)
- Adverse events and hospitalization up to 30 days after last study drug
- Overall survival
- Radiologic assessment (CT, PET/CT, or MRI)
- Research laboratory blood samples at PD only.

For patients who discontinue treatment due to progressive disease or relapse, follow up assessments will include:

- Overall survival
- Subsequent anti-lymphoma therapy (including the time of initiation of therapy and best response to first subsequent anti-lymphoma treatment utilized after discontinuation from this study)
- Adverse events and hospitalization up to 30 days after last study drug (Safety visit)
- SPM

7.3.1 Survival Follow Up

Once subject progresses or starts use of alternative antineoplastic therapy (for subjects who have not withdrawn consent), they will be contacted approximately q 12 weeks (± 2 weeks) for 1 year and then q 24 weeks (± 4 weeks) from the last dose of study drug by clinic visit or telephone to assess survival and the use of alternative antineoplastic therapy and stem cell transplant. Subjects will be contacted until: death, consent withdrawal, lost to follow up, or study termination, whichever comes first.

7.3.2 Missed Evaluations

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

7.4 Description of Procedures

7.4.1 Medical History

The subject's medical history through review of the medical records and by interview will be collected and recorded. A disease history including date of initial diagnosis and baseline symptoms and severity should be recorded.

7.4.2 Physical Examination

The physical exam should include the general state of the subject, examination of the skin, eyes, ear, nose, throat, lungs, heart, abdomen, extremities, lymphatic system. Nervous system should be included if clinically indicated.

7.4.3 Vital signs

Vital signs including weight, blood pressure, heart rate, respiratory rate, and temperature will be recorded. Height will only be recorded during the screening phase, Visit 1.

7.4.4 ECOG PS

Table 6: Performance status definitions

Status	ECOG PS Definition
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 (ie, 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

7.4.5 Concomitant Medications

All concomitant medications including over the counter medications and supplements should be recorded starting during the screening phase and continued through the treatment phase as well as up to 30 days after last study drug dose. Concomitant medications will be available in the electronic medical record.

7.4.6 Adverse Events

Only laboratory abnormalities which result in signs or symptoms that require intervention or follow up and are considered clinically significant should be recorded as AEs. See Section 10 for more details. All other AEs whether serious or non-serious will be entered in PDMS/CORe (the electronic case report form) from the time of signed and dated ICF up until 30 days after the last dose of study drugs. The Principal Investigator or designee will be responsible for assigning attribution to the study drugs.

7.4.7 CT, PET/CT and MRI Scans

A CT scan (with contrast unless contraindicated) of the neck, chest, abdomen and pelvis are required for disease assessment. A "diagnostic quality" combined PET/CT with IV and PO (or water) contrast is an acceptable alternative to CT scans. In addition, if independent CTs are performed, a PET can also be used to augment tumor assessment. In the case where a CT with contrast is contraindicated, an alternative would be an MRI of the chest, abdomen, and pelvis.

In general, follow-up assessments will be done by CT scans. PET-CT scan is encouraged and should be done at baseline and repeated to confirm complete remission and/or at treatment discontinuation, unless the subject's insurance will not cover a PET as part of standard of care. In this situation, CTs are acceptable alternatives. For lymphomas that are not FDG-avid at screening, PET does not need to be repeated in subsequent assessments.

7.4.8 Response Assessment

Response assessment will be completed by the Principal Investigator using Cheson 2014 Lugano Criteria. At screening, up to 6 target lesions will be selected and followed for the duration of the study. Information on extranodal involvement can also be recorded. The best ORR will be documented.

7.4.9 Hematology

Hematology studies must include a complete blood count (CBC) with differential. Coagulation studies performed at screening will include a PT and PTT.

7.4.10 Serum Chemistry

Chemistry must include electrolytes (sodium, potassium, chloride, bicarbonate), blood urea nitrogen, creatinine, glucose, calcium, alkaline phosphatase, ALT, AST, total bilirubin, albumin, total protein, LDH, β2-microglobulin), and uric acid.

7.4.11 Coagulation

Coagulation studies performed at screening will include PT/INR and activated PTT.

7.4.12 Hepatitis Serologies

Hepatitis serologies include Hepatitis C antibody, Hepatitis B surface antigen, Hepatitis B core antibody. For patients with a positive Hepatitis C antibody, Hepatitis C viral PCR should be performed to evaluate for active infection.

7.4.13 HIV Serologies

HIV serologies include antibodies to HIV 1 and 2.

7.4.14 Creatinine Clearance

Determination of creatinine clearance using the modified Cockcroft-Gault estimate (utilizing actual body weight) should be calculated during the Screening phase, C1D1, C1D8, C1D15, C1D22, C2D1, C2D15 and at the start of each subsequent cycle to determine dose of lenalidomide (Table 2).

7.4.15 Pregnancy Test

During screening, two serum pregnancy tests will be required for women of childbearing potential. Females of childbearing potential are defined as: all females who are menstruating, amenorrheic from previous treatments, under 50 years of age, and/or perimenopausal, and do not qualify for the females not of reproductive potential category.

Females not of reproductive potential are defined as: females who have been in natural menopause for at least 24 consecutive months, or who have had a hysterectomy and/or bilateral oophorectomy, or female children who have not started menstruating and will not be required to undergo pregnancy testing.Females of reproductive potential must also adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program, Appendix 13.6.

Urine pregnancy tests should be performed as clinically indicated for women of childbearing potential.

7.4.16 Bone Marrow Biopsy and Aspirate

An unilateral bone marrow biopsy and aspirate will be done at screening or up to 90 days before study entry. Thereafter, bone marrow biopsy and aspirate will only be required to confirm CR if it was positive at screening. Minimal residual disease assessment should be done on marrow using PCR for t(14;18) detection during screening and repeated when bone marrow assessments are performed as outlined above.

7.4.17 ECG

An electrocardiogram will be conducted during screening to evaluate for clinically significant cardiac arrhythmias.

7.4.18 Biomarkers

40 ml of blood sample [one red top tube (10 ml) and 3 heparin containing green top tubes (30 ml)] will be collected prior to rituximab on Cycle1, Day 1, Cycle 1, Day 15, Cycle 2, Day 1, and on Cycle 7, Day 1. At the time of documented PD, blood biomarker collection should be performed (+/- 4 weeks). These

samples will be transported within 6 hours of collection to Dr. Neelapu's laboratory for processing at the South Campus Research Building I, Room 4.3206, at M. D. Anderson Cancer Center (MDACC). Blood from red top and green top tubes will be processed for isolation of serum and PBMC, respectively using standard laboratory protocols. The isolation of serum and PBMC may also be performed at the Clinical and Translational Research Center (CTRC) Laboratory at MDACC using standard laboratory protocols.

