University of Pennsylvania UPenn # UPCC 02408

A Phase II Trial of Lenalidomide (Revlimid®) + Rituximab with and without Dexamethasone in Recurrent Small B-Cell Non-Hodgkin Lymphomas (NHL) Resistant to Rituximab

Supporter:

Celgene Corporation
86 Morris Ave,
Summit, NJ 07901
1-800-742-3107

Study Product: *Lenalidomide (Revlimid®)*

Protocol Number: Celgene # RV-NHL-PI-296
UPenn # UPCC 02408
NCT00783367

IND Number: *Exempt*

Date: **3/24/2014**
Updated 8/24/2018

CONFIDENTIAL

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Principal Investigator:

Signature of Investigator	Date

Printed Name of Investigator

Stephen J. Schuster, MD

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, instructions from Celgene representatives, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

Supporter:	**Celgene Corporation** **86 Morris Ave,** **Summit, NJ 07901** **1-800-742-3107**
Study Location:	University of Pennsylvania
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List of Abbreviations

AE	Adverse event
ADCC	Antibody-dependent cell cytotoxicity
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
BUN	Blood urea nitrogen
CDC	complement-dependent cell cytotoxicity
CFR	Code of Federal Regulations
CLL	Chronic Lymphocytic Leukemia
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTC	Common toxicity criteria
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMEA	European Agency for Evaluation of Medicinal Products
FCBP	Female of child bearing potential
FDA	Food and Drug Administration
G-CSF	Granulocyte colony stimulating factor, filgrastim (Neupogen®)
GCP	Good clinical practice
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IFN	Interferon
Ig	Immunoglobulin
IL-	Interleukin-
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
IWRC	International Workshop Response Criteria for NHL
LD	Longest diameter
LDH	Lactate dehydrogenase
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activity
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NHL	Non-Hodgkin Lymphoma
OS	Overall survival
PBMC	Peripheral Blood monocytic cell
PD	Progressive disease

PR	Partial response
RBC	Red blood cell (count)
RECIST	Response Evaluation Criteria in Solid Tumors (Committee)
RR	Response rate
SAE	Serious adverse event
SD	Stable disease
TPP	Therapeutics Product Program
TSH	Thyroid stimulating hormone
TTP	Time to progression
WBC	White blood cell (count)
WHO	World Health Organization

Study Summary

Title	*Phase II Trial of Lenalidomide (Revlimid®)+ Rituximab with and without Dexamethasone in Recurrent Small B-cell Non-Hodgkin Lymphomas (NHL) Resistant to Rituximab*
Protocol Number	*Celgene# RV-NHL-PI-296* *UPenn # UPCC 02408*
Phase	*Phase II*
Methodology	*Open label*
Study Duration	*Patients will receive therapy until disease progression, development of unacceptable toxicity, or voluntary withdrawal, whichever occurs first*
Study Center(s)	*Single*
Objectives	*To evaluate the potential of Revlimid to overcome resistance to Rituximab*
Number of Subjects	*45 evaluable subjects*
Diagnosis and Main Inclusion Criteria	• Previously treated, histologically confirmed follicle center lymphoma (grades 1, 2 and 3a), marginal zone lymphoma, SLL with <5,000 lymphocytes/ mm^3, lymphoplasmacytic lymphoma with <3gm/ml IgM, or mantle cell lymphoma. • Flow cytometry or immunohistochemistry must confirm CD20 antigen expression. • Patients must have been treated with rituximab in combination with chemotherapy or as monotherapy and must have had less than a partial response or progressive disease within 6 months of any dose of rituximab. • ECOG 0-2 • Age>18 • Measurable disease
Study Product	For study participants, Celgene Corporation will provide lenalidomide at no charge through the Revlimid REMS® program.
Duration of administration	Lenalidomide will be given until withdrawal from trial, i.e either until disease progression with <3 months estimated life expectancy in Part I or any progression of disease after rituximab component of protocol therapy (part II).
Statistical Methodology	Fisher's exact test for response rate. Paired comparisons of time to progression (TTP) of previous, rituximab-containing treatment regimen to TTP in this study for each individual patient. McNemar's test for comparison of response rates in previous treatment to response rate in this study.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Although there is a wide array of treatment modalities available and initial response rates are high, most patients with small B-cell, or so-called "low grade", non-Hodgkin lymphomas (NHL) will eventually develop recurrent or refractory disease and many ultimately die from lymphoma-related complications. Chemotherapy and radiation therapy have clearly provided benefits to patients with these disorders, yet the potential for cure is limited and thus new approaches are under investigation. The monoclonal antibody rituximab (directed against the B-cell antigen CD 20) has received Food and Drug Administration (FDA) approval for patients with relapsed low-grade NHL. In a pivotal trial of 166 patients with relapsed low grade NHL, a response rate of 48% was observed with a median time to progression (TTP) of 12 months in responders. [1] A higher response rate was observed in patients receiving rituximab as second-line therapy compared to those patients following three or more prior chemotherapy regimens. In low-grade NHL patients who initially respond (time to progression of at least 6 months) and then relapse after single agent rituximab therapy, an overall response rate of 40% has been reported following re-treatment with median TTP of about 18 months after second administration. [2] However, approximately 50% of patients may not respond to initial treatment and almost all patients with low-grade B-cell lymphomas will experience disease progression at some point following rituximab therapy. To overcome rituximab resistance, it is paramount to thoroughly understand the mechanisms involved. Multiple mechanisms have been proposed for the activity of rituximab, including antibody-dependent cellular cytotoxicity (ADCC) [3-5], complement-dependent cytotoxicity (CDC) [5,6], and a direct pro-apoptotic effect [7,8].

1.1.1 Fc Receptor Polymorphisms

Although F(ab')2 rituximab homodimers were shown effective in inducing apoptosis of B-cell lymphoma cell lines in vitro [8], other works have recently established the importance of ADCC as a predominant mechanism of lymphoma cell clearance and that Fcγ receptors (R) are critical for the in vivo actions of rituximab in NHL. In a xenograft model of human lymphoma, knocking out the Fcγ R-loci in mice resulted in complete abrogation of response to rituximab. In contrast, knocking out the inhibitory Fcγ RIIb in mice resulted in enhanced response to rituximab in the same xenograft model. [9] In addition, the recent demonstration in NHL patients that response to rituximab is dependent on specific Fcγ RIIIa polymorphisms supports the importance of ADCC in the in vivo activity of rituximab. [10]The activating Fcγ R on natural killer (NK) cells and monocytes (Fc γ RIIIA) and on monocytes (Fc γ RIIa) mediates ADCC. Genomic polymorphisms corresponding to phenotype expression of valine (V) or phenylalanine (F) at amino acid 158 on the Fcγ RIIIa greatly influences the affinity of IgG1 to the Fcγ receptor. Stronger binding of antibody to homozygous FcRIIIa-158V has been demonstrated. Similarly, polymorphism related to expression of histidine (H) or arginine (R) at amino acid 131 in Fcγ RIIa affects the binding of IgG1. In the abovementioned study of 49 patients with previously untreated follicular lymphoma, patients homozygous for the Fcγ Ra-158V (V/V) had a

significantly higher response rate to rituximab than those with the phenylalanine (F/F) genotype (67%). [10]Furthermore, polymerase chain reaction (PCR) detection of bcl-2 re-arranged cells was significantly lower in the homozygous V/V group. In contrast, Fcγ RIIa-131 polymorphisms were not associated with response to rituximab. In a second study, both Fcγ RIIIa-158 (V/V) and Fcγ RIIa-131 (H/H) correlated with response and progression-free survival following treatment with rituximab. [11]This study will describe any prognostic significance observed for different Fcγ RIIIa receptor polymorphisms on response to combination rituximab – lenalidomide therapy.

1.1.2 Complement-dependent cell Lysis

Rituximab is capable of binding C1q and in vitro studies indeed have demonstrated the ability of the antibody to mediate complement-dependent cell Lysis (CDC) of human B-lymphoid cell lines. [12] These findings are corroborated by the observation that complement is consumed during treatment with rituximab and levels of side effects correlate with severity of the side effects associated with rituximab-infusion. [13] The precise role of CDC in rituximab therapy and its potential contribution to rituximab resistance are unclear and require further study.

1.1.3 CD20 signaling and direct pro-apoptotic effect

In addition to CDC, binding of rituximab appears to induce CD20-dependent caspase activation through increased calcium conductivity with subsequent IL-10 down regulation, invoking several signaling pathways. [14] Gene expression profiling of rituximab resistant follicular lymphoma revealed differential expression of genes involved in cellular immune response, including cytokines, complement and T-cell receptor signaling, suggesting a more profound role of the microenvironment than the malignant cells in rituximab resistance. [15,16] This is further supported by observations that loss of CD20 expression is not an important mechanism of rituximab resistance. This is corroborated by the effectiveness of CD20 radio-immunoconjugates in this setting. [17]

1.1.4 Enhancing ADCC and targeting the microenvironment

With our current understanding highlighting the apparent role of ADCC and the immunological microenvironment in the response to rituximab, several approaches to stimulate effector cell function have been suggested to augment the response to rituximab and overcome resistance. For instance, various human studies have evaluated the role of cytokines in combination with rituximab, including IFN-α, Il-12, and Il-2, demonstrating safety and effector cell enhancement.[18] For example, IFN-α, an immunomodulatory cytokine that induces antigen expression and enhances cytotoxicity, has been combined with rituximab in a phase II trial with 38 patients. While the overall survival did not differ significantly from that expected with rituximab alone, time to progression in responding patients appeared prolonged. [19] Trials combining IL-2 with rituximab suggested prolonged time to progression in patients with follicular lymphoma.[20,21] These trials suggest that targeting the microenvironment to modulate antigen expression as well as enhance cytotoxicity could potentially overcome resistance to rituximab.

1.1.5 Lenalidomide: an immunomodulator

One agent, which may potentially augment the activity of rituximab in NHL and thus potentially overcome rituximab resistance, is lenalidomide (Revlimid®), a proprietary IMiD™ compound of Celgene Corporation. Lenalidomide is a potent thalidomide derivate with immunomodulatory properties including stimulation of T-cell proliferation as well as production of IL-2 and

interferon-gamma in addition to other cytokines. The biological effects of IMiD™ compounds are presumed to be mediated by: (1) activation of the innate (e.g., NK cells) and adoptive (e.g., T-cells) immune systems, and (2) inhibition of angiogenesis. Treatment of lymphoma-bearing SCID mice with a combination of Rituximab and IMiD™ compounds demonstrated augmented/synergistic anti-tumor activity compared to monotherapy of either agent alone. This synergistic activity was attributed to an NK cell expansion (demonstrated by flow cytometric analysis) and further confirmed by in vivo NK cell depletion studies. [22,23] Moreover, increased production of IFN α, IL-2, and IL-12 enhanced NK cell- and monocyte-mediated tumor cell ADCC.[24] Lenalidomide-mediated enhancement of chemokine production by NK cells in the context of NK cell-mediated ADCC of tumor cells suggests the concomitant promotion of chemoattraction and potential infiltration of tumor-specific T-cells.[25] Interestingly, Lenalidomide strongly inhibits T-regulatory cell proliferation and suppressor-function. It inhibits IL-2-mediated generation of FOXP3 positive CTLA-4 positive $CD25^{high}$ $CD4^{+}$ T-regulatory cells from PBMCs by up to 50%. Furthermore, suppressor function of pre-treated T-regulatory cells against autologous responder-cells is abolished or markedly inhibited without drug related cytotoxicity.[26] These results provide a strong rationale for combination of lenalidomide with IgG1 antibodies to tumor-specific surface antigens in cancer patients.

