Phase II Study of Lenalidomide and Rituximab in Subjects with Previously Untreated Indolent Non Hodgkin's Lymphoma

STUDY DRUG		**Revlimid®, lenalidomide and Rituxan®, rituximab**
PROTOCOL NUMBER:		**UCDCC# 224** **Celgene # RV--NHL-PI-0488**
VERSION DATE:		**09/10/18**
AMENDMENT:		**16**
PROTOCOL HISTORY:		**4; 05/04/10** **5; 12/09/10** **6; 04/22/11** **7; 08/01/11** **8; 04/09/12** **9; 12/26/12** **10; 03/26/13** **11; 11/25/13** **12; 3/14/14** **13: 06/19/15** **14: 02/08/16** **15: 09/08/17**
IND:		**108,415**

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

_____
Signature of Site Principal Investigator

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Date

_____
Printed Name of Site Principal Investigator

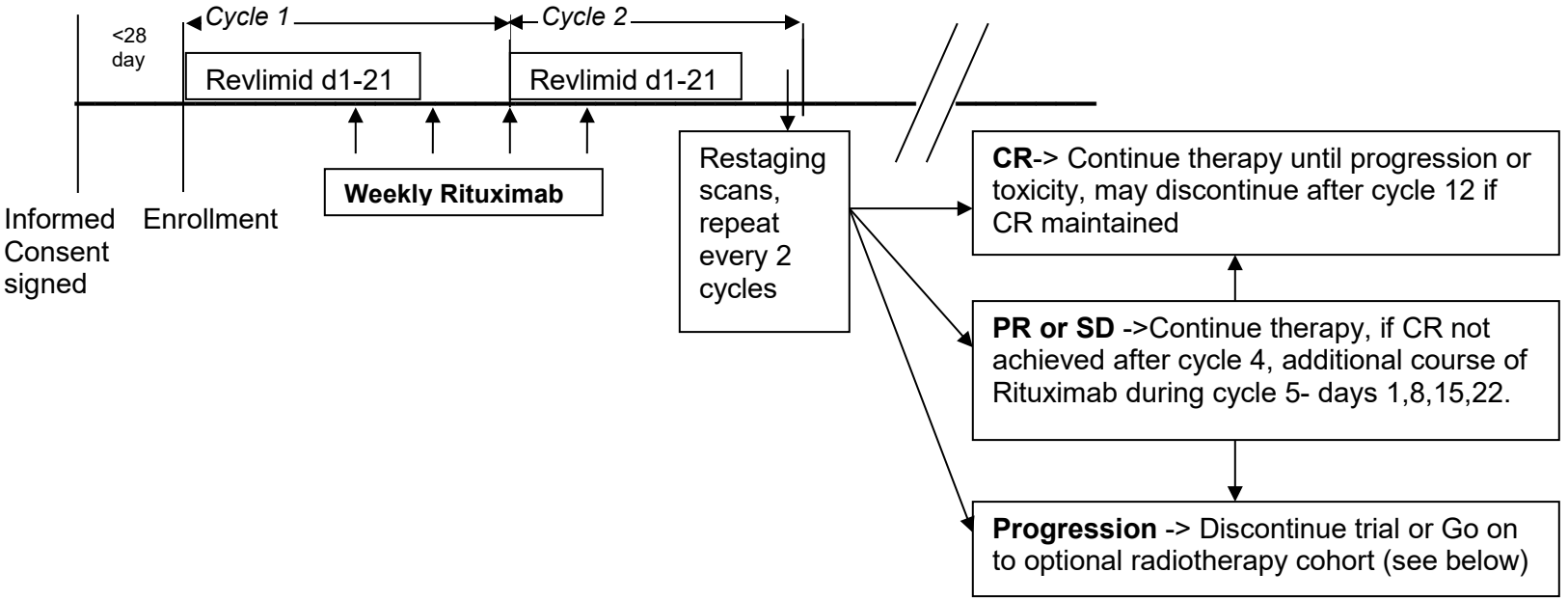
Institution Name: _____

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.