7.4.19 Tumor Tissue Biopsy

For subjects with PD on radiologic assessment, a tumor biopsy to confirm PD is optional. Tumor samples may be analyzed by gene expression profiling, immunohistochemistry, flow cytometry, or other methods to define biomarkers that predict response or resistance to lenalidomide, rituximab and ibrutinib therapy.

In consenting patients, core needle biopsies and fine needle aspirates (FNA) will be obtained at Screening by Interventional Radiology from accessible lymph node under ultrasound or CT-scan guidance. At the time of confirmed PD, if a tumor biopsy is planned as part of routine clinical practice, for consenting patients, a fresh tumor sample should be collected for biomarker analyses and processed. Whenever feasible, up to 3 cores will be obtained using 18 or 20 gauge needles as deemed appropriate by an Interventional Radiologist. The three cores will be processed as follows: 1) the first core biopsy specimen will be preserved in RNAlater for microarray studies; 2) second core will be formalin-fixed and paraffin-embedded for IHC; and 3) third core will be snap frozen for DNA, RNA, or protein isolation. FNA sample will be analyzed by flow cytometry. These samples will be transported in RNAlater (core # 1)/formalin (core # 2)/normal saline (cores # 3 and FNA) within 6 hours of collection on ice to Dr. Neelapu's laboratory for processing at the South Campus Research Building I, Room 4.3206, at MDACC. If fresh biopsies are not feasible, archival tissue from prior tumor biopsy may be used for biomarker studies.

7.4.20 Determination of FLIPI Score

During the screening phase, subject's FLIPI score will be calculated and recorded as outlined in Appendix 13.7

7.7.21 Determination of Tumor Burden Status

During the screening phase, subject's tumor burden, either high or low will be determined using the GELF criteria as outlined in Appendix 13.8.

8. SUBJECT COMPLETION AND WITHDRAWAL

8.1 Completion

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

8.2 Treatment Discontinuation

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

- Confirmed PD
- Unacceptable toxicity: an intercurrent illness or AE that prevents further study drug administration beyond 28 days
- Treatment discontinuation by subject beyond 28 days
- Investigator decision
- Subject becomes pregnant

All subjects, regardless of reason for discontinuation of study treatment will undergo a treatment termination visit and followed for progression and survival.

8.3 Study Exit/Withdrawal

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

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

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

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

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

9. STATISTICAL METHODS

9.1 General Considerations:

This is an open-label, Phase 2 study investigating the efficacy and safety of ibrutinib combined with rituximab and lenalidomide in previously untreated subjects with FL. The study will include 60 subjects in one treatment arm.

9.1.1 Response Assessment

Response assessments will be done and recorded by the Principal Investigator. The response criteria are based on the revised criteria for malignant lymphoma described in the Lugano Criteria, international Working Group for NHL (Cheson 2014).

9.1.2 Safety Monitoring

The Principal Investigator or a physician designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart, Appendix 13.1 and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.03. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment. The study investigators and data coordinators are responsible for entering the data and safety for this study including causality. For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

Safety data will be monitored by the Principal Investigator and in accordance with institutional policies. The Investigator will record the action taken with the study drugs as a result of an AE or SAE, as applicable (e.g., discontinuation, interruption, or reduction of study drugs, as appropriate) and report if concomitant and/or additional treatments were given for the event. AEs and SAEs will be reviewed on an ongoing basis to identify safety concerns.

For subjects with a history of Hepatitis B or C, standard of care monitoring for viral reactivation will be conducted. Subjects with a history of Hepatitis B will be required to undergo hepatitis B reactivation prophylaxis unless contraindicated.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered or death (due to the SAE).

Janssen and Celgene shall notify the Investigator via an IND Safety Report of the following information: Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected, any changes on the investigational brochure or any other safety information that changes the risk/benefit profile of ibrutinib or lenalidomide during the conduct of the study; any finding from tests in laboratory animals that suggests a significant risk for human subjects; including reports of mutagenicity, teratogenicity, or carcinogenicity. The Principal Investigator shall notify his/her IRB promptly of these new serious and unexpected AEs or significant risks to subjects. The Investigator must keep copies of all AE information, including correspondence with Janssen, Celgene, and the IRB, on file.

9.2 Definition of Analysis Populations

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

- All treated population: The subjects who enrolled in the study and had at least 1 dose of study drug.
- Response evaluable population: The subjects in the all treated population who have measurable disease at baseline and have at least one adequate post-treatment disease assessment by the investigator.
- Safety analysis population: All enrolled subjects who receive at least 1 dose of study drug (same as the all treated population).

The all treated population will be used for analyzing efficacy endpoints unless specified otherwise. The response evaluation population will be used for sensitivity analysis of efficacy endpoints. The safety population will be used for safety analysis.

9.3 Endpoint Data Analysis

9.3.1 Baseline Characteristics

Subject demographics (age, sex, race/ethnicity) and other baseline characteristics (ECOG PS, disease burden, FLIPI score) will be summarized. Summary statistics will include means, standard deviations, and medians for continuous variables and proportions for categorical variables. Compliance parameters including number of completed cycles, number of dose modifications, and reasons for discontinuation will also be similarly summarized.

9.3.2 Primary Efficacy Endpoint

The primary efficacy endpoint is PFS rate at 2 years. Response will be assessed by the investigator based on the 2014 Cheson Lugano criteria. The 2-year PFS rate will be calculated and corresponding 95% CI will be derived.

9.3.2.1 Analysis Methods

The primary analysis for all efficacy endpoints will be conducted based on the all treated population. PFS is defined as the time from the treatment start date (Cycle 1, Day 1) until the first date of objectively documented progressive disease or date of death from any cause. Patients will be censored at the last follow-up date if progression or death has not occurred during follow-up. If a patient has missing data (incomplete CT scan), all other available CT, PET/CT or MRI of the patient will be used for the analysis. Kaplan-Meier method will be used to estimate the PFS. Corresponding 95% CI will be summarized. Cox proportional hazards models will be used to assess the effects of patient prognostic factors on time-to-event endpoints. The final analysis will be performed when the last patient is followed for 3 years after last study drug dose.

9.3.3 Secondary Efficacy Endpoints

- CR rate at 120 weeks (± 4 weeks) will be determined by the PI (Cheson, Lugano classification 2014). The number and percentage of subjects with a CR at 120 weeks will be tabulated.