1.2 Preclinical Data

Lenalidomide inhibits the proliferation of Namalwa (Burkitt's lymphoma derived) and Jeko-1 and Rec-1 (both mantle cell lymphoma derived) NHL cell lines, and this was associated with G0/G1 phase arrest. When lenalidomide and dexamethasone were combined simultaneously a clear synergistic interaction was observed related to hypophosphorylation of the Rb protein and activation of caspase-3 and -8, leading to extensive apoptosis.

Non anti-proliferative concentrations of lenalidomide markedly inhibited the production of the pro-angiogenic factors VEGF, IL-8 and PDGF. The inhibition of VEGF production by Lenalidomide appears to be through the down-regulation of VEGF gene transcription. The up-regulation of p21 gene expression may partially explain the anti-proliferative effect of lenalidomide on NHL cells. However, lenalidomide had no effect on cyclin D1 and p53 gene expression. These anti-proliferative and anti-angiogenic activities of lenalidomide on a variety of NHL cells support the potential study of lenalidomide in patients with NHL. [3 22,23] In particular, the anti-proliferative data provide a rationale for combination with dexamethasone.

Lenalidomide is a potent enhancer of NK cell and monocyte-mediated tumor cell ADCC. There were similar enhancing effects on various tumor cells using trastuzumab (Her-2+ breast cancer), cetuximab (EGFR+ colorectal cancer), and rituximab (CD20+ NHL cells). There was no enhancing effect with the non-ADCC inducing IgG2a-isotype antibody panitumumab. Enhancement of NK cell-mediated ADCC requires both antibody binding to Fc-γ receptors plus IL-2 or IL-12 signaling (i.e., lenalidomide alone does not cause an effect). The NK cell stimulatory effect is due to enhanced Fc-γ receptor signaling, likely via inhibition of phospho-SHIP-1, leading to enhanced granzyme B and Fas-L expression. Enhancement of chemokine production by IgG-stimulated NK cells suggests the concomitant promotion of chemoattraction and potential infiltration of tumor-specific T-cells. Lenalidomide enhances monocyte-mediated ADCC of antibody-coated tumor cells, which is completely blocked by a neutralizing anti-IL-12 monoclonal antibody. [24,25] These results provide a strong rationale for combination of lenalidomide with IgG1 antibodies to tumor-specific surface antigens in cancer patients.

Lenalidomide inhibits IL-2-mediated generation of FOXP3 positive CTLA-4 positive $CD25^{high}$ $CD4^{+}$ T-regulatory cells from PBMCs by up to 50%. Furthermore, the suppressor function of pre-treated T-regulatory cells against autologous responder-cells is abolished or markedly inhibited without drug related cytotoxicity. Also, Balb/C mice exhibit 25% reduction of lymph node T-regulatory cells after lenalidomide treatment. Inhibition of T-regulatory cell function was not due to changes in TGF-beta or IL-10 production but was associated with decreased T-regulatory cell FOXP3 expression. [26] In conclusion, these data provide one explanation for the adjuvant properties of lenalidomide and suggests that they may help overcome an important barrier to tumor-specific immunity in cancer patients.

1.3 Clinical Data

A phase I/II study evaluating lenalidomide with rituximab for the treatment of relapsed/refractory mantle cell lymphoma was presented in 2007 at the 49th Annual Meeting of the American Society of Hematology (ASH). 18 patients were enrolled in this trial, all of which had previously been treated with rituximab. The study indicated that 70% of patients achieved responses with 30% of patients achieving complete responses when given the combination therapy. [27] The most common Grade 3/4 adverse events observed were neutropenia, febrile neutropenia, thrombocytopenia and myalgia. A separate study evaluated lenalidomide oral monotherapy for relapsed/refractor mantle-cell NHL in 15 patients. Objective response was noted in 53% with manageable side effects. [28] A study of 45 high-risk patients with relapsed or refractory CLL, treated with lenalidomide oral monotherapy, showed an overall response rate of 47%, with 9% of the patients attaining a complete remission. Fatigue, thrombocytopenia, and neutropenia were the most common adverse effects noted in 83%, 78%, and 78% of the patients, respectively. [29]

1.4 Rationale

Based on these vitro and in vivo studies, we propose to evaluate the potential of lenalidomide to overcome rituximab resistance. As pre-clinical data and published clinical data suggest a synergistic effect between lenalidomide and dexamethasone, we propose initial treatment with both drugs for two 28-day treatment cycles (Part I or "priming") for subjects enrolled to Cohort 1. This combination in itself should have clinical efficacy. The priming phase in Part I will allow the study of immune-modulatory effects on T-cell subsets and cytokine milieu induced by the combination of lenalidomide and dexamethasone prior to the addition of rituximab. A reduced dose of lenalidomide 10 mg daily was chosen as the starting dose, given the heavily pre-treated patient population and the potential for lenalidomide-related myelosuppression. After the first lenalidomide – dexamethasone treatment cycle, the lenalidomide dose can be increased by one dose level based on patient-specific tolerance (see Section 6 for full details). After response assessment following two cycles of lenalidomide – dexamethasone, patients with responsive or stable disease, and patients with progressive disease with an estimated life expectancy of > 3 months will enter Part II with lenalidomide - dexamethasone and rituximab to evaluate the potential reversal of rituximab resistance as measured by response to rituximab and progression-free survival following rituximab.

Subjects enrolled to Cohort 2 of protocol treatment will receive treatment on the same schedule as those subjects in Cohort 1 (10 mg lenalidomide daily, weekly rituximab during Cycle 3), but

weekly dexamethasone will be eliminated from the study treatment plan. Response assessments will be conducted at the same timepoints (at the end of cycles 2 and 5).

To study the immunomodulatory effect of lenalidomide, as well as its possible role in host-associated rituximab resistance, we will analyze changes in peripheral blood mononuclear cells (PBMC) constitution (e.g., changes in NK cell, activated NK cell, activated T cell and Treg numbers) following exposure to lenalidomide and correlate various cell subtype levels and changes to the objective response rates to therapy with rituximab + lenalidomide with and without dexamethasone, compared to Part I with lenalidomide with and without dexamethasone alone. In addition, plasma samples both pre- and post-therapy will be tested for changes in plasma cytokines (i.e., interferon-gamma, GM-CSF, sIL-2R, IL-2, IL-10, IL-12, Rantes) in an attempt to correlate anti-tumor activity to lenalidomide-associated immunomodulatory effects on these cytokines. It is hypothesized that at least some of the immunomodulatory effects of lenalidomide may be mediated through the release of immunostimulatory cytokines. The proposed correlative studies seek to assay plasma cytokine levels pre- and post-therapy and correlate values with clinical outcome.

2 Study Objectives

2.1 Primary Objectives

2.1.1 To determine the response rate to lenalidomide + rituximab therapy with and without dexamethasone in relapsed small B-cell lymphomas with rituximab resistance.

2.2 Secondary Objectives

2.2.1 To determine time to progression after lenalidomide + rituximab therapy with and without dexamethasone in relapsed small B-cell lymphomas with rituximab resistance and compare the time to progression for the previous rituximab-containing regimen

2.2.2 To compare the response rate for the previous rituximab-containing regimen to that obtained subsequently to lenalidomide + rituximab therapy with and without dexamethasone.

2.2.3 To determine the toxicity profile of lenalidomide + rituximab therapy with and without dexamethasone in patients who have received a previous rituximab-containing combination regimen.

2.2.4 To correlate FcγRIIIa receptor polymorphism profiling with response to lenalidomide - dexamethasone + rituximab therapy in relapsed small B-cell lymphomas with rituximab resistance (Cohort 1 only).

2.2.5 To evaluate changes in NK cells, activated NK cells, activated T cells, T regs, and several plasma cytokines following exposure to lenalidomide - dexamethasone and lenalidomide - dexamethasone + rituximab therapy and correlation of observed changes to objective response rates.

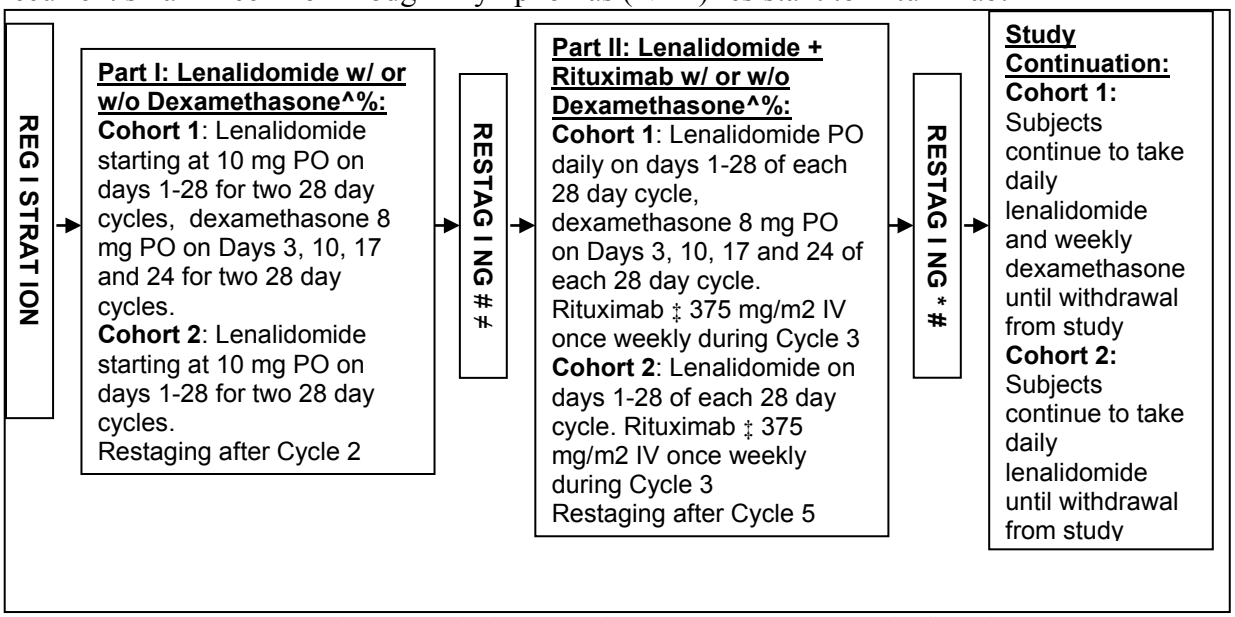
2.2.6 To determine the presence or absence of minimal residual disease after Part I and Part II of protocol therapy using a PCR-based assay of DNA.

2.2.7 To determine whether 1) a decrease in serum albumin by $\geq$ 0.3 g/dL at commencement of cycle 2 from baseline predicts a response (CR/PR)to protocol therapy and whether 2) a baseline serum albumin $\leq$ 4.1 g/dL predicts no response (SD/PD) to protocol therapy.