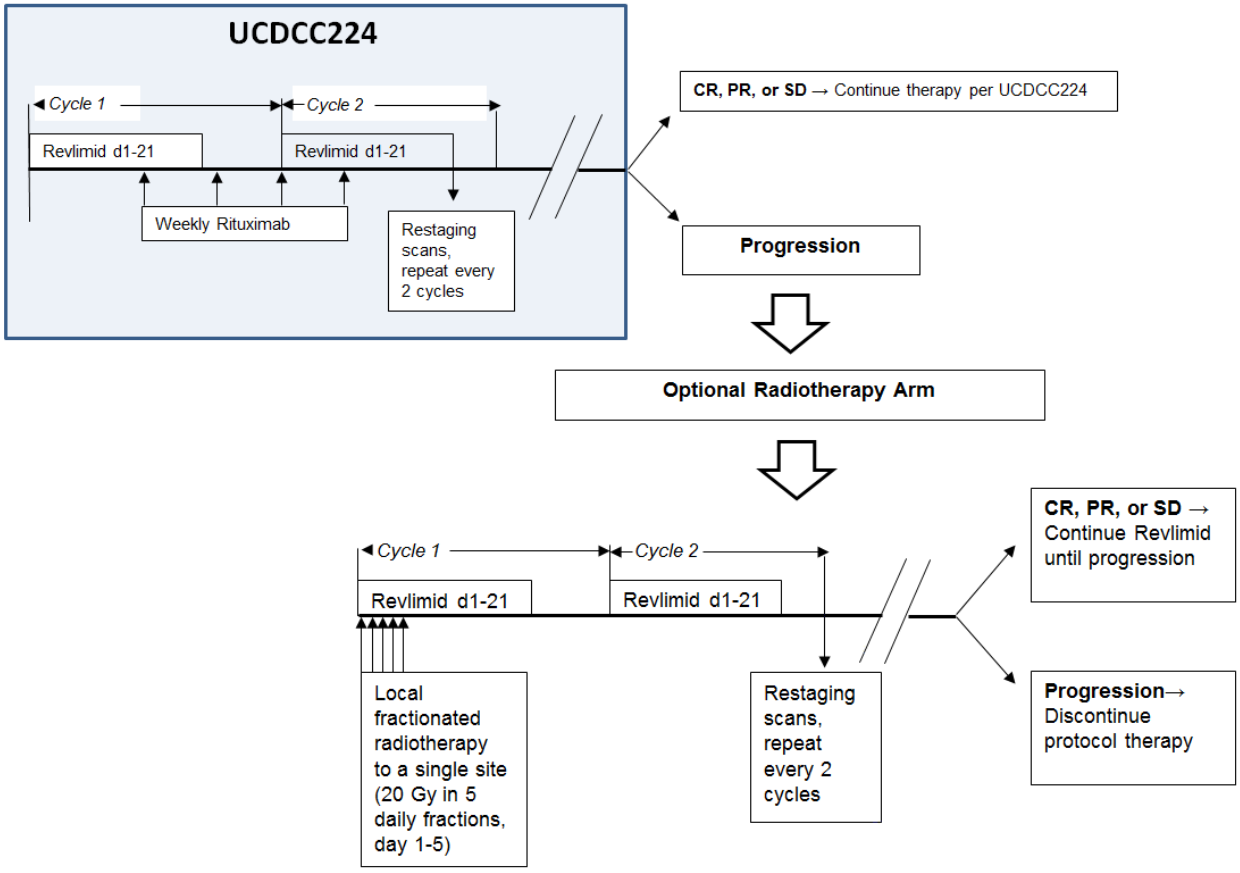
Supporter:	Celgene Corporation 86 Morris Ave, Summit, NJ 07901 1-800-742-3107
Coordinating Center:	University of California Davis Comprehensive Cancer Center Clinical Trials Support Unit (CTSU) 4501 X Street, Sacramento, CA 95817
Principal Investigator:	Joseph Tuscano, MD University of California, Davis (UCD) UC Davis Comprehensive Cancer Center [redacted]
Co-investigators:	Megan Daly, MD Robert O'Donnell, MD, PhD Carol Richman, MD Theodore Wun, MD Jeanna Welborn, MD Mrinal Dutia, MD Eric Dean, MD (Sutter)
Participating Center(s):	Sutter Pacific Medical Foundation Santa Rosa, CA 95403*
Statistician:	Laurel Beckett, PhD Professor and Chief, Division of Biostatistics Department of Public Health Sciences School of Medicine Division of Biostatistics, MS1C University of California, [redacted]