- ORR (CR + PR) will be assessed by the investigator based on Cheson, Lugano 2014. The number and percentage of subjects with an ORR will be tabulated. The best ORR will be recorded.

- DOR will be measured from the time by which measurement criteria for CR or PR, whichever is recorded first, is met until death or the first date by which progressive disease is documented. Subjects who are progression free and alive at the time of clinical cut-off or have unknown

status will be censored at the last tumor assessment. Subjects with no baseline disease assessment will be censored on cycle 1, day 1. Non-responders will be excluded from the analysis for DOR. Kaplan-Meier methodology will be used to estimate event-free curves, median, and 95% CI.

- EFS will be measured from the date of cycle 1, day 1 to the date of first documented progression, transformation to diffuse large B-cell lymphoma, initiation of new anti-lymphoma treatment, or death. Kaplan-Meier methodology will be used to estimate event-free curves, median, and 95% CI.

- TTNT will be measured from the date of cycle 1, day 1 to the date of first documented administration of any anti-lymphoma treatment (chemotherapy, radiotherapy, immune therapy, radioimmunotherapy, or other experimental therapy). Kaplan-Meier methodology will be used to estimate event-free curves, median, and 95% CI.

- OS will be measured from the date of cycle 1, day 1 to the date of death regardless of cause. For subjects who have not died, subjects will be censored at the time of last contact. Kaplan-Meier methodology will be used to estimate event-free curves, median, and 95% CI.

9.3.4 Safety Analysis

Analysis of safety data will be conducted on the safety population. Safety summaries will include tabulations in the form of tables and listings. The frequency (number and percentage) of treatment-emergent AEs will be reported. Additional AE summaries will include AE frequency by AE severity and by relationship to study drug.

Clinically significant abnormal laboratory values will be summarized.

9.3.5 Exploratory Analyses

The objective is to identify predictive and pharmacodynamic biomarkers after therapy with rituximab plus lenalidomide with ibrutinib in subjects with previously untreated FL and marginal zone lymphoma.

- Immunophenotyping of PBMCs to determine alteration in immune cell subsets
    - PBMC will be stained with multiple antibodies and analyzed with up to 12-parameter flow cytometry.
- Identification of signaling pathways or biomarkers that predict sensitivity or resistance by gene expression profiling (GEP)
    - GEP will be performed on tumor biopsies obtained at baseline in consenting subjects to determine predictive biomarkers. The primary focus of the analysis of GEP data will be to evaluate the 41-gene effector T cell signature previously described [36]. But other gene signatures specific to other immune cell subsets and tumor signaling pathways,

developed by our group will also be explored. Univariate Cox analysis will test whether pretreatment levels of the signature significantly correlate with PFS. If so, techniques like leave-one-out cross-validation will be applied to assess the robustness of the signature, to the extent possible in a single dataset. We will also assess its significance as compared to the predictive power of random signatures. The baseline signature will also be tested in exploratory multivariate analysis with additional variables, principally the FLIPI score, and for its ability to predict complete response. Changes in signature levels post-treatment levels will be correlated with ultimate response, and, via landmark analysis, with PFS.

  - Pharmacodynamic effects of combination therapy will be assessed in peripheral blood. Blood samples will be collected at baseline, Cycle 1, Day 1, Cycle 2, Day 1, and Cycle 7, Day 1. Lenalidomide affects multiple immune cell subsets and its effects may be assessed by multiparametric flow cytometry in PBMCs as previously described [24]. Since ibrutinib has been shown to inhibit ITK in Th2 cells and skew the polarization of CD4+ T cells to Th1 phenotype, we will also assess the ratio of Th1: Th2 cells in the PBMC by intracellular cytokine assay. Furthermore, alteration of various cytokines and chemokines will be assessed in the plasma by multiplex assays. The various cellular subsets measured at baseline will be compared with on-therapy time points and correlated with best clinical response and PFS

- Determination of alteration of cytokines and chemokines

9.3.6 Handling of Biomarker Samples

Samples obtained for biomarker research including peripheral blood or tumor tissue will be maintained in Dr. Neelapu's lab until study termination, at which time they will be destroyed as per institution policies.

9.4 Handling of Missing Data

Subjects lost to follow up will be included in the statistical analyses up to the point of their last evaluation or contact.

Data for subjects without disease progression or death will be censored at the date of the last tumor assessment and before the date of initiation of alternative anticancer therapy. Subjects with no post-baseline assessment will be censored on cycle 1, day 1.

9.5 Determination of Sample Size

The primary endpoint is PFS. It is expected that the experimental regimen will achieve better efficacy compared to the standard of care for this population. We will enroll a total of 60 patients with an accrual rate of 4 patients per month. All patients will be followed for at least 3 years or until death. The final analysis will be performed when the last patient is followed for 3 years. When the sample size is 60, a two-sided 95% CI for the PFS rate at 2 years will extend 0.106 from the observed rate for an expected rate of 77% (nQuery Advisor 7.0).

9.6 Trial Monitoring

Due to the fast accrual planned for the study and long median PFS time expected for the experimental regimen, a formal futility monitoring rule is not feasible.

Because of the limited number of patients who have received the combination treatment, for patient safety we will monitor the prohibitive toxicity, defined as any treatment-related death or frequent discontinuation of treatment during cycles 1 and 2. The prohibitive toxicity rate of 15% or higher will be considered unacceptable. The prior probability of the rate is assumed to follow a Beta (0.3, 1.7) distribution with two patients worth of information. We will monitor patients by a cohort size of 10. At any time after at least 10 patients have completed toxicity evaluations, the trial will be stopped if the following statement is true

$$\Pr[\text{prohibitive toxicity rate} > 15\% \mid \text{data}] > 0.95,$$

which means that the trial will be stopped for toxicity if the posterior probability of the rate being greater than 15% is greater 95%.

Patients will be monitored by a cohort size of 10 according to the following stopping boundaries for prohibitive toxicity at cycles 1 and 2.

Number of patients evaluated	Stop if ≥ prohibitive toxicities observed
10	4-10
20	7-20
30	9-30
40	11-40
50	13-50
60	Always stop with this many patients

Operating characteristics for the stopping rules

For prohibitive toxicity monitoring

True Prohibitive Toxicity Rate	**Probability Stop Early**	**Average sample size**
0.05	0.0011	59.95
0.10	0.0157	59.23
0.15	0.0902	56.46

0.20	0.2956	49.65
0.25	0.5924	39.48
0.30	0.8337	29.33

The above stopping boundaries and operating characteristics are calculated using MultcLean (v.2.1.0) design software downloaded from http://biostatistics.mdanderson.org/SoftwareDownload.