3 Study Design

3.1 General Design

Phase II Trial of Lenalidomide (Revlimid®) + Rituximab with and without Dexamethasone in recurrent small B cell non-Hodgkin lymphomas (NHL) resistant to Rituximab:



^ Close monitoring for tumor lysis syndrome (TLS) should be initiated concurrent with the initiation of lenalidomide-dexamethasone in Part I (see Section 3.2). Subjects will receive tumor lysis prophylaxis if clinically indicated. All subjects should remain well hydrated during at least the first 7 days of Cycle 1. Close monitoring for TLS and the need for TLS prophylaxis should be repeated during at least the first 7 days of Part II treatment. Additional TLS monitoring and prophylaxis may be employed at any time at the investigator's discretion. Tumor flare occurring during the first 1-2 weeks of Cycles 1, 2 and 3 should be recorded as AEs and not as progressive disease (PD). Tumor flare should be treated symptomatically with non-steroidal anti-inflammatory agents (NSAIDs) and other measures as needed

***** Follow-up staging 3 months after first dose of Rituximab (i.e after 5 months) then after months 12, 18 and 24 (as counted from enrollment of trial), then yearly until disease progression , development of unacceptable toxicity, or voluntary withdrawal, whichever occurs first.

‡ In patients with absolute lymphocyte count>20,000/ul, prior to rituximab infusion, close monitoring for tumor lysis syndrome should be initiated and those patients should receive appropriate supportive care (e.g., allopurinol, intravenous hydration, additional laboratory test monitoring, etc.). A modified dosing scheme is suggested for those patients with absolute lymphocyte count>20,000/ul (see 6.2)

At time of progression or relapse, a biopsy is recommended. If a biopsy is performed, and the patient consented to allow their tissue to be kept for future unknown use, the pathology specimen will be asservated at the U Penn Tissue Core facility.

≠ Subjects with CR, PR, SD or PD with an estimated life expectancy of >3 months will continue to Part II of the trial

% The lenalidomide dose may be escalated to 15mg daily at the beginning of Cycle 2 of Part I based on patient-specific tolerance as defined in Section 6. The lenalidomide dose during Part II will be determined by dose modification guidelines in Section 6. For patients in Cohort I, the dexamethasone dose during Part II may also be adjusted due to toxicities experienced during Part I. After Part II, patients with SD, PR or CR will continue to receive study treatment as per the schedule above in 28-day cycles until disease progression, development of unacceptable toxicity, or voluntary withdrawal, whichever occurs first.

We plan to include previously treated, histological confirmed follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma with <5000 lymphocytes / mm^3, lymphoplasmacytic lymphoma with < 3gm/ml IgM or mantle cell lymphoma with confirmation of CD20 antigen expression by flow cytometry or immunohistochemistry on the diagnostic biopsy. Paraffin blocks and/or frozen material from the initial biopsy or biopsy at relapse will be requested in all cases, but are not required for protocol eligibility.

Subjects must have been treated with rituximab in combination with chemotherapy or as monotherapy and must have refractory or progressive lymphoma. Subjects must have had less than a partial response or progressive disease within 6 months of any dose of rituximab.

Subjects must have measurable disease (see Section 3.3). Subjects will need staging to be completed within 60 days prior to registration.

Forty-five subjects will be enrolled to this study. The first twenty-five evaluable subjects will be enrolled to Cohort 1 of study treatment, which will consist of daily dosing of lenalidomide, weekly dosing of dexamethasone and weekly dosing of rituximab during Cycle 3, as described below. Cohort 2 will consist of twenty subjects. These subjects will follow the same treatment schedule as those in Cohort 1, but will not receive weekly dexamethasone.

In Part I of the study, subjects in both cohorts will receive lenalidomide 10 mg PO once daily on Days 1-28 every 28 days for two 28-day cycles. Subjects in Cohort 1 will also receive dexamethasone 8 mg PO once weekly (dosing on Days 3, 10, 17 and 24 is suggested, but not required) for two 28-day cycles. Serum and plasma samples for ancillary studies will be collected for all subjects upon entry into the trial, after 2 cycles of study therapy, and at the investigator's discretion in subjects with extended remissions. Subjects will be restaged after the first 2 cycles (Part I) prior to Part II and will continue with Part II (with rituximab) unless progression of disease is documented with life expectancy estimated to be <3 months during Part I.

In Part II, all subjects will receive lenalidomide once daily Days 1-28 over 28 days as well as Rituximab 375mg/m2 IV once weekly during cycle 3. Subjects enrolled in Cohort 1 will also receive dexamethasone PO once weekly during each 28 day treatment cycle. The doses of lenalidomide and dexamethasone (for subjects in Cohort 1) during Part II will be determined by dose modification guidelines in Section 6. All subjects will be restaged 3 months after first rituximab infusion (prior to cycle 6). Again, serum and plasma samples for ancillary studies will be collected at this point. Following Part II, subjects in Cohort 1 will continue on lenalidomide once daily on Days 1-28 every 28 days and dexamethasone once weekly until disease progression, development of unacceptable toxicity, or voluntary withdrawal, whichever occurs first.

Subjects in Cohort 2 will continue on lenalidomide once daily on days 1-28 of each 28 day cycle. Restaging for all subjects will be performed on months 12, 18 and 24 (as counted from enrollment of trial) and then yearly until disease progression, development of unacceptable toxicity, or voluntary withdrawal, whichever occurs first. These restaging assessments may be performed +/- 2 months from these timepoints, or at the clinical discretion of the treating physician.

Subjects are required to receive prophylactic anti-coagulation with aspirin, Coumadin or low molecular weight heparin due to the increased risk of thrombosis reported with lenalidomide therapy. Coumadin should only be used with caution and close monitoring of INR. Prophylactic anti-coagulation should be held for platelet counts < 50,000/mm^3 and restarted when platelet counts are ≥ 50,000/mm^3.

3.2 Required Data

Guidelines for pre-study testing

To be completed within 60 days before registration:

- Radiological imaging (e.g., CT or MRI) which is utilized for tumor measurement. If a fusion PET-CT has been obtained and is deemed satisfactory for anatomic evaluation of lesions, a separate diagnostic contrasted CT study will not be required.

- Review of diagnostic pathology material to confirm the diagnosis

- Paraffin blocks and/or frozen material from the initial biopsy or biopsy at relapse will be requested in all cases, but are not required for protocol eligibility.

To be completed within 28 days before registration, or on date of registration

- All blood studies
- History and physical exam

3.3 Table of Events

Tests & Observations (see footnote M)	**Prior to study**	**Prior to starting Cycles 1-6**	**Restaging after Part I**	**Restaging after Part II and subsequent follow-up***
History	X			
Physical Examination	X	X	X	X
Height	X			
Weight, BSA**	X		X	
Performance Status	X	X	X	X
Tumor measurements	X	A	X	X
Drug toxicity Assessment		X	X	X,N
Register into Revlimid REMS® program	X,O			
EKG	X			
Laboratory Studies (see footnote M)				
CBC, Differential, Platelets	X	X,H	X	X
Serum Creatinine, BUN	X	X,	X	X
Serum Electrolytes	X	X,	X	X
Total Protein, Albumin	X	X	X	
AST,ALT, Alk. Phos., Bilirubin	X	X	X	X
ESR, CRP, Fibrinogen	X^	X, ^	X^	X,C^
Uric acid/Phosphate/LDH/Ca^{++}	X	X,J	X	X,C
Serum or urine b-HCG***	X, B	B	X	B
Serum IgG, IgA, IgM	X^	X,C^	X^	C^
FCR Polymorphism Sample (see 3.5)	X^			
Blood and Plasma Sample (see 3.5)	X		X	D
HACA				E^
HBsAg, HepCAb, HBcAb	F			F
TSH (repeat only if clinically indicated)	X			
Staging (see footnote M)				
CT / MRI (chest/abd/pelvis) / PET-CT	X		X	X
CT Scan/MRI (neck)	G		G	G
Bone Marrow Asp& BX (unilateral)	P		K	K
Histologic Review	X		L	L

** Follow-up staging on months 12, 18 and 24 as counted from enrollment, then yearly until disease progression, development of unacceptable toxicity, or voluntary withdrawal, whichever occurs first. Physical exams and study labs should be done monthly for the first 6 months, every two months for cycles 7-13 and every three months thereafter (+/- 2 weeks). After the first 6 months of weekly labs, subjects will continue to have a CBC monthly while on-study.*

*** Although doses are recalculated prior to each treatment, the actual dose of rituximab to be given need not change unless the calculated dose changes by ≥ 10%. NOTE THAT LENALIDOMIDE DOSES ARE NOT BASED ON WEIGHT OR BSA.*

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

^ Subjects enrolled into Cohort 1 only. Not applicable for subjects enrolled into Cohort 2.

A If accessible to physical examination, please record measurements

B Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide (prescriptions must be filled within 7 days). FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix A: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

C Perform for the first 6 cycles

D Obtained prior to beginning Cycle 6 and at the investigator's discretion in subjects with durable remissions.

E Perform upon completion of rituximab therapy (before initiation of Cycle 4) and at the End of Cycle 10

F Patients with known hepatitis B or C are not eligible for this study. Negative results are required for participation. This will be based on the subject's medical history. Note: Baseline Hepatitis B/C testing is not required.

G Perform if nodes are palpable.

H Weekly throughout cycles 1-6, monthly thereafter.
J During Cycles 1 on Day 3, 4, or 5 and on Day 8. During the cycle of rituximab therapy (cycle 3) on Days 3, 4, or 5, and on Days 8 to monitor for tumor lysis syndrome. Additional assessments may be done at any time.
K If initially positive, repeat only in patients who are demonstrated to be in CR/Cru by all other criteria.
L At time of progression or relapse, a biopsy is recommended to be performed. If a biopsy is performed, patients may separately consent to allow their tissue to be kept for future unknown research.
M If Physical examination, vital signs, weight and ECOG performance status were done within 7 days of Day 1, they do not need to be repeated at Study Day 1.An unscheduled visit can occur at any time during the study. Source must be maintained for these unscheduled visits. The date for the visit and any data generated must be recorded on the appropriate CRF. Source documents for these unscheduled visits must also be maintained.
N An additional safety assessment will be done 30 days (+/- 7 days) following the last dose of study drug.
O Lenalidomide must be prescribed through and in compliance with the Revlimid REMS® program of Celgene Corporation. Prescriptions must be filled within 7 days. Consideration should be given to prescribing lenalidomide 5 to 7 days in advance of Day 1 of each cycle to allow time for required patient and prescriber surveys, and drug shipment to patient. Any unused Revlimid® (lenalidomide) should be returned to the patient for disposition in accordance with the Revlimid REMS® program.
P If patient has a history of bone marrow involvement at baseline.

3.4 Guidelines for Evaluation of Measurable Disease

- **Clinical lesions** will only be considered measurable when they are superficial (e.g skin nodules, palpable lymph nodes).
- **Chest X-ray** lesions are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Conventional CT and MRI** should be performed with cuts of 10mm or less in slice thickness contiguously. Spiral CT should be performed using a 5mm contiguous reconstruction algorithm. This applies to the chest, abdomen, and pelvis. Head & neck and extremities usually require specific protocols.
- **Ultrasound** should not be used to measure tumor lesions that are clinically not easily accessible when the primary endpoint of the study is objective response evaluation. It is a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination
- **PET/CT** may be performed as an alternative to CT or MRI at the investigator's discretion

3.5 Correlative Science

All correlative studies will be performed upon completion of the trial as a batch run.