***Sutter Pacific Medical Foundation will not be participating in the optional radiotherapy cohort**

TRIAL DESIGN



Optional Radiotherapy Cohort



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1 Protocol Synopsis

PROTOCOL TITLE: Phase II study of Lenalidomide and Rituximab in Patients with Previously Untreated Indolent Non-Hodgkin's Lymphoma	
PROTOCOL NUMBER:	UCDCC# 224 Celgene # RV-NHL-PI-0488
DATE PROTOCOL FINAL:	05/04/10
STUDY DRUG:	Revlimid® (lenalidomide) and Rituximab
INDICATION:	Previously Untreated Indolent Lymphoma
STUDY PHASE:	Phase II

BACKGROUND AND RATIONALE:

Non-Hodgkin's lymphomas (NHL) are a very heterogeneous group of malignancies. Depending on their pathologic diagnosis, each subtype of NHL can behave differently. Indolent lymphomas are generally incurable with standard therapeutic approaches and typically have a chronic course with repeated relapses and progression despite therapy. There is no standard of care for patients with indolent lymphoma and no treatment approach has consistently demonstrated a survival advantage. In general, the treatment strategy is to monitor the patient closely and initiate therapy when there are indications. The majority of patients with NHL are elderly. In fact, the greatest increase in incidence of NHL is in the elderly male population over the past 20 years. There is little question that the magnitude and duration of response in patients who cannot maintain dose intensity or receive standard chemotherapeutics is often inferior. Therefore, development of regimens that are more tolerable and exploit unique and different mechanisms of action are needed.

Lenalidomide is currently approved by the FDA for multiple myeloma and myelodysplastic syndrome and is being studied in other hematological conditions including lymphomas. Although the exact anti-tumor mechanism of action of lenalidomide is unknown, a number of mechanisms are postulated to be responsible for lenalidomide's anti-tumor activity. In laboratory models, lenalidomide can enhance T- and NK-cell synapse formation with tumor B cells to enhance immune-mediated cytotoxicity. Lenalidomide has also been shown to reverse the impaired ability of T cells to form immunological synapses, a process that appears to be defective in lymphomas and leukemias. Lenalidomide also exerts antiproliferative activity via upregulation of tumor-suppressor genes (including p21 and SPARC) that results in G1 cell-cycle arrest, caspase activation, and apoptosis.

Multiple clinical studies have established that lenalidomide is a promising agent in the treatment of lymphomas. NHL-003 study by Czuczman et al evaluated the role of lenalidomide as monotherapy in 217 patients with relapsed/refractory aggressive Non-Hodgkin's Lymphoma. Among these, 50% patients had Diffuse large B cell Lymphoma, 26% Mantle Cell Lymphoma, 9% Follicular

Lymphoma Grade III, and 15% transformed lymphoma. The ORR for all 217 patients was 35%, with 13% complete response, 22% partial response, and 21% had stable disease. Responses were observed in all histological types. Median progression-free survival for all patients was 3.5 months and the median duration of response for the 77 responders was 11.6 months. The primary side effect of lenalidomide was reversible myelosuppression.

The efficacy and safety of lenalidomide was also shown in relapsed/refractory mantle cell lymphoma [3,4, 5]. Czuczman et al evaluated lenalidomide monotherapy with an overall response rate of 41%. Zaja et al studied lenalidomide in combination with dexamethasone, with a 50% overall response rate. Wang et al reported an overall response rate of 53% for the combination of lenalidomide with rituximab. These studies also demonstrated a favorable toxicity profile for lenalidomide and the combinations.

Rituximab has known clinical activity in patients with CLL and NHL. A monoclonal antibody directed against CD20 antigen on B-lymphocytes, rituximab binds to the antigen on the cell surface (activating complement-dependent cytotoxicity) and to human Fc receptors which mediates cell killing through an antibody-dependent cellular toxicity.

The rationale for combining these two agents originates from the hypothesis that enhancement of host immune effector mechanisms may augment the clinical efficacy of rituximab without significantly increasing toxicity. In fact, in animal models and human trials improved efficacy has been observed when various biologics have been combined with rituximab. The improved efficacy often correlated with various measures of host immune function including IL-2, IL-21, GM-CSF, and INF.