Any treatment-related death occurring beyond cycle 2 will result in pause in accrual pending complete evaluation and discussion between the Principal Investigator and the FDA.

10. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information is the responsibility of the PI and will be conducted in accordance with Institution policies.

The PRINCIPAL INVESTIGATOR will provide safety information to Janssen Scientific Affairs, LLC on adverse events, special situations including pregnancies and product quality complaints as defined below:

This Study has been designated as an interventional study. As such, all adverse events regardless of causality and special situations excluding those from subjects not exposed to a Janssen Medicinal Product and product quality complaints with or without an adverse event as described in this section will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported for 30 days after the last dose of study drug.

For the purposes of this study, the Janssen medicinal product is: Ibrutinib (Imbruvica)

10.1 Adverse Event Definitions and Classifications

10.1.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal (investigational or non-investigational) product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to the medicinal (investigational or non-investigational) product. For the purposes of this study, AEs include events which are either new or represent detectable exacerbations of pre-existing conditions. The following are not considered an AE:

- Pre-existing condition: A pre-existing condition is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.

- Pre-planned or elective hospitalization: A hospitalization planned before signing the ICF is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs which prolongs the hospitalization or meets any of the SAE criteria, the event will be considered an SAE. Hospitalizations for social reasons, solely for the administration of treatment, or due to long travel distances are not SAEs.
- Diagnostic testing and procedures: Testing and procedures should not be reported as AEs or SAEs but rather the cause for the test or procedure should be reported.
- Asymptomatic treatment related lymphocytosis: This event should not be considered an AE. Patients with treatment-related lymphocytosis should remain on treatment and continue with all study-related procedures.

10.1.2 Serious Adverse Event

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Is suspected transmission of any infectious agent via a medicinal product
- Is medically important
- Development of a secondary malignancy, excluding superficial, non-melanoma skin cancers or carcinoma in situ.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious

Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time a signed and dated ICF is obtained until 30 days following the last dose of study drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This will include the development of a secondary malignancy, except superficial, non-melanoma skin cancers or carcinoma in situ.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy. Safety data includes adverse events, product quality complaints (PQCs), and special situations including pregnancies.

10.1.2.1 Pregnancy

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study, or within 28 days of the subject's last dose of lenalidomide or ibrutinib, are considered immediately reportable events. Lenalidomide and/or ibrutinib are to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Janssen Scientific Affairs, LLC , using the Janssen Serious Adverse Event Form - and Celgene Drug Safety using the Pregnancy Initial Report Form, immediately by facsimile or email. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Janssen Scientific Affairs, LLC – using the Janssen Serious Adverse Event Form, and Celgene Drug Safety using the Pregnancy Follow-Up Report Form, immediately about the outcome of the pregnancy (either normal or abnormal outcome). If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Janssen Scientific Affairs, LLC

and Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the investigational product should also be reported to Janssen Scientific Affairs, LLC using the Janssen Serious Adverse Event Form, and Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event. Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking lenalidomide should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

The Principal Investigator is responsible for ensuring that these cases from clinical studies are complete and if not are promptly followed-up. This includes ensuring the reports are fully investigated and thoroughly documented by the Principal Investigator and that follow-up information is summarized e.g. hospital records, coroner's reports, autopsy results and recorded on the appropriate forms.

Because the effect of the Janssen medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen medicinal product will be reported by the PRINCIPAL INVESTIGATOR **within 24 hours of their knowledge of the event** using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

10.1.3 Severity Criteria (Grade 1-5)

Definitions found in the CTCAE (version 4.03) will be used for grading the severity of AEs. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions for each referenced AE. If a subject experiences an AE not listed in the CTCAEv4.03, the following grading system should be used to assess severity:

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

10.1.4 Causality (Attribution)

The Principal Investigator or designee is to assess the causal relationship using the following definitions:

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

10.1.5 Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

http://www.imbruvica.com/hcp/?utm_source=google&utm_medium=cpc&utm_campaign=Imbruvica&utm_term=imbruvica&utm_content=ibrutinib-+Exact|mkwid|ssjPpM0Gh_dc|pcrid|39412243694

10.1.6 J&J Medicinal Product

For the purposes of this study, the Janssen medicinal product is: Ibrutinib (Imbruvica)

10.2 Documenting and Reporting of Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections are recorded.

When a report contains a Janssen product, an identifiable patient, and identifiable reporter, the following events represent Special Reporting Situations:

- overdose of a Janssen medicinal product
- pregnancy exposure (maternal and paternal)
- exposure to a medicinal product from breastfeeding
- suspected abuse/misuse of a medicinal Janssen product
- inadvertent or accidental exposure to a medicinal Janssen product
- any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- unexpected therapeutic or clinical benefit from use of a Janssen medicinal product
- medication error involving a Janssen product (with or without patient exposure to the medicinal Janssen product, e.g., name confusion)
- suspected transmission of any infectious agent via a medicinal product.

These safety events may not meet the definition of an adverse event; however, from Janssen Scientific Affairs, LLC perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

10.2.1 Adverse Event Reporting Procedures

10.2.1.1 All Adverse Events

All subjects who receive treatment will be considered evaluable for toxicity (safety analysis population). All serious events will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study related procedure (which may include contact for follow up safety). Serious adverse events will be reported for 30 days after the last dose of study drug.

In general, the Principal Investigator must immediately report to Janssen Scientific Affairs any serious adverse event and Special Reporting Situations, whether or not considered drug related. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death as a result of anaphylactic reaction or fatal hepatic necrosis). In that case, the investigator must immediately report the event to Janssen Scientific Affairs. The Principal Investigator must record non-serious adverse events and report them to Janssen Scientific Affairs according to the timetable for reporting as specified either in the protocol or to fulfill regulatory reporting requirements.

For each subject, AEs SAEs, and Special Reporting Situations should be recorded after informed consent is obtained until the subject has completed participation in the study as follows:

- A Serious Adverse event or Special Reporting Situations must be reported if it occurs during a subject's participation in the Study (whether receiving Study Product or not) and within 30 days of receiving the last dose of Study Product.

Any serious adverse event or Special Reporting Situations that is ongoing when a subject completes his/her participation in the Study must be followed until any of the following occurs:

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

10.2.1.2 Recording of Adverse Events, Serious Adverse Events and Special Reporting Situations

Recording should be done in a concise manner using standard, acceptable medical terms. . All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a Janssen medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a Janssen medicinal product.