The correlative studies detailed below may be altered at the discretion of the Principal Investigator.

3.5.1 FcR Polymorphism

Genomic polymorphisms corresponding to phenotype expression of valine (V) or phenylalanine (F) at amino acid 158 on the Fcγ RIIIa will be analyzed fluorescent automated cycle sequencing of Taq PCR products

3.5.2 Peripheral Blood FACS Analysis

PBMCs will be subjected to FACS analysis for expression of CD3, CD4, CD8, CD25, CD39, CD73, CD127, FOXP3, CD122, CD212 (IL-12R), HLA-DR, CD14, CD19, CD56, CD69, FAS-L and granzyme B as well as additional antigens as indicated. Flow cytometry to detect

intracellular cytokine production in individual cells in peripheral blood, or from cells in the ELISA assays will also be performed to test production of IL-2, IL-10, interferon-γ, TGF-β and other cytokines as indicated.

Treg function will be determined following isolation of $CD4^+CD25^+$ cells from PBMC using published criteria. CD 39 and CD73 will be used to identify memory T reg cells. Functional tests include inhibition of T cell proliferation driven by α-CD3 plus α-CD28 mAb exposure, reduction in T cell IL-2 or interferon-γ production and reduced cytolytic activity. Sorting of cells into additional populations ($LAG3^{+/-}$, $CD27^{+/-}$, $CD8^{+/-}$, $Ki\text{-}67^{+/-}$) may also be attempted prior to suppression testing. *Foxp3* message will be ascertained by flow cytometry. If primary tissue is available, IHC for CD3, CD4, CD8, FOXP3, and CD56 will be performed.

3.5.3 Plasma Cytokine Analysis

Samples will be saved until the end of study for a batch run. At that time, cytokines will be tested using commercial ELISA kits (R&D Systems, Minneapolis, MN). Cytokines to be tested include interferon-γ, GM-CSF, sIL-2R, IL-2, IL-4, IL-10, IL-12, Rantes and TGF-β.

3.5.4 Minimal Residual Disease Analysis

If a paraffin embedded diagnostic tissue specimen is available, this material will be used to generate patient specific probes for detection of minimal residual disease in blood at baseline and during protocol therapy (at the end of Part I, prior to starting Cycle 6, and at the investigator's discretion in subjects who experience a durable remission) using a PCR assay. This assessment will be performed using a portion of the peripheral blood collected for ancillary studies (see Section 3.5.3) and will not require blood collection beyond that performed during the study for other analyses.

3.6 Correlative Science Sample Submission

3.6.1 FcR Polymorphism Sample Procurement (Cohort 1 Only)

If a patient has consented and agreed to allow their blood to be used for research studies (Research related Studies Consent Form, see Appendix J), Peripheral blood will be collected prior to treatment for analysis of FcR polymorphisms. 20ml of peripheral blood in two yellow (ACD) or purple (EDTA) top Vacutainer® tubes. The tubes should be inverted 8-10 times to mix the tube additive and then refrigerated until shipped. Samples should be labeled with the patient's initials, study number, patient study ID# and date and time of collection. A log sheet (Correlative Science Form A) must be sent with the specimen and a copy retained in the investigator's file. This sample can be obtained at baseline, or at any time during a subject's participation in this study.

3.6.2 FcR Polymorphism Sample Submission

Blood samples should be send to:

Kathakali Addya, PhD
Molecular Diagnosis and Genotyping Facility
7 Gates West
3400 Spruce Street
Philadelphia, PA 19104

3.6.3 Peripheral Blood and Plasma Sample Procurement

If a patient has consented and agreed to allow their blood to be used for research studies 8 green top (heparin) tubes and 1 red top tube will be collected at the following timepoints: prior to treatment, prior to beginning Cycle 3 of treatment, and prior to beginning Cycle 6. If the 3rd blood/plasma sample is missed (i.e. prior to beginning Cycle 6), it can be drawn at a later time point. Samples should be labeled with the patient's initials, study number, patient study ID# and date and time of collection. A completed "Clinical Research Sample – Information and Processing Record" from the Human Immunology Core must be sent with the specimen and a copy of Correlative Science Form B should be retained in the patient's study chart.

Peripheral blood for MRD analysis in subjects with extended remissions will be collected as 3mL in EDTA tube. This will be performed during a routine blood draw. This will only be performed if the patient has consented and agreed to allow their blood to be used for research studies.

3.6.4 Peripheral Blood Sample Submission

Samples for ancillary studies should be sent on the same day they are obtained to:

Nicole Aqui MD
Division of Transfusion Medicine
University of Pennsylvania
272 John Morgan
3620 Hamilton Walk
Philadelphia, PA 19104
Office: 215 746-1195
Lab: 215 746-1199
Fax: 215 746-1100

Samples for MRD testing will be sent to:
Adaptive Biotechnologies
Attention: Clinical Lab
1551 Eastlake Ave E, Ste 200
Seattle, WA 98102

3.6.5 Paraffin-embedded tissue block submission

If a patient has consented to allow their tissue to be kept for future unknown use, only one tissue block will be needed to accommodate both histological confirmation and future correlative science studies. At time of progression or relapse, if a patient has consented to allow their tissue to be kept for future unknown use, and if a biopsy has been performed, these pathology specimens will be sent for pathology review and future correlative science studies to:

Tumor Tissue Bank Core Facility
Hospital of the University of Pennsylvania
Department of Pathology & Laboratory Medicine
6.119 Founders Pavilion, 3400 Spruce Street
Philadelphia, PA 19104

Phone: 215-615-1673
Fax: 215-349-5910

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

- **Documentation of disease**
    - Previously treated, histological confirmed follicle center lymphoma, grade 1-3a, marginal zone lymphoma, small lymphocytic lymphoma with < 5000 lymphocytes /mm³ or lymphoplasmacytic lymphoma with <3gm/ml IgM, mantle cell lymphoma by WHO classification (see Appendix F).
    - Bone marrow biopsies as sole means of diagnosis are not acceptable. Fine needle aspirates are not acceptable.
    - Institutional flow cytometry or immunohistochemistry must document CD20 antigen expression. Past documentation of CD20 antigen expression is admissible.
- **Prior treatment**
    - Patients must have been treated with rituximab in combination with chemotherapy or as monotherapy and must have refractory or progressive disease. Subjects must have had less than a partial response or progressive disease within 6 months of any dose of rituximab.
- Age $\geq$ 18
- ECOG performance status 0-2 (see Appendix B)
- Measurable disease must be present either on physical examination or imaging studies. Non-measurable disease alone is not acceptable. Any tumor mass > 2cm is considered measurable.
- Lesions that are considered non-measurable, but assessable include the following:
    - Bone lesions (lesions if present should be noted)
    - Ascites
    - Pleural/pericardial effusion
    - Lymphangitis cutis/pulmonis
    - Bone marrow (involvement by non-Hodgkin lymphoma should be noted)
- Patients with a history of intravenous drug abuse or any behavior associated with increased risk of HIV infection should be tested for exposure to the HIV virus.

- Understand and voluntarily sign an informed consent form.
- Able to take aspirin (81 or 325 mg) daily as prophylactic anticoagulation. Patients intolerant to ASA may use warfarin or low molecular weight heparin
- Laboratory test results within these ranges:
    - Absolute neutrophil count ≥ 1000/mm³
    - Platelet count ≥ 75,000 /mm³
    - Serum creatinine ≤ 2.0 mg/dL
    - Total bilirubin ≤ 1.5 mg/dL (unless due to Gilbert's syndrome)
    - AST (SGOT) and ALT (SGPT) ≤ 2.5 x ULN or ≤ 5 x ULN if hepatic metastases are present.
- Disease free of prior malignancies for ≥ 5 years with exception of currently treated basal cell or squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix or breast.
- All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of Revlimid REMS®.
- Females of childbearing potential (FCBP)[†] must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to and again within 24 hours of prescribing lenalidomide (prescriptions must be filled within 7 days) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. See Appendix: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

4.2 Exclusion Criteria

- Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from following study procedures.

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

- Pregnant or breast-feeding females. (Lactating females must agree not to breast feed while taking lenalidomide).
- Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.
- Use of any other experimental drug or therapy within 28 days of baseline.
- Known hypersensitivity to thalidomide.
- The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide or similar drugs.
- Any prior use of lenalidomide.
- Known positive for HIV or active infectious hepatitis, type A, B or C. Patients who test positive or who are known to be infected are not eligible due to an increased risk of infection with this regimen. An HIV test is not required for entry in this protocol, but is required if the patient is perceived to be at risk.
- Known CNS involvement by lymphoma.

4.3 Subject Recruitment and Screening

This clinical trial can fulfill its objectives only if patients appropriate for the trial are enrolled. All relevant medical and other considerations should be taken into account deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy and therefore only enroll patients for whom the agents administered are appropriate. Although they will not be considered as formal eligibility (exclusion) criteria, as part of the decision-making process physicians should recognize that the following might increase the risk to the patients entering this protocol:

Serious medical illness or psychiatric condition, which would prevent compliance with treatment or informed consent.

Medical conditions such as uncontrolled infection, uncontrolled diabetes mellitus or cardiac disease, which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.

Patients at high risk of hepatitis B infection should be screened before starting treatment. Carriers of hepatitis B should be closely monitored for evidence of active HBV infection and hepatitis during and for several months after rituximab treatment.

Lenalidomide increases the risk of thrombotic events in patients who are at high risk or with a history a thrombosis, in particular when combined with other drugs known to cause thrombosis. When lenalidomide is combined with other agents such as steroids (e.g. dexamethasone,

prednisone), anthracyclines (Doxil, Adriamycin) and erythropoietin the risk of thrombosis is increased. Due to the known increased risk of thrombotic events associated with the combination of lenalidomide and dexamethasone subjects will receive aspirin (81 or 325 mg) or some other form of prophylaxis as deemed appropriate. Low molecular weight heparin may be utilized in patients that are intolerant to ASA. Coumadin should be used with caution and close monitoring of INR.

Patients with absolute lymphocyte count >20,000/ul should be closely monitored for tumor lysis syndrome. These patients should receive appropriate supportive care and prophylaxis (e.g., allopurinol, intravenous hydration, additional laboratory test monitoring, etc.) prior to rituximab infusion. A modified dosing scheme is suggested for those patients with absolute lymphocyte count>20,000/ul (see 6.2).

4.4 Early Withdrawal of Subjects

Subjects will be removed from protocol for any of the following reasons:

- Any clinical adverse event, laboratory abnormality or inter-current illness, which, in the opinion of the investigator, indicates that, continued treatment with study therapy is not in the best interest of the subject.

- Any toxicity requiring discontinuation as outlined in the dose modifications criteria in Table 2, Section 6.1.3.

- The subject declines further therapy.

- The subject experiences progression of disease after the first 2 cycles of study treatment (Part I) with estimated life expectancy < 3 months or relapse of lymphoma/progression of disease after having received rituximab (see also Section 7).

- It is deemed in the best interest of the subject. In this instance, the Principal Investigator should be notified.

- Termination of the study by the supporter, Celgene.

- Pregnancy

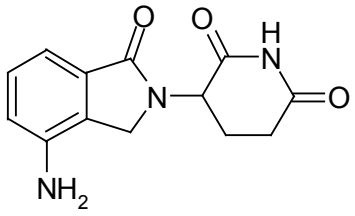
- The reason(s) for withdrawal should be noted in the case report form and in the subject's medical record. Survival data on patients that withdraw from the trial will be recorded. Statistical analysis will be performed on an intent-to-treat basis.