We at UC Davis have studied the combination of lenalidomide and rituximab in relapsed/ refractory indolent NHL, and it appears to be safe and active with an acceptable side effect profile. 16 patients have been enrolled as of December 2009. 10 of the 16 patients were considered heavily pre-treated, and 7 rituximab refractory. Overall response rate in a preliminary analysis was remarkable at 75%, with 31% CR and 44% PR [6]. The toxicity profile was safe, with the most common grade 3 and 4 events being fatigue, neutropenia and lymphopenia. The protocol was amended after two patients developed tumor lysis syndrome, to include tumor lysis prophylaxis with allopurinol and reducing the initial dose of lenalidomide from 25 to 20 mg. No additional patients developed tumor lysis after this modification.

Fowler et al also recently presented their data on front-line therapy of indolent B-cell non-Hodgkin's lymphoma with a combination of lenalidomide and rituximab. Patients received lenalidomide at a dose of 20 mg orally on days 1-21 and rituximab 375 mg/m2 IV on day 1 of each cycle, for up to 6 cycles of therapy. Among the 28 patients enrolled, overall response rate was 86%, with a complete response in 75%. The combination was well tolerated with the most common grade 3 and 4 adverse events being myalgia, neutropenia and rash.[7]

These results are encouraging and further studies are warranted to explore the combination of lenalidomide and rituximab in front-line treatment of previously untreated indolent lymphoma.

Radiotherapy is frequently employed as a treatment strategy for indolent lymphoma, either as curative intent therapy for early stage (I/II) disease, or a palliation for symptomatic advanced disease. Low grade lymphoma is typically exquisitely sensitive to radiotherapy, with palliative responses identified in high percentage of patients treated with doses as low as 4 Gy over 2 fractions [8-9]. Local radiotherapy is consistently well-tolerated in this patient population with low rates of grade 3+ toxicity [8].

Emerging clinical data suggest local radiotherapy may exhibit potent systemic immunomodulatory effects when delivered in combination with systemic immunotherapy agents, and in select cases may generate a systemic response (in non-radiotherapy target lesions) in patients previously refractory to immunotherapy alone. Case reports/series in melanoma patients describe impressive systemic effects following local radiotherapy in patients previously refractory to the immune checkpoint (CTLA-4) inhibitor ipilimumab [10-11]. Such effects are not well-studied yet for lenalidomide, However, lenalidomide is a potent immunomodulatory agent that exhibits both tumoricidal and anti-proliferative effects. There is evidence that lenalidomide may exert its antitumor effects by reversing the defective ability of T cells and NK cells to form synapses with malignant B cells thereby enhancing immune-mediated cytotoxicity. We hypothesize that in the presence of tumor antigens that are released as a result of local tumor irradiation, lenalidomide will mediate a response at distant sites in patients that were previously refractory to lenalidomide.

We propose employing this strategy in patients who progress on the combination of lenalidomide and rituximab. Patients will continue lenalidomide while undergoing local radiotherapy to a single site of disease, with re-staging every 2 months to assess for local and distant response. Lenalidomide will then be continued until disease progression.

1. Corral LF, Kaplan G et al. Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha. J Immunol. 1993;163:380-386.

2. Witzig T, Czuczman M, et al. Durable Responses After Lenalidomide Oral Monotherapy in Patients with Relapsed or Refractory (R/R) Aggressive Non-Hodgkin's Lymphoma (a-NHL): Results From An International Phase 2 Study (CC-5013-NHL-003)
Blood (ASH Annual Meeting Abstracts) 2009: Abstract 1676

3. Zaja F, Fanin R, et al. Salvage Treatment with Lenalidomide and Dexamethasone in Patients with Relapsed Refractory Mantle Cell Lymphoma. Blood (ASH Annual Meeting Abstracts) 2009: Abstract 1713

4. Wang L, Romaguera J et al. A Phase I/II Study of Lenalidomide in Combination with Rituximab in Relapsed/Refractory Mantle Cell Lymphoma. Blood (ASH Annual Meeting Abstracts) 2009: Abstract 2719.

5. Zinzani PL, Czuczman MS et al. Confirmation of the Efficacy and Safety of Lenalidomide Oral Monotherapy in Patients with Relapsed or Refractory Mantle-Cell Lymphoma: Results of An International Study (NHL-003) Blood (ASH Annual Meeting Abstracts) 2008 112: Abstract 262

6. Dutia M, Tuscano JM et al. R^2: Preliminary Results of a Phase II Study of Lenalidomide and Rituximab in Relapsed/Refractory Indolent Non-Hodgkin's Lymphoma (NHL) Blood (ASH Annual Meeting Abstracts) 2009: Abstract 1679

7. Fowler N, Sananeigo F et al. A Biologic Combination of Lenalidomide and Rituximab for Front-Line Therapy of Indolent B-Cell Non-Hodgkin's Lymphoma. Blood (ASH Annual Meeting Abstracts) 2009: Abstract 1714.