The adverse event recorded should not be a procedure or a clinical measurement (i.e. a laboratory value or vital sign) but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement.

Preexisting conditions that worsen in severity or frequency during the Study should also be recorded (a preexisting condition that does not worsen is not an adverse event).

Further, a procedure or surgery is not an adverse event; rather, the event leading to the procedure or surgery is considered an adverse event. Any event requiring in-patient hospitalization that occurs during the course of a subject's participation in a trial must be reported as an SAE. Hospitalizations that do not meet the criteria for SAE reporting are:

- Reasons described in the Protocol, e.g. drug administration, Protocol-required testing
- Surgery or procedure planned prior to entry into the Study.

If, in the Principal Investigator's judgment, a clinical significant worsening from baseline is observed in any laboratory or other test parameter (e.g. electrocardiogram (ECG), angiogram), physical exam finding, or vital sign, a corresponding clinical adverse event should be recorded.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the adverse event, whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, "hepatitis" and not "elevated liver function tests" should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an adverse event, using appropriate medical terminology (e.g. thrombocytopenia, peripheral edema, QT prolongation).

Janssen Scientific Affairs will provide to the Principal Investigator IND safety reports/SUSAR (Serious Unexpected Suspect Adverse Reaction) reports generated by Janssen Scientific Affairs for the Study Product as they become available until all subjects have completed their last Study visit.

- Toxicities that are not serious are AEs, and they will be required to be entered/recorded into PDMS/CORe.
- Toxicities that become serious will be required to be entered/recorded into PDMS/CORe and reported using the eSAE application. [A paper copy can be printed for you to fax to the company.]

10.2.1.3 Procedures for Reporting AEs, SAEs, Pregnancies, Special Reporting Situation, and Product Quality Complaints (PQCs) for Janssen Medicinal Products to Janssen Scientific Affairs

SAE, Adverse Events of Special Interest (AESI), Pregnancies, and Special Reporting Situations

In clinical trials (including reports unblinded as to treatment for blinded studies) involving the Study Product regardless of whether causality with the administration of the Study Product is suspected by the Principal Investigator.

The Principal Investigator will transmit these reports on the Janssen Serious Adverse Event Form in accordance with Section 10.2.1.3.2, in English within 24 hours of becoming aware of the event(s) along with their determination of whether the event was caused by a Janssen product.

All available clinical information relevant to the evaluation of an SAE, Adverse Events of Special Interest, and Special Reporting Situations including pregnancy reports (with or without an AE) including paternal exposure are required.

- A study case is not considered complete until all clinical details needed to interpret the case are received and the event has resolved, or otherwise explained, or the patient is lost to follow-up. Reporting of follow-up information should follow the same timeline as initial reports.

- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Study Drug in the course of the Study, by facsimile within 24 hours of such report or correspondence being sent to applicable health authorities.

Product Quality Complaints

Any product quality complaints (PQC) regarding ibrutinib, with or without an AE, (including reports of suspicion of counterfeiting, diversion, or tampering, and suspected transmission of pathogens) will be transmitted by the Institution and the Principal Investigator in the form provided by Janssen Scientific Affairs in accordance with Section 10.2.1.3.2, in English, within 24 hours of becoming aware of the event(s).

Reconciliation of SAEs

At a minimum, on a quarterly basis and at the end of the Study, Janssen Scientific Affairs will provide to the Principal Investigator, a listing of all SAEs reported to Janssen Scientific Affairs. Principal Investigator will review this listing and provide any discrepancies to the Janssen Scientific Affairs.

Upon request, Principal Investigator shall provide Janssen Scientific Affairs with a summary list of all SAEs, and AEs of Special Interest and Special Reporting Situation reports to date, for reconciliation purposes.

10.2.1.3.1 Reporting Timelines for Ibrutinib

All safety information covered in Section 10.2.1.3 (SAEs, Adverse Events of Special Interest, Pregnancies, Special Reporting Situations, and PQCs) should be reported to Janssen Scientific Affairs, LLC within 24 hours of becoming aware of the event(s).

All non-serious AEs should be reported according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

10.2.1.3.2 Transmission Methods for Janssen Scientific Affairs, LLC

Investigator Communications with Janssen:

Janssen Scientific Affairs, L.L.C.
Address: 800 Ridgeview Drive
Horsham, PA 19044

Email: IIS-BIO-VIRO-GCO@its.jnj.com

Fax: 866-451-0371

The following methods are acceptable for transmission of safety information to Janssen Scientific Affairs:

- Facsimile (fax), receipt of which is evidences in a successful fax transmission report to 1-866-451-0371

- Reporting may be done electronically only upon written approval by Janssen Scientific Affairs, which approval must acknowledge that the electronic transmission is in an acceptable encrypted email format. Without such acknowledgement, the approval to use an electronic transmission shall not be valid.

Telephone (for business continuity purposes, if fax or authorized electronic system is nonfunctional).

10.2.1.3.3 Individual Case Safety Report (ICSR)

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a Janssen medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected Janssen medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

10.2.1.4 Expedited Reporting by Investigator to Celgene

SAEs are defined above, Section 10.1.2. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (RV-CL-FL-PI-005632) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

Investigator Communications with Celgene:

Celgene Corporation

Global Drug Safety and Risk Management

Connell Corporate Park

300 Connell Dr. Suite 6000

Berkeley Heights, NJ 07922

Fax: (908) 673-9115

E-mail: drugsafety@celgene.com

10.2.1.5 Maintenance of Safety Information

Safety information will be maintained in PDMS/CORe. At a minimum, at the end of the treatment phase (=”last patient off treatment”) as well as the end of the follow-up phase (=”last patient out”) of the Study, the Principal Investigator shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent review of the safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affairs’ request. The data must also be available at the request of the IND Office, the FDA, and the IRB.

10.2.2 Events of Special Interest for Ibrutinib

Specific AEs, will be followed as part of standard safety monitoring activities by the Investigator. These events will be reported to Janssen within 24 hours of awareness irrespective of seriousness (i.e. serious and non-serious AEs) following the procedures described in Section 10.2.1.

10.2.2.1 Major Hemorrhage

Major hemorrhage is defined as any hemorrhagic event that is Grade 3 or greater in severity or that results in 1 of the following: intraocular bleeding causing loss of vision, the need for a transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization, or prolongation of hospitalization.

Events meeting the definition of hemorrhage will be captured as an AESI according to section 10.2.2.