5 Drug Formulation, Availability and Preparation

5.1 Lenalidomide

REVLIMID® (Lenalidomide), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:

Chemical Structure of Lenalidomide



3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione

The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

Lenalidomide is off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

5.1.1 Mechanism of Action

The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory and anti-angiogenic properties. Lenalidomide inhibited the secretion of pro-inflammatory cytokines and increased the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide inhibited cell proliferation with varying effectiveness (IC50s) in some but not all cell lines. Of cell lines tested, lenalidomide was effective in inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5) but was much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell lines without chromosome 5 deletions. Lenalidomide inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 in vitro.

5.1.2 Pharmacokinetics and Drug Metabolism

Absorption:

Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co-administration with food does not alter the extent of absorption (AUC) but does reduce the maximal plasma concentration (Cmax) by 36%. The pharmacokinetic disposition of lenalidomide is linear. Cmax and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Pharmacokinetic sampling in myelodysplastic syndrome (MDS) patients was not performed. In multiple myeloma patients, maximum plasma concentrations occurred between 0.5 and 4.0 hours post-dose both on Days 1 and 28. AUC and Cmax values increase proportionally with dose following single and multiple doses. Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

Distribution:

In vitro (^{14}C)-lenalidomide binding to plasma proteins is approximately 30%.

Metabolism and Excretion:

The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours.

5.1.3 Supplier

Celgene Corporation will supply Revlimid® (lenalidomide) to study participants at no charge through the Revlimid REMS® program. 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 Celgene's Revlimid REMS® program.

5.1.4 Dosage form

Lenalidomide will be supplied as capsules for oral administration.

5.1.5 Packaging

Lenalidomide will be shipped directly to patients. Bottles will contain a sufficient number of capsules for one cycle (28 days) of dosing**.**

5.1.6 Storage

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

5.1.7 Prescribing Information

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 Revlimid REMS® program. Per standard Revlimid REMS® 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 Celgene's Revlimid REMS® program. Prescriptions must be filled within 7 days. ***Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle***.

5.1.8 Special Handling Instructions

Females of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves.

5.2 Rituximab (Rituxan®, IDEC-C2B8)

Rituximab is clinically indicated for the treatment of CD20+ non-Hodgkin lymphomas, and will be billed to the patient and/or insurance. Please refer to the agent's package insert for additional information.

5.2.1 Availability

Rituximab is commercially available in 10ml and 50ml single-use vials containing 100 or 500 mg of antibody, respectively at concentration of 10 mg/ml.

5.2.2 Storage and Stability

Intact vials should be stored under refrigeration. Dilute solutions for infusion (1-4mg/ml) are stable for 24 hours under refrigeration, and for an additional 24 hours at room temperature.

5.2.3 Preparation

The desired dose of rituximab should be diluted in 0.9% NaCL or D5W to a final concentration of 1-4mg/ml. Mix by inverting the bag gently.

5.2.4 Administration

Rituximab will be administered by IV infusion as described in 6.2. Patients must be pretreated with acetaminophen and diphenhydramine prior to each dose of rituximab.

5.2.5 Toxicity

The most serious adverse events associated with rituximab include severe infusion reactions, Tumor Lysis syndrome and severe muco-cutaneus reactions. Severe infusion reactions consisting of hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock may be fatal. Most reported fatal reactions occurred within 24 hours of the first dose of rituximab. If a reaction occurs, the infusion should be stopped until the symptoms resolve, and then restarted at a 50% slower rate. Because severe infusion reactions have been noted more frequently in patients with high leukocyte counts, such patients should be observed closely.

Tumor Lysis syndrome resulting in renal failure has been described and occasional fatalities noted. Tumor Lysis syndrome is more likely in patients with high numbers of circulating malignant cells. These patients should receive appropriate supportive care and prophylaxis (e.g., allopurinol, intravenous hydration, additional laboratory test monitoring, etc.) prior to rituximab infusion.

Severe muco-cutaneus reactions associated with rituximab include Stevens-Johnson syndrome and toxic epidermal necrolysis. The onset of these reactions has been from 1-3 weeks.

Less severe infusion reactions are common with rituximab. These include fever, chills and dyspnea. The mechanism of rituximab infusion reactions is thought to be the release of cytokines. Infusions should be interrupted until symptoms resolve, and restarted at a 50% slower

rate. Pretreatment with acetaminophen and diphenhydramine before each dose of rituximab may minimize the likelihood/severity of infusion reactions.

Recent reports describe hepatitis B reactivation with fulminant hepatitis, hepatic failure and death in some patients receiving rituximab in combination with chemotherapy. The median time to diagnosis of hepatitis was approximately 4 months after starting rituximab and approximately 1 month after last dose.

A report in the literature described an increase in fatal infection in HIV-related lymphoma patients when rituximab was used in combination with CHOP chemotherapy, as compared to CHOP alone. Patients with HIV infection are not eligible for entry on this research study.

6 Dose Modifications and Management of Toxicities

6.1 Lenalidomide and Dexamethasone

Administration: For subjects in both Cohorts 1 and 2 with baseline creatinine clearance of >30 ml/min, the initial dose of lenalidomide for investigation is 10 mg/day, orally on days 1 - 28, repeated every 28 days (28 day cycle). The initial dose for subjects with a baseline creatinine clearance of <30 ml/min will be 5 mg orally on days 1 – 28 of each 28 day cycle. Dosing will be at approximately the same time each day. Prescriptions must be filled within 7 days.
For patients in Cohort 1 only, the initial dexamethasone dose will be 8mg PO once weekly (dosing on days 3, 10, 17 and 24 are suggested but not required), repeated every 28 days.
Subjects enrolled to Cohort 2 will not receive dexamethasone as part of protocol therapy.

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

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

Subjects experiencing adverse events may need study treatment modifications (See 6.1.3).

Lenalidomide Dose Escalation Evaluation and Instruction: All subjects shall be evaluated after first cycle of lenalidomide for dose escalation. If no drug-related toxicity of ≥ Grade 3 was noted, dose escalation to the next dose level is permissible at the start of Cycle 2 during Part I (see Section 6.1.1 for lenalidomide dose levels). No dose escalation shall be permitted upon entry into Part II of the trial or at any other time except at the start of Cycle 2 during Part I.

Record of administration: Accurate records of all study drug administration (including prescribing and dosing) will be made in the source documents.

6.1.1 Dose Continuation, Modification and Interruption

Subjects will be evaluated for AEs at each visit with the NCI CTCAE v5.0(Appendix C: NCI CTCAE v5.0) used as a guide for the grading of severity. Refer to the Dose Modification Steps below, and to Sections 6.1.2 and 6.1.3 for full instruction on initiation of a new cycle of therapy and dose modifications during a cycle of therapy.

Dose Modification Steps

Table 1: LENALIDOMIDE Dose Reduction Steps	
Dose Level +1	15 mg daily on Days 1-28 every 28 days
Starting Dose	**10 mg daily on Days 1-28 every 28 days**
Dose Level – 1	5 mg daily on Days 1-28 every 28 days
Dose Level – 2	5 mg every other day during Days 1-28 every 28 days
Dose Level - 3	Subjects with extended remissions (response > 1 year) may have their dose adjusted at the discretion of the Principal Investigator; any dose adjustments at Dose Level -3 must be approved in writing by the Medical Monitor.

6.1.2 Instructions for initiation of a New Cycle

A new course of treatment may begin on the scheduled Day 1 of a new cycle if:

- The ANC is ≥ 1000 /mm³
- The platelet count is ≥ 50,000 /mm³;
- Any drug-related rash or neuropathy that may have occurred has resolved to ≤ grade 1 severity;
- Any other drug-related adverse events that may have occurred have resolved to ≤ grade 2 severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above. If lenalidomide dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle. **If lenalidomide dosing was omitted for the remainder of the previous cycle or if the new cycle is delayed due to toxicity newly encountered on the scheduled Day 1**, **then the new cycle will be started with a one-level dose reduction of lenalidomide.**

If subjects experience cytopenias and do not meet study requirements to resume lenalidomide, they may proceed with rituximab as described in the protocol.

6.1.3 Instructions for dose modifications or interruption during a cycle

Table 2: Lenalidomide Dose Modifications

NCI CTC Toxicity Grade	Onset Day 2-21 of Cycle	Onset ≥ Day 22 of Cycle
Grade 3 neutropenia associated with fever (temperature ≥ 38.5º C) or Grade 4 neutropenia	• Hold (interrupt) lenalidomide dose (missed doses of lenalidomide are not made up). • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 28. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the lenalidomide dose maintained.	• Omit lenalidomide for remainder of cycle • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level. If neutropenia is the only toxicity for which a dose reduction is required. G-CSF may be used and the lenalidomide dose maintained for the next cycle at the investigators discretion.
Thrombocytopenia ≥Grade 3 (platelet count < 50,000/mm³)	• Hold (interrupt) lenalidomide dose and prophylactic anti-coagulation, if applicable. • Follow CBC weekly. • If thrombocytopenia resolves to ≤ grade 2 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 28. See Section 6.3 for instructions for restarting prophylactic anti-coagulation.	• Omit lenalidomide for remainder of cycle • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level.
Non-blistering rash **Grade 3** **Grade 4**	• If Grade 3, hold (interrupt) lenalidomide dose. Follow weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 28. • Discontinue lenalidomide. Remove patient from study.	• Omit lenalidomide for remainder of cycle. • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level. • Discontinue lenalidomide. Remove patient from study.
Desquamating (blistering) rash- any Grade	• Discontinue lenalidomide. Remove patient from study.	• Discontinue lenalidomide. Remove patient from study.

Table 2: Lenalidomide Dose Modifications		
NCI CTC Toxicity Grade	**Onset Day 2-21 of Cycle**	**Onset ≥ Day 22 of Cycle**
Neuropathy **Grade 3**	• Hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 28.	• Omit lenalidomide for the remainder of the cycle. • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level.
Grade 4	• Discontinue lenalidomide. Remove patient from study.	• Discontinue lenalidomide. Remove patient from study.
Venous thrombosis/embolism ≥ Grade 3	• Hold (interrupt) lenalidomide and start anticoagulation; restart lenalidomide at investigator's discretion (maintain dose level).	• Omit lenalidomide for remainder of cycle.
Hyperthyroidism or hypothyroidism	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level.	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level.
other non-hematologic toxicity ≥ Grade 3 attributable to lenalidomide	• Hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 2 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 28.	• Omit lenalidomide for remainder of cycle. • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level.

NOTE: If subjects do not have adequate hematological recovery within 28 days of their last study treatment, lenalidomide will be discontinued and not restarted. However, the subjects will still be followed for response assessment and included in endpoint analyses.

Table 3: Dose Modification for Dexamethasone (Cohort 1 Patients Only)		
Use Common Terminology Criteria for Adverse Events (CTCAE) v5.0 unless otherwise specified		
CTCAE CATEGORY	**ADVERSE EVENT**	**DOSAGE CHANGE**
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, consider dexamethasone dose reduction and/or schedule modification.