10.2.2.2 Intracranial Hemorrhage

Any intracranial hemorrhage adverse event, including subdural hematoma/hemorrhage, epidural hematoma/hemorrhage and intracerebral hemorrhage, of any grade severity, will be captured as an event of special interest according to Section 10.2.2.

10.2.2.3 Second primary malignancy

In addition to all routine AE reporting, all new malignant tumors, including solid tumors, skin malignancies and hematologic malignancies, are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

Every report sent to the drug company will be required to be entered in the eSAE application, including AESIs.

11. STUDY ADMINISTRATION

11.1 Regulatory and Ethical Compliance

This clinical study was designed and will be implemented in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practices, with the ethical principles laid down in the Declaration of Helsinki, and in compliance with our IRB guidelines.

The Investigator or his/her authorized representative will be provided a copy of the IRB letter that grants formal approval and a copy of the IRB approved ICF before entering subjects in this study.

11.2 Informed Consent

The ICF will document the study-specific information the Investigator or his/her designee provides to the subject and the subject's agreement to participate.

The Investigator or designee (designee must be listed on the Delegation of Authority log), must explain in terms understandable to the subject the purpose and nature of the study, study procedures, anticipated benefits, potential risks, possible AEs, and any discomfort participation in the study may entail. Each subject must provide a signed and dated ICF before any study-related (nonstandard of care)

activities are performed. The original and any amended signed and dated ICFs must remain in the subject's file. A copy of each signed consent form must be given to the subject.

11.3 Quality Control and Quality Assurance

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki and in accordance with FDA regulations and the guidelines of Good Clinical Practices.

11.4 Protected Subject Health Information Authorization

Information on maintaining subject confidentiality in accordance with our local and national subject privacy regulations must be part of the informed consent process. A HIPPA consent form will be used. The investigator or designee must explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with the Principal Investigator and his/her designees, regulatory agencies, and the IRB. The Investigator will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. If a subject withdraws permission to use protected health information, it is the Investigator's responsibility to obtain the withdrawal request in writing from the subject and to ensure no further data will be collected from the subject. Any data collected before withdrawal will be used in the analysis of the study results.

11.5 Record Retention

The Investigator/study staff must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Essential documentation includes, but is not limited to, the package insert signed protocols and amendments, IRB approval letters, signed ICFs (including subject confidentiality information), drug dispensing and accountability records, signed (electronically), dated and completed CRFs, and documentation of CRF corrections, SAE forms transmitted to Janssen Scientific Affairs, or designee, and notification of SAEs and related reports, source documentation, and all relevant correspondence and other documents pertaining to the conduct of the study.

11.6 Investigational Drug Accountability

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

Accountability records for ibrutinib and lenalidomide must be maintained and readily available for inspection by representatives of Janssen Scientific Affairs or Celgene and are open to inspections by regulatory authorities at any time.

11.7 Investigator Responsibilities

The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Janssen Scientific Affairs, LLC, Attn: Sean Murphy (smurphy8@its.jnj.com) and Patricia Corbin (IIS-BIO-VIRO-GCO@its.jnj.com); and Celgene Corporation as a supporter of this study as follows.

Celgene Corporation

Attn: Medical Affairs Operations

Connell Corporate Park

400 Connell Drive Suite 700

Berkeley Heights, NJ 07922

The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above (Section 10.1.2) are present. The investigator is responsible for reporting adverse events to Celgene as described.

11.8 Publication of Study Results

The results of this study may be used for papers, abstracts, posters, or other material presented at scientific meetings or published in professional journals or as part of an academic thesis by an Investigator. In all cases, to avoid disclosures that could jeopardize proprietary rights and to ensure accuracy of the data, Janssen Scientific Affairs reserves the right to preview all manuscripts and abstracts related to this study, allowing the Investigator sufficient time to make appropriate comments before submission for publication. The Investigators shall be listed as lead authors on manuscripts and reports of study results.

11.9 Study Completion

The study is expected to be completed approximately 3 years after the last subject's last study drug dose.

12. REFERENCES

1. Brice, P., et al., *Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte.* J Clin Oncol, 1997. **15**(3): p. 1110-7.
2. Solal-Celigny, P., et al., *Follicular lymphoma international prognostic index.* Blood, 2004. **104**(5): p. 1258-65.

3. Federico, M., et al., *Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project.* J Clin Oncol, 2009. **27**(27): p. 4555-62.
4. Dave, S.S., et al., *Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells.* N Engl J Med, 2004. **351**(21): p. 2159-69.
5. Rambaldi, A., et al., *Monitoring of minimal residual disease after CHOP and rituximab in previously untreated patients with follicular lymphoma.* Blood, 2002. **99**(3): p. 856-62.
6. Salles, G., et al., *Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: results of the GELA-GOELAMS FL2000 study.* Blood, 2008. **112**(13): p. 4824-31.
7. Horning, S.J., *Natural history of and therapy for the indolent non-Hodgkin's lymphomas.* Semin Oncol, 1993. **20**(5 Suppl 5): p. 75-88.
8. Friedberg, J.W., et al., *Follicular lymphoma in the United States: first report of the national LymphoCare study.* J Clin Oncol, 2009. **27**(8): p. 1202-8.
9. Rummel, M.J., et al., *Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial.* Lancet, 2013. **381**(9873): p. 1203-10.
10. Marcus, R., et al., *Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma.* J Clin Oncol, 2008. **26**(28): p. 4579-86.
11. Salles, G., et al., *Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial.* Lancet, 2011. **377**(9759): p. 42-51.
12. Flinn, I.W., et al., *Open-label, randomized, noninferiority study of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of advanced indolent NHL or MCL: the BRIGHT study.* Blood, 2014.
13. Galustian, C., et al., *Thalidomide-derived immunomodulatory drugs as therapeutic agents.* Expert Opin Biol Ther, 2004. **4**(12): p. 1963-70.
14. Yang, Y., et al., *Exploiting synthetic lethality for the therapy of ABC diffuse large B cell lymphoma.* Cancer Cell, 2012. **21**(6): p. 723-37.
15. Gandhi, A.K., et al., *Immunomodulatory agents lenalidomide and pomalidomide co-stimulate T cells by inducing degradation of T cell repressors Ikaros and Aiolos via modulation of the E3 ubiquitin ligase complex CRL4(CRBN.).* Br J Haematol, 2014. **164**(6): p. 811-21.
16. Kronke, J., et al., *Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells.* Science, 2014. **343**(6168): p. 301-5.
17. Lu, G., et al., *The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins.* Science, 2014. **343**(6168): p. 305-9.
18. Scharpfenecker, M., et al., *Thalidomide ameliorates inflammation and vascular injury but aggravates tubular damage in the irradiated mouse kidney.* Int J Radiat Oncol Biol Phys, 2014. **89**(3): p. 599-606.
19. Wu, L., et al., *lenalidomide enhances natural killer cell and monocyte-mediated antibody-dependent cellular cytotoxicity of rituximab-treated CD20+ tumor cells.* Clin Cancer Res, 2008. **14**(14): p. 4650-7.
20. Ramsay, A.G., et al., *Follicular lymphoma cells induce T-cell immunologic synapse dysfunction that can be repaired with lenalidomide: implications for the tumor microenvironment and immunotherapy.* Blood, 2009. **114**(21): p. 4713-20.
21. Reddy, N., et al., *Immunomodulatory drugs stimulate natural killer-cell function, alter cytokine production by dendritic cells, and inhibit angiogenesis enhancing the anti-tumour activity of rituximab in vivo.* Br J Haematol, 2008. **140**(1): p. 36-45.