Table 3: Dose Modification for Dexamethasone (Cohort 1 Patients Only)		
Use Common Terminology Criteria for Adverse Events (CTCAE) v5.0 unless otherwise specified		
CTCAE CATEGORY	**ADVERSE EVENT**	**DOSAGE CHANGE**
	≥Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart dexamethasone at reduced dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If toxicity recurs, discontinuation of dexamethasone may be considered.
	Acute pancreatitis	Discontinue dexamethasone and do not resume
Cardiovascular	Edema ≥Grade 3 (limiting function and unresponsive to therapy or anasarca)	Hold dexamethasone until symptoms adequately controlled. Use diuretics as needed. Restart dexamethasone with consideration of dexamethasone dose reduction and/or schedule modification. If toxicity recurs, discontinuation of dexamethasone may be considered.
Neurology	Confusion or Mood alteration ≥ Grade 2 (interfering with function +/- interfering with activities of daily living)	Hold dexamethasone until symptoms adequately controlled. Restart dexamethasone with consideration of dexamethasone dose reduction and/or schedule modification. If toxicity recurs, discontinuation of dexamethasone may be considered.
Musculoskeletal	Muscle weakness ≥ Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living)	Hold dexamethasone until symptoms adequately controlled. Restart dexamethasone with consideration of dexamethasone dose reduction and/or schedule modification. If weakness persists, consider further dexamethasone dose reduction and/or schedule modification, or discontinuation.
Metabolic	Hyperglycemia ≥ Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, consider dexamethasone dose modification and/or schedule modification, or discontinuation.
Any Other Toxicity Attributed to Dexamethasone	≥ Grade 3 or higher	Hold dexamethasone until symptoms adequately controlled. Restart dexamethasone with consideration of dexamethasone dose reduction and/or schedule modification. If toxicity recurs, discontinuation of dexamethasone may be considered.

6.2 Rituximab

Rituximab 375mg/m2 will be administered by IV infusion once weekly during cycle 3. The initial rate during the first infusion should be 50mg/hr. The infusion rate may be increased, if tolerated, by 50mg/hr increments every 30 minutes to a maximum of 400mg/hr. If administration is well tolerated during the first infusion, subsequent infusions of therapy may begin at a rate of 100 mg/hr. If tolerated, the rate may be increased by 100 mg/hr increments every 30 min to a maximum rate of 400 mg/h.

Close monitoring for tumor lysis syndrome (TLS) and TLS prophylaxis should be initiated during Cycles 1 on Day 3, 4, or 5 and on Day 8. During the Cycle 3, tumor lysis labs should be drawn at one timepoint between days 3-5 and on day 8 after each subject's first dose of rituximab. . Additional assessments may be done at any time (see Sections 3.2 and 6.3). Extra care should be taken with TLS monitoring and with TLS prophylaxis in patients with an absolute lymphocyte count>20,000/ul, and those patients should receive appropriate supportive care (e.g., allopurinol, intravenous hydration, additional laboratory test monitoring, etc.).

6.2.1 Infusion and Hypersensitivity reactions

In subjects with absolute lymphocyte count ≥20,000/ul, special attention will be given to TLS monitoring and TLS prophylaxis (Section 6.2) and the rituximab infusion shall be modified as follows: 50 mg absolute dose on Day 1, 150 mg absolute dose on Day 2 and (375mg/m^2-200mg) on Day 3.

Rituximab infusions must be interrupted if any infusion reactions (e.g., fever, chills, dyspnea etc.) ≥ grade 1 occur. When the symptoms have resolved completely, the infusion may be restarted at half the previous rate. If tolerated, rituximab may be gradually re-escalated to the initial infusion rate. If patients experience a second infusion reaction, the rituximab infusion should be stopped. At the investigator's discretion, patients unable to complete the full dose of rituximab may resume the incomplete treatment on the following day after dexamethasone 20 mg po is given the night before and the morning of retreatment.

Infusion reactions are distinct from hypersensitivity reactions, but they may have overlapping manifestations. Hypersensitivity reactions to rituximab are non-IgE mediated and may also respond to decreases in infusion rates. For hypersensitivity reactions>grade1, rituximab should be interrupted and the reaction treated with antihistamines, steroids and/or epinephrine. Following complete resolution of grade 1or 2 reactions, rituximab may be restarted at half the previous rate and re-escalated as above. For grade 3 or 4 hypersensitivity reactions, rituximab should be discontinued.

6.2.2 Dermatology Toxicity

In the instance of ≥ grade 3 erythema multiforme, remove patient from the protocol therapy.

6.3 Ancillary Therapy

Patients should receive full supportive care, including transfusion of blood and blood products, epoietin, antibiotics, antiemetics etc, when appropriate. The reasons for treatment, dosage and dates of treatment should be recorded.

6.3.1 Tumor Lysis Prophylaxis

Close monitoring for tumor lysis syndrome (TLS) should be initiated concurrently with the initiation of study treatment in Part I for all subjects. Subjects may receive tumor lysis prophylaxis if clinically indicated. All subjects should remain well hydrated during at least the first 7 days of Cycles 1. Close monitoring for TLS and the need for TLS prophylaxis should be repeated during at least the first 7 days of Part II of treatment (the first 7 days of Cycle 3). Additional TLS monitoring and prophylaxis may be employed at any time at the investigator's discretion.

Subjects who are felt to be at high risk for tumor lysis syndrome should receive prophylaxis with allopurinol. Other subjects should receive tumor lysis prophylaxis if clinically indicated. All subjects should be instructed to maintain adequate hydration and maintain urinary output. To maintain fluid intake, subjects should be instructed to drink 8 to 10 eight ounce glasses of water each day for at least the first 7 days of Cycle 1. Hydration levels should be adjusted according to age and clinical status, and lowered if the subject's cardiovascular status indicates the possibility of volume overload. Close monitoring for TLS and TLS prophylaxis (allopurinol, if possible, and oral hydration as above) should be repeated during at least the first 7 days of Part II treatment (the cycle including rituximab). Additional TLS monitoring and prophylaxis may be employed at any time at investigator discretion.

6.3.2 Tumor Flare Reaction

Tumor flare occurring during the first 1-2 weeks of Cycles 1, 2 and 3 should be recorded as AEs and not as progressive disease (PD). Tumor flare should be treated symptomatically with non-steroidal anti-inflammatory agents (NSAIDs) and other measures as needed.

6.3.3 Prophylactic Anti-coagulation

Lenalidomide increases the risk of thrombotic events in patients who are at high risk or with a history a thrombosis, in particular when combined with other drugs known to cause thrombosis. When lenalidomide is combined with other agents such as steroids (e.g. dexamethasone, prednisone), anthracyclines (Doxil, Adriamycin) and erythropoietin the risk of thrombosis is increased. Due to the known increased risk of thrombotic events associated with the combination of lenalidomide and dexamethasone subjects will receive aspirin (81 or 325 mg) or some other form of prophylaxis as deemed appropriate. Low molecular weight heparin may be utilized in patients that are intolerant to ASA. Coumadin should be used with caution and close monitoring of INR. Prophylactic anti-coagulation should be held for platelet counts < $50{,}000/mm^3$ and restarted when platelet counts are $\geq 50{,}000/mm^3$. Prophylactic anti-coagulation may be discontinued if dexamethasone is discontinued unless subjects are receiving erythropoietin.

6.3.4 Prohibited concomitant therapy

Concomitant use of sargramostim (GM-CSF), other anti-cancer therapies, including radiation, thalidomide, or other investigational agents is not permitted while subjects are receiving study drug during the treatment phase of the study.

7 Response Definition (see Appendix D + E)

7.1 Complete Response (CR)

7.1.1 Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all-disease related symptoms if present before therapy, and normalization of those biochemical abnormalities (e.g., lactate dehydrogenase [LDH] definitely assignable to NHL.

7.1.2 All lymph nodes and nodal masses must have regressed to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to ≤ 1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).

7.1.3 The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size. For instance, spleens thought to be of normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes. The determination of splenic volume or splenic index by CT scan is cumbersome and not widely used. Any macroscopic nodules in any organs detectable on imaging techniques should no longer be present. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.

7.1.4 If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site. The sample on which this determination is made must be adequate (>20 mm biopsy core). Flow cytometry, molecular, or cytogenetic studies are not considered part of routine assessment to document persistent disease at the present time.

7.2 Complete Response/Unconfirmed (Cru)

CR/unconfirmed (CRu) includes those subjects who fulfill criteria 1 and 3 above, but with one or more of the following features:

7.2.1 A residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.

7.2.2 Indeterminate bone marrow (increased number or size of aggregates without cytological or architectural atypia).

7.3 Partial Response (PR)

7.3.1 ≥50% decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features: (a) they should be clearly measurable in at least two perpendicular dimensions, (b) they should be from as disparate regions of the body as possible, and (c) they should also include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

7.3.2 No increase in the size of the other nodes, liver, or spleen.

7.3.3 Splenic and hepatic nodules must regress by at least 50% in the SPD.

7.3.4 With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.

7.3.5 Bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease; however, if positive, the cell type should be specified in the report, e.g., large-cell lymphoma or low-grade lymphoma (i.e., small, lymphocytic small cleaved, or mixed small and large cells.)

7.3.6 No new sites of disease.

7.4 Stable Disease (SD)

7.4.1 Stable disease is defined as less than a PR (see above) but is not progressive disease (see below).

7.5 Relapsed Disease (RD)

7.5.1 Appearance of any new lesion or increase by ≥50% in the size of previously involved sites. (only applies to subjects that achieve a CR).

7.5.2 ≥50% increase in greatest diameter of any previously identified node greater than 1 cm in its short axis or in the SPD of more than one node.

7.6 Progressive Disease (PD)

7.6.1 ≥50% increase from nadir in the SPD of any previously identified abnormal node for PRs or non-responders.

7.6.2 Appearance of any new lesion during or at the end of therapy which is >1.5 cm by radiologic evaluation or greater than 1 cm by physical examination.

7.7 Molecular Complete Response (MCR)

7.7.1 For subjects with clonal immunoglobulin heavy chain gene rearrangement, or Bcl2/IgH rearrangement by PCR, MCR will be defined as the inability to detect a previously detectable malignant clonal population of cells using a PCR-based assay on bone marrow and/or peripheral blood specimens.

7.8 Response Rates

7.8.1 ***Response to Lenalidomidewith and without Dexamethasone***: Response rate is defined as the percentage of subjects who attain complete response (CR), complete response unconfirmed (CRu), or partial response (PR) after two cycles of –study treatment (lenalidomide-dexamethasone for Cohort 1 subjects; lenalidomide monotherapy for Cohort 2 subjects. Subjects may be scored as having progressive disease (PD) after 2 cycles of –study treatment and will be removed from the study if the estimated life expectancy is < 3 months at that time. Following an intent-to-treat analysis plan, all subjects who receive one day of chemotherapy will be included in the denominator for this response rate.

7.8.2 ***Response to Lenalidomide + Rituximab with and without Dexamethasone:*** Response to lenalidomide plus rituximab with and without dexamethasone is defined as the percentage of subjects in complete remission (CR), complete remission unconfirmed (CRu), partial response (PR), or with stable disease (SD) at the 3 months post-rituximab evaluation. Only subjects who receive rituximab are included in the denominator for this secondary response rate.

7.9 Time to progression (TTP)

TTP is defined as the time from the first day of protocol therapy to the first event defining progression of disease or last subject contact. TTP is defined for all subjects receiving protocol therapy, following an intent-to-treat analysis plan. TTP from rituximab is defined for patients receiving rituximab (Part II) from the first day of rituximab therapy to the first event defining treatment failure.

7.10 Progression free survival (PFS)

PFS is defined as the time from first day of protocol therapy to disease progression, death due to any cause or last subject contact. PFS is defined for all subjects entered on the study, following an intent-to-treat analysis plan. A secondary analysis will also include a calculation of PFS from day of rituximab infusion.

7.11 Overall Survival (OS)

Overall survival is defined as the time from first day of protocol therapy to death due to any cause or last subject contact.

7.12 Safety evaluation

Data from all subjects who receive any study drug will be included in the safety analyses. Subjects who entered the study and did not take any of the study drug(s) and had this confirmed, will not be evaluated for safety.

The severity of the toxicities will be graded according to the NCI CTCAE v3.0 whenever possible.

8 Statistical Plan

Statistical design and analysis

Design. This study will enroll 45 evaluable subjects, all of whom have had lymphoma progression or failure to respond within six months of being treated with rituximab alone or with a rituximab-containing regimen. Twenty-five patients will be enrolled into Cohort 1, which will consist of daily dosing of lenalidomide and weekly dosing of dexamethasone. An additional twenty patients will be enrolled into Cohort 2, in which patients will receive daily dosing of lenalidomide, but will not be treated with weekly dexamethasone. Subjects with documented Rituxan-refractory disease will be enrolled to the study and treated for two 28-day cycles with lenalidomide – dexamethasone (Cohort 1) or lenalidomide alone (Cohort 2). After this first treatment period, termed Part I, subjects will be re-evaluated and subsequently treated with

lenalidomide – dexamethasone and rituximab (Cohort 1) or lenalidomide and rituximab (Cohort 2) in combination. A subject who does not complete rituximab therapy as part of this study will be considered non-evaluable and may be replaced by enrolling an additional subject. However, all subjects will be included in the intent-to-treat analysis.

Power to detect adverse effects. With 45 subjects, we will have 90% power to detect any unforeseen toxicity whose prevalence is at least 5.0%. The half-width of the confidence interval for any fraction (toxicity or response) will extend no more than +/- 15% around the estimate.

Treatment response. We will use McNemar's test to compare the fractions of patients responding to rituximab therapy without (baseline) and with revlimid. In the baseline period, we estimate that 10% of patients will have responded to rituximab, although all will ultimately fail within 6 months. Assuming a modest kappa (intra-subject correlation) of 10%, with 45 patients we have 87% power to detect a significant effect of revlimid treatment if the treatment-period response rate is 35%.

Time to progression. We will compute a 95% confidence interval for the ratio of median TTP under revlimid+rituximab to the median TTP under rituximab alone, using the nonparametric method of Jung and Su (1995). If the interval excludes 1, we will declare the difference to be statistically significant.

To evaluate the power of this design, we assumed that TTP in the baseline (rituximab only) period would be statistically independent of TTP in the follow-up (combination treatment) period. This will lead to a conservative estimate of the power, as positive correlation of failure-time endpoints generally increases power for paired comparisons (e.g., see Mick et al. 2000). Assuming that median TTP in the baseline period is 3 months, we calculated the power to detect significance in a test of the null hypothesis that median TTP is the same in both periods. If the median TTP in the follow-up period is doubled, to 6 months, then the power is 83%; if the median TTP is tripled, to 12 months, then the power is essentially 100%. Thus power is satisfactory if there is a substantial increase in the median TTP.

Design and analysis of correlative studies. In correlative studies, we will compare mean changes in immunologic phenotype parameters (fraction $Th2^+$ cells, NK cells and Treg cells) between the subjects who experience a remission (expected to be up to 80%, or 36 of 45 subjects) and those who do not (as few as 20%, or 9 of 45 subjects). As we do not yet know the likely values of these immunologic parameters, we estimate the power in terms of the difference in means as a fraction of the common standard deviation (SD). The basic analysis is a t test comparing mean change in the two groups. Calculations show that if the standardized difference is equal to 1 SD, then the power is 75%, whereas if the standard difference is 1.25 SDs, then the power is 91%. Thus the power of this correlative analysis is reasonable as long as there is a reasonably large difference in mean change between the remission and non-remission groups.

Analysis of serum albumin as a biomarker. We will test the hypotheses that 1) a decrease in serum albumin by $\geq$ 0.3 g/dL at commencement of cycle 2 from baseline predicts a response (CR/PR)to protocol therapy and that 2) a baseline serum albumin $\leq$ 4.1 g/dL predicts no response (SD/PD) to protocol therapy. From preliminary analysis of our first eleven patients, we will assume the same breakdown of responses (3 non-responders: 8 responders). Using this

assumption, we will have 80% power with a two-tailed alpha of 0.05 to detect an odds ratio of 2.6; this is 10 times less than expected.

9 Safety and Adverse Events

9.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening[1]
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity[2]
- a congenital anomaly or birth defect
- an important medical event[3]
- positive pregnancy

1 "Life-threatening" as defined by CTCAE Version 5.0.

2 "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

3 Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such 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. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

Note: Hematologic toxicities will not be captured as serious adverse events.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Unexpected adverse events

An adverse event related to therapy is considered unexpected (or unanticipated) if the event severity and/or frequency is not described in the investigator brochure and/or protocol.

Related adverse events

An adverse event is considered related to participation in the research if there is a reasonable possibility that an event was caused by an investigational product, intervention or research-required procedures. For the purposes of this study, "reasonable possibility" means there is evidence to suggest a causal relationship.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor (S. Schuster) of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor (S. Schuster) should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- All Grade 3 and 4 lab abnormalities not present at baseline should be captured as adverse events*.
- Any lab abnormality requiring clinical intervention or dose modification will also be captured as an adverse event*.

* This excludes lymphopenia.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

9.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All treatment-emergent adverse events occurring during the study period (after initiation of study treatment) must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

Toxicity will be scored using CTCAE Version 5.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP homepage (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

9.3 Reporting of Adverse Events

9.3.1 Pregnancies

Pregnancy of a female subject or the female partner of a male subject occurring while the subject is on lenalidomide or within 4 weeks after the subject's last dose of lenalidomide are considered expedited reportable events. If the subject is on lenalidomide, it is to be discontinued

immediately and the subject is to be instructed to return any unused portion of lenalidomide to the Investigator. The pregnancy must be reported to Celgene Corporation Worldwide Drug Safety Surveillance (WWDSS) within 24 hours of the Investigator's knowledge of the pregnancy by phone and facsimile using the SAE Form.

The Investigator will follow the pregnant female until completion of the pregnancy, and must notify Celgene Corporation Safety Surveillance of the outcome as specified below. The Investigator will provide this information as a follow-up to the initial SAE.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for Expedited Reporting of SAEs to Celgene (i.e., report the event to Celgene Corporation Drug Safety Surveillance by facsimile within 24 hours of the Investigator's knowledge of the event).

Any suspected fetal exposure to lenalidomide must be reported to Celgene within 24 hours of being made aware of the event. The pregnant female should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the in utero exposure to lenalidomide should also be reported.
In the case of a live "normal" birth, Celgene Corporation Drug Safety Surveillance should be advised as soon as the information is available.

Celgene Drug Safety Contact Information:
Celgene Corporation
Drug Safety Surveillance
86 Morris Avenue
Summit, N.J. 07901

Toll Free: (800)-640-7854
Phone: (908) 673-9667
Fax: (908) 673-9115
e-mail: drugsafety@celgene.com

9.3.2 Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment**.**

9.4 Reporting of Serious Adverse Events

9.4.1 Study Supporter Notification by Investigator

All serious adverse events must be reported to the study supporter, Celgene, by telephone or FAX within 24 hours of being aware of the event. A Serious Adverse Event (SAE) form on a FDA 3500A or MEDWATCH form with the Celgene Reference Number #RV-NHL-PI-296 must be completed by the investigator and faxed to the study supporter within 24 hours of being aware of the event. The initial report must be as complete as possible, including details of the causal relationship between the event and the investigational product(s) if available. 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 MEDWATCH. A final report to document resolution of the SAE is required. 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. Report serious adverse events by phone and facsimile to:

Celgene Corporation
Drug Safety Surveillance
86 Morris Avenue
Summit, N.J. 07901

Toll Free:	(800)-640-7854
Phone:	(908) 673-9667
Fax:	(908) 673-9115
e-mail:	drugsafety@celgene.com

At the time of the initial report, the following information should be provided:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following 48 hours, the investigator must provide further information to Celgene on the serious adverse event in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to Celgene.

9.4.2 DSMC /IRB Notification by Investigator

DSMC and IRB Notification:

Report events to local regulatory review committees per institutional requirements.

9.4.3 FDA Notification by Investigator

Adverse drug reactions that are **Serious, Unlisted/unexpected, and at least possibly associated to the drug,** and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) in writing. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

The investigator shall notify the FDA by telephone or by facsimile transmission of any adverse drug reactions that are **Serious, Unlisted/unexpected, and at least possibly associated to the drug,** including unexpected fatal or life-threatening experience associated with the use of the drug, as soon as possible but no later than 7 calendar days from the sponsor's (investigator's) original receipt of the information.

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor (investigator) will submit the adverse event in a written report to the FDA as soon as possible, but no later than 7 calendar days from the time the determination is made.

Each phone call or fax shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND if applicable.

9.4.4 Adverse event updates/IND safety reports

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 finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Events that are found to be unexpected and probably/definitely related, or that may pose significant risks to subjects, should be submitted to the IRB/CTSRMC within 10 working days of notification.

The Investigator must keep copies of all SAE information, including correspondence with Celgene and the IRB/DSMC, in the Study Regulatory Binder.

10 Data Handling and Record Keeping

10.1 Analyses and Reporting

Data will initially be analyzed and reported 3 months after the twenty-fifth patient completes dose four of rituximab. All subsequent data collected will be analyzed and reported in a follow-up clinical report.

10.2 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Celgene affirms the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws. Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

10.3 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

10.4 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be

printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

10.5 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement. In such an instance, it is the responsibility of the sponsor to inform the institution as to when these documents no longer need to be retained. The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

10.6 Exceptions and Deviations

Exceptions (prospective action):
An ***exception*** is defined as a one-time, unintentional action or process that departs from the IRB and CTSRMC approved study protocol, intended for one occurrence. If this action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects, advance documented approval from the local regulatory review committees, per institutional guidelines, is required. Exceptions will not be allowed unless reviewed and approved first by the Study Medical Monitor and the Study Principal Investigator, and then subsequently by the ACC DSMC, and IRB. Principal Investigator and Medical Monitor approval must be received first and included in with the IRB/DSMC submission. All entities should be given sufficient time to evaluate this request.

Deviation (retrospective action):
A ***deviation*** is defined as a one-time, unintentional action or process that departs from the approved study protocol, involving one incident and identified retrospectively. If the deviation disrupts study progress, such that the study design or outcomes may be compromised, or the deviation compromises the safety and/or welfare of study subjects, the deviation must be reported within 48 hours of PI knowledge to local regulatory review committees per institutional guidelines.
Reports should include the following information the following information:

- Protocol number
- Subject number
- Description of the exception or deviation
- Impact on subject safety
- Impact on data integrity

Deviations that are assessed by the PI to not disrupt the study progress, such as not affecting the study design or outcome, or compromising the safety and/or welfare of study subjects, should be documented in site records and contain documentation of the PI's assessment.