22. Zhang, L., et al., *Synergistic antitumor effects of lenalidomide and rituximab on mantle cell lymphoma in vitro and in vivo.* Am J Hematol, 2009. **84**(9): p. 553-9.
23. Wang, M., et al., *Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular and transformed lymphoma: a phase II clinical trial.* Leukemia, 2013. **27**(9): p. 1902-9.
24. Fowler, N.H., et al., *Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial.* Lancet Oncol, 2014. **15**(12): p. 1311-8.
25. Martin, P., Jung S, Johnson J, *CALGB 50803 (Alliance): a Phase 2 Trial of Lenalidomide Plus Rituximab in Patients with Previously Untreated Follicular Lymphoma.* 12-ICML Hematol Oncol 2013; 31 (Suppl. 1): abstract 63, 2013.
26. Wang, M.L., et al., *Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma.* N Engl J Med, 2013. **369**(6): p. 507-16.
27. Gopal, A.K., et al., *PI3Kdelta inhibition by idelalisib in patients with relapsed indolent lymphoma.* N Engl J Med, 2014. **370**(11): p. 1008-18.
28. Advani, R.H., et al., *Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies.* J Clin Oncol, 2013. **31**(1): p. 88-94.
29. Byrd, J.C., et al., *Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia.* N Engl J Med, 2013. **369**(1): p. 32-42.
30. Fowler, N., Neelapu, SS, Hagemeister, FB, et al, *Lenalidomide and rituximab for untreated indolent lymphoma: Final results of a phase II study.* Blood (ASH Annual Meeting Abstracts) 2012 120: Abstract 901, 2012.
31. Kanellis, G., et al., *Identification of MNDA as a new marker for nodal marginal zone lymphoma.* Leukemia, 2009. **23**(10): p. 1847-57.
32. Arribas, A.J., et al., *Nodal marginal zone lymphoma: gene expression and miRNA profiling identify diagnostic markers and potential therapeutic targets.* Blood, 2012. **119**(3): p. e9-e21.
33. Novak, U., et al., *The NF-{kappa}B negative regulator TNFAIP3 (A20) is inactivated by somatic mutations and genomic deletions in marginal zone lymphomas.* Blood, 2009. **113**(20): p. 4918-21.
34. Casulo, C., et al., *Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study.* J Clin Oncol, 2015.
35. sargent, D., Shi, Q, De Bedout, Sabine, et. al., *Evaluation of complete response rate at 30 months (CR30) as a surrogate for progression-free survival (PFS) in first-line follicular lymphoma (FL) studies: Results from the prospectively specified Follicular Lymphoma Analysis of Surrogacy Hypothesis (FLASH) analysis with individual patient data (IPD) of 3,837 patients (pts).* . Journal of Clinical Oncology, 2015 ASCO Annual Meeting (May 29 - June 2, 2015). Vol 33, No 15_suppl (May 20 Supplement), 2015: 8504, 2015.
36. Westin, J.R., et al., *Safety and activity of PD1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: a single group, open-label, phase 2 trial.* Lancet Oncol, 2014. **15**(1): p. 69-77.

13. APPENDICES

13.1 Study Flow Chart

	Screening Phase	Treatment phase						End of Treatment		Follow up Phase
Treatment Cycle/Title	Screening Visit	1[a]	2[a]	3	To be repeated up to 12 cycles 4	5	6	Early Treatment Termination Visit	End of Treatment Visit	Follow up visits[b]
Scheduling Window[c] (Days)	-28 to -1	± 2	± 2	± 2	± 2	± 2	± 2	± 14	± 14	q 12 weeks (± 2 weeks) for the 1 year and then q 24 weeks (± 4 weeks)
Clinical/Administrative Assessments										
Informed Consent[d]	X									
Inclusion/Exclusion Criteria	X	X								
Demographics and Medical History	X									
Record FLIPI score	X									
Record Tumor burden	X									
Concomitant Medication Review[e]	X	Day 1, 8, 15, 22	Day 1, 15	X	X	X	X	X	X	
Drug accountability			X	X	X	X	X	X	X	
Rituximab Administration[f]		Day 1, 8, 15, 22	X	X	X	X	X			
Dispense ibrutinib and lenalidomide		X	X	X	X	X	X			
Review Adverse Events[g]		Day 1, 8, 15, 22	Day 1, 15	X	X	X	X	X	X[g]	X[g]
Physical Examination	X	Day 1, 8, 15, 22	Day 1, 15	X	X	X	X	X	X	X
Vital Signs and Weight[h]	X	Day 1, 8, 15, 22	Day 1, 15	X	X	X	X	X	X	X
ECOG Performance Status	X	Day 1, 8, 15, 22	Day 1, 15	X	X	X	X	X	X	X
ECG	X									
Laboratory Assessment										
Pregnancy Test – Serum b-HCG[i]	X									
PT/INR and aPTT[j]	X									
HIV 1 and 2 antibody	X									
HBsAg, anti-Hep Bc, Hep C Ab[k]	X									
CBC with Differential	X	Day 1, 8, 15, 22	Day 1, 15	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel	X	Day 1, 8, 15, 22	Day 1, 15	X	X	X	X	X	X	X
Creatinine clearance (modified Cockcroft-Gault)	X	Day 1, 8, 15, 22	Day 1, 15	X	X	X	X			
TSH	X							X	X	
Bone marrow biopsy and aspirate[l]	X									
Biomarkers Blood Collection[m]		X	X					X[m]	X[m]	X[m]
Biomarkers Tissue Collection[n]	X[n]							X[n]	X[n]	X[n]
Radiologic Assessment										
Response Assessment: CT/PET/or MRI[o]	X				X			X[p]	X	X