Reportable Deviations

Any accidental or unintentional deviation from the approved protocol, identified retrospectively, that in the opinion of the investigator or as defined by the protocol, placed one or more participants at increased risk, compromises the rights or welfare of subjects, and/or disrupts the study design, is considered a reportable event and must be reported to the Study Principal Investigator, Study Medical Monitor, IRB, and ACC DSMC within 10 working days of notification. Principal Investigator and Medical Monitor approval/acknowledgement must be received first and included in with the IRB/DSMC submission. Deviations to protect subjects from immediate harm/danger should be reported immediately following the event to the entities outlined above.

10.7 Protocol amendments

Any amendment to this protocol must be agreed to by the Principal Investigator and reviewed by Celgene. Amendments should only be submitted to IRB/EC after consideration of Celgene review. Written verification of IRB/EC approval will be obtained before any amendment is implemented.

10.8 Premature discontinuation of study

The responsible local clinical Investigator as well as Celgene have the right to discontinue this study at any time for reasonable medical or administrative reasons. Possible reasons for termination of the study could be but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality.
- Inaccurate or incomplete data collection.
- Falsification of records.
- Failure to adhere to the study protocol.

Any possible premature discontinuation would be documented adequately with reasons being stated, and information would have to be issued according to local requirements (e.g., IRB/EC, regulatory authorities, etc.).

11 Study Monitoring, Auditing, and Inspecting

11.1 Study Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. This will include a regular assessment of the number and type of serious adverse events.

The investigator will permit study-related monitoring, audits, and inspections by the DSMC, IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection

instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

This study will be audited by the Data and Safety Monitoring Committee (DSMC) six months from the first subject enrolled and every six month thereafter for the duration of the study. This schedule may be changed at the discretion of the DSMC. The study team will ensure all study related regulatory documents and subject charts are available and organized prior to the arrival of the auditor. Issues identified by the auditors will be addressed within 10 days of receipt of the letter of findings.

On-going Monitoring: During the course of the trial, safety and data quality monitoring will be performed in an on-going manner by the Research Nurse (Ellen Napier, CRNP) and the PI(Stephen Schuster). The PI will review all Adverse Events in "real-time" to ensure appropriateness of the data and timeliness of reporting. The PI will ensure that all amendments to the protocol and consent form are distributed to the IRB and CTSRMC prior to implementing any changes that may be required as a result of on-going monitoring. The PI will also ensure that all renewals are received in a timely manner and all IRB correspondences are maintained.

11.2 Medical Monitor

The Medical monitor for this study will be Adam Waxman M.D. Dr. Waxman is not directly involved in the trial and is not collaborating with the sponsor/investigator in any other trial. In this role, Adam Waxman, M.D. will review all AEs including grading, toxicity assignments, all other safety data and activity data observed at each dose level prior to escalating to the next dose. Adam Waxman, M.D. may recommend reporting of adverse events and relevant safety data not previously reported and may recommend suspension or termination of the trial. The Medical Monitor will be asked to review study data at least quarterly (every 3 months) or more frequently depending on enrollment.

11.3 Safety Monitoring

Interim analyses of toxicity are to be performed quarterly or every three patients on-study.

This investigator initiated protocol is considered high risk as per the Abramson Cancer Center Data and Safety Monitoring Plan. As such, high risk protocols are audited approximately six months from their first subject accrual and approximately every six month thereafter for the duration of the study. However, this schedule may be changed at the discretion of the DSMC. The PI will be notified in advance of the selection of their protocol for review and cases are randomly selected. A formal report is written to the PI by the DSMC. The committee may alter the frequency of re-monitoring based on the audit findings and degree of deficiencies. If an audit is unacceptable due to major deficiencies, representatives from the DSMC meet with the PI to discuss the findings of the audit and necessary corrective actions. If the deficiencies involve subject safety or serious regulatory violations, the Cancer Center Director, DSMC Chair, and DSMC Administrative Director will meet to discuss necessary actions concerning study status. The PI is given five business days to respond to these findings. An evaluation of the deficiencies will be re-evaluated upon receiving the PI's response. At this time, if the DSMC Chair and the

Administrative Director do not find the response satisfactory, the IRB and OHR will be alerted of the actions taken by the ACC.

Quarterly team meetings will also be held throughout the course of this study in order to discuss the protocol, ongoing patients, toxicity data, and recruitment issues.

11.4 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the supporter, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

The Investigator will permit study-related audits by Celgene or its representatives providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

The Investigator, or a designated member of the Investigator's staff, must be available at some time during audits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each visit and be made available to the Celgene representative so that the accuracy and completeness may be checked.

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Ethical Considerations

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the supporter before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the supporter.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent

form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent. Documentation of the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files.

13 Study Finances

13.1 Funding Source

The study and ancillary research will be in part funded through financial support from Celgene Corporation.

13.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study supporter prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

14 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the supporter for the purposes of performing the study, will be published or passed on to any third party without the consent of the study supporter. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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16 Appendix

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

Risks Associated with Pregnancy

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

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

Criteria for Females of Childbearing potential:

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

The investigator must ensure that:

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

Females of childbearing potential (FCBP)† must agree to use two reliable forms simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) during dose interruptions and 4) for at least 28 days after discontinuation from the study. The two methods of reliable contraception must include one highly effective method (i.e. intrauterine device (IUD), hormonal [birth control pills, injections, or implants], tubal ligation, partner's vasectomy) and one additional effective (barrier) method (i.e. latex condom, diaphragm, cervical cap). FCBP must be referred to a qualified provider of contraceptive methods if needed.

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective method listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

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

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 50 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting study drug:

Female Subjects:

- FCBP must have two negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to prescribing lenalidomide. The first pregnancy test must be performed within 10-14 days prior to prescribing lenalidomide and the second pregnancy test must be performed within 24 hours prior to prescribing lenalidomide (prescriptions must be filled within 7 days). The subject may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative.of contraception

Male Subjects:

- Must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy.

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

During study participation and for 28 days following discontinuation from the study:

All Subjects:

- If pregnancy or a positive pregnancy test does occur in a study subject or the partner of a male study subject during study participation, lenalidomide must be immediately discontinued.

Female Subjects:

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

Male Subjects:

- Must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy.

Additional precautions

- Patients should be instructed never to give lenalidomide to another person.
- Female patients should not donate blood during therapy and for at least 28 days following discontinuation of lenalidomide.
- Male patients should not donate blood, semen or sperm during therapy or for at least 28 days following discontinuation of lenalidomide.
- Only enough lenalidomide for one cycle of therapy may be prescribed with each cycle of therapy.

Appendix B: ECOG Performance Status Scale

SCORE	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, 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.

Appendix C: NCI CTCAE Version 5.0

Toxicity will be scored using NCI CTCAE Version 5.0 for toxicity and adverse event reporting. A copy of the NCI CTC Version 5.0 can be downloaded from the CTEP homepage: (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All appropriate treatment areas have access to a copy of the CTCAE Version

Appendix D: International Workshop Response Criteria (IWRC) for Non Hodgkin's Lymphoma

Complete Response (CR)

Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all-disease related symptoms if present before therapy, and normalization of those biochemical abnormalities (e.g., lactate dehydrogenase [LDH] definitely assignable to NHL.

All lymph nodes and nodal masses must have regressed to normal size (□1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to □1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).

The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have of the difficulties in accurately evaluating splenic and hepatic size. For instance, spleens thought to be of normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes. The determination of splenic volume or splenic index by CT scan is cumbersome and not widely used. Any macroscopic nodules in any organs detectable on imaging techniques should no longer be present. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.

If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site. The sample on which this determination is made must be adequate (>20 mm biopsy core). Flow cytometric, molecular, or cytogenetic studies are not considered part of routine assessment to document persistent disease at the present time.

Complete Response/Unconfirmed (Cru)

CR/unconfirmed (CRu) includes those subjects who fulfill criteria 1 and 3 above, but with one or more of the following features:

A residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.

Indeterminate bone marrow (increased number or size of aggregates without cytological or architectural atypia).

Partial Response (PR)

>50% decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features: (a) they should be clearly measurable in at least two perpendicular dimensions, (b) they should be from as disparate regions of the body as possible, and (c) they should also include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

No increase in the size of the other nodes, liver, or spleen.

Splenic and hepatic nodules must regress by at least 50% in the SPD.

With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.

Bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease; however, if positive, the cell type should be specified in the report, e.g., large-cell lymphoma or low-grade lymphoma (i.e., small, lymphocytic small cleaved, or mixed small and large cells.)

No new sites of disease.

Stable Disease (SD)

Stable disease is defined as less than a PR (see above) but is not progressive disease (see below).

Relapsed Disease (RD)

Appearance of any new lesion or increase by >50% in the size of previously involved sites. (only applies to subjects that achieve a CR).

>50% increase in greatest diameter of any previously identified node greater than 1 cm in its short axis or in the SPD of more than one node.

Progressive Disease (PD)

>50% increase from nadir in the SPD of any previously identified abnormal node for PRs or nonresponders.

Appearance of any new lesion during or at the end of therapy which is >1.5 cm by radiologic evaluation or greater than 1 cm by physical examination

Appendix E: Response Criteria for NHL

RESPONSE CRITERIA FOR LYMPHOMA

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	Normal	Normal	Normal	Normal
CRu	Normal	Normal	Normal	Indeterminate
	Normal	Normal	> 75% decrease	Normal or indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥ 50% decrease	≥ 50% decrease	Irrelevant
	Decrease in liver/spleen	≥ 50% decrease	≥ 50% decrease	Irrelevant
Relapse/ Progression	Enlarging liver/spleen, new sites	New or increased	New or increased	Reappearance

Appendix F: WHO classification of B-NHL

- Chronic lymphocytic leukemia/Small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia
- Splenic marginal zone lymphoma
- Plasma cell neoplasms
    - Plasma cell myeloma
    - Plasmacytoma
    - Monoclonal immunoglobulin deposition diseases
    - Heavy chain diseases
- Extranodal marginal zone B cell lymphoma (MALT lymphoma)
- Nodal marginal zone B cell lymphoma
- Follicular lymphoma
- Mantle cell lymphoma
- Diffuse large B cell lymphoma
- Mediastinal (thymic) large B cell lymphoma
- Intravascular large B cell lymphoma
- Primary effusion lymphoma
- Burkitt lymphoma/leukemia
- Lymphomatoid granulomatosis

Appendix G: Ann Arbor Staging System of Lymphoma

Stage I

Involvement of a single lymph node region (I) OR involvement of a single extra-lymphatic organ or site (IE).

Stage II

Involvement of two or more lymph node regions on the same side of the diaphragm (II) OR localized involvement of an extra-lymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (IIE).

Stage III

Involvement of lymph nodes regions on both sides of the diaphragm (III) which may also be accompanied by localized involvement of extra-lymphatic organ or site (IIIE) or by involvement of the spleen (IIIS) or both (IIISE).

Stage IV

Diffuse or disseminated involvement of one or more extra-lymphatic organs or tissues with or without associated lymph node involvement.

Identification of the presence or absence of symptoms should be noted with each stage designation:

A = asymptomatic

B = fever (>38°C), drenching night sweats, or weight loss greater than 10% of body weight