a. For each Cycle, assessment is assumed to be on Day 1 unless otherwise specified.
b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status as per the follow-up schedule until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first. Survival assessments will continue up to 3 years after the last study drug.
c. Treatment cycles are 28 days; however the treatment cycle interval may be increased due to toxicity according to the dose modification guidelines provided in Section 5.4. If the interval is increased, all procedures except for response assessment should be performed based on the new dosing schedule
d. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 28 days prior to the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.
e. Record all medications taken within 28 days of screening visit. Concomitant medications – Enter new medications started through the treatment phase as well as up to 30 days after the last study drug dose. Record all medications taken for SAEs as defined in Section 10.1.2.
f. Rituximab administration will occur on day 1 of each cycle unless otherwise specified. Hypersensitivity reaction should be managed according to institution policy.
g. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.03. All AEs, will also be evaluated for seriousness and AESI handled as discussed in Section 10.2.2. Unresolved abnormal labs that are drug related AEs should be followed weekly until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range. AEs will be monitored until end of study.
h. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at Screening visit 1 only.
i. For women of child-bearing potential, a serum pregnancy test should be performed 10-14 days and 24 hours prior to the initial prescription of lenalidomide. Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.
j. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. For subjects requiring anticoagulation during the study (warfarin is contraindicated) appropriate coagulation tests should be done when clinically indicated to monitor anticoagulation.
k. These screening tests need to be finalized prior to the first dose of rituximab. HCV RNA will be performed if Hep C Ab is positive.
l. All subjects will have bone marrow biopsy/aspirate performed at baseline (within 90 days of study entry). Subsequent bone marrow assessments will only be performed in subjects who have bone marrow involvement at baseline to confirm disease response (CR).
m. Biomarker blood samples will be collected and processed as outlined in Section 7.4.18. On Cycle 1, Day 1, Cycle 1, Day 15, Cycle 2, Day 1 and Cycle 7, Day 1. Research blood test will be collected prior to rituximab dosing. At the time of documented PD, blood biomarker collection should be performed (±4 weeks).
n. If a fresh biopsy is being pursued as part of standard clinical practice, for consenting patients, fresh tumor can be collected as outlined in Section 7.4.19. If this is not possible, archival tumor tissue (paraffin embedded) when available should be collected at Screening for biomarker analyses for consenting patients. At the time of confirmed PD, if a tumor biopsy is planned as part of routine clinical practice, for consenting patients, a fresh tumor sample should be collected for biomarker analyses and processed as outlined in Section 7.4.19.
o. Disease response assessment is based upon Cheson 2014 lymphoma response criteria. “Diagnostic quality” PET-CT with oral contrast/or water and IV contrast should be performed at Screening unless there is a contraindication or not covered by insurance. If CT scans have already been completed, a PET can be performed at Screening. PET/CT or CT and PET should be repeated to confirm complete remission and/or at treatment discontinuation if covered by insurance. For lymphomas that are not FDG-avid, PET does not need to be repeated in subsequent assessments. CTs of the neck, chest, abdomen, and pelvis with IV contrast will otherwise be conducted at baseline for those who do not undergo diagnostic quality PET-CT, at approximately Cycle 4, Day 1 (± 7 days), Cycle 7, Day 1 (± 7 days), at the completion of treatment and during the follow up phase. During the follow-up phase, response assessment should occur every 12 weeks (± 2weeks) for 4 assessments, then every 24 weeks (±4 weeks) until study completion, PD, withdrawal of consent, death, or lost to follow up, whichever comes first. When a contraindication prevents CT, an MRI of the chest, abdomen/pelvis can be substituted.
p. In subjects who discontinue study therapy without confirmed disease progression, a radiological assessment should be performed at the time of treatment discontinuation (i.e. date of discontinuation ± 2 weeks). If previous scan was obtained within 4 weeks prior to the date of discontinuation, then a repeat scan at treatment discontinuation isn’t mandatory.

13.2 Response Assessment

Appendix 2: Response Assessment. Cheson Lugano Classification 2014.

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

13.3 Modified Cockcroft-Gault estimation of CrCl:

Modified Cockcroft-Gault estimation of creatinine clearance (CrCl):

(Cockcroft, 1976; Luke 1990)

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})} \quad \textbf{(Males)}$$

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})} \times 0.85 \quad \textbf{(Females)}$$

13.4 Child Pugh Calculation

Clinical or laboratory characteristic	Points*		
	1	2	3
Albumin (g/dL)	>3.5g	2.8-3.5	<2.8
Total bilirubin (md/dL)	<2	2-3	>3
INR	<1.7	1.7-2.3	>2.3
Ascites	None	Mild/moderate (diuretic-responsive)	Severe (diuretic-refractory)
Encephalopathy	None	Grade 1-2 (precipitant-induced)	Grade 3-4 (chronic)

*Child-Pugh Score is obtained by adding the score for each parameter.

Child-Pugh Class:

A= 5-6 points

B= 7-9 points

C= 10-15 points

13.5 Drugs known to prolong QT

13.6 REMS

13.7 Determination of FLIPI Score

FLIPI (Solal-Celigny, 2004)

Score 1 point for each of the following risk factors:

- Hemoglobin, g/dL < 12 g/L
- Number of nodal areas >4 (The spleen is considered as an extranodal site and not a nodal area)
- Age, years > 60
- LDH level > normal
- Ann Arbor Stage III/IV

RISK GROUPS	Number of Factors
Low	0-1
Intermediate	2
High	3-5

13.8 Determination of Tumor Burden (GELF criteria)

Normal lactate dehydrogenase
Largest nodal or extranodal mass < 7 cm
No more than 3 nodal sites with a diameter > 3 cm
Less than 5×10^9/L circulating tumor cells
Hemoglobin > 10 g/dL, absolute neutrophil count $> 1.5 \times 10^9$/L, platelets $> 100 \times 10^9$/L
No significant serous effusions
No risk of organ compression or compromise
Spleen ≤ 16 cm by CT scan

If patients meet all the above criteria and are without B symptoms (drenching night sweats, fever that is non-infectious, weight loss > 10% of body weight, fatigue, or pruritus), they are considered low tumor burden by the Groupe D'Etude des Lymphomes Folliculares (GELF) criteria. (Khal. ASH Education 2012) If they do not meet all of the above criteria, they are considered high tumor burden.