8. Hoskin, P.J., et al., *4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial.* Lancet Oncol, 2014. **15**(4): p. 457-63.

9. Rossier, C., et al., *Low-dose radiotherapy in indolent lymphoma.* Int J Radiat Oncol Biol Phys, 2011. **81**(3): p. e1-6.

10. Grimaldi, A.M., et al., *Abscopal effects of radiotherapy on advanced melanoma patients who progressed after ipilimumab immunotherapy.* Oncoimmunology, 2014. **3**: p. e28780.

11. Hiniker, S.M., D.S. Chen, and S.J. Knox, *Abscopal effect in a patient with melanoma.* N Engl J Med, 2012. **366**(21): p. 2035; author reply 2035-6.

STUDY OBJECTIVES:

Primary:

Response rate (overall and complete) to the combination of lenalidomide and rituximab in patients with previously untreated indolent Non-Hodgkin's Lymphoma.

Secondary:

Time to progression, safety, tolerability, duration of response, overall survival, cytokine profile changes.

Response rate (overall and complete) in non-target lesions following local radiation with concurrent lenalidomide in patients previously refractory to the combination of lenalidomide and rituximab.

STUDY DESIGN:

The study will be a multi-institution, phase II clinical trial in patients with previously untreated indolent Non-Hodgkin's lymphoma. Patients will receive lenalidomide 20 mg daily, on days 1-21 of a 28 day cycle. Rituximab 375 mg/m2 will be administered weekly for 4 doses starting day 15 of cycle 1, to be repeated if patient does not achieve a complete response after cycle 4, on days 1, 8, 15 and 22 of cycle 5. Therapy with lenalidomide may be discontinued after twelve cycles if the patient achieves a complete response.

Patients progressing on lenalidomide and rituximab will be offered treatment in a radiotherapy cohort. Patients will continue lenalidomide at the current dose, on days 1-21 of a 28 day cycle. Local fractionated radiotherapy will be delivered to a single site of disease days 1-5 of a 28 day

cycle to 20 Gy in 4 Gy fractions. Re-staging will be performed every 2 months, and lenalidomide will be continued until disease progression or intolerance.

STUDY ENDPOINTS:

Primary:

Complete response (CR), near complete response (CRu), or partial response (PR), stable disease (SD) of 4 months.

Secondary:

Time to disease progression, tolerability, duration of response, overall survival, and tumor control rate from the start of treatment.

Measurement of immune profile

STUDY DURATION:	**TOTAL SAMPLE SIZE:**
Patients will be enrolled over 2yrs.	Approximately 30 patients Of the 30 total patients 10 progressing patients will be offered optional treatment on the radiotherapy arm
DOSING REGIMEN(S):	**STUDY DRUG SUPPLIES:**
Lenalidomide will be initiated at 20 mg daily, days 1-21 of a 28 day cycle, to be continued until disease progression, unacceptable toxicity or after twelve cycles if the patient has achieved a complete response. Rituximab 375 mg/m2/wk x 4 weeks, to begin Day 15 of cycle 1. After 4 cycles of therapy if patient does not achieve CR, the patient will receive a second course of Rituximab. Blood samples for companion study to assess immune profiles will be obtained within 1 week prior to starting treatment & then on days 15, 30, 60 and 120, and then at the end of treatment or when treatment is discontinued for any reason. Additional blood draws for immunologic profiling at day 15, 30 after starting radiation therapy and at the time of progression for patients taking part in the additional radiation therapy cohort. If the patient progresses within 8 weeks, the blood draw	Celgene Corporation will supply lenalidomide as 5 mg capsules.

at progression will not be done. After progression: Lenalidomide will be continued at the current dose, days 1-21 of a 28 day cycle. Radiotherapy will be delivered in a single course of 20 Gy in 5 daily fractions of 4 Gy each, day 1-5 of a 28 day cycle. Lenalidomide will be continued until disease progression, unacceptable toxicity or after twelve cycles if the patient has achieved a complete response.	

2 Schedule of Study Assessments

Procedure	Screening ≤ 28days from Baseline (First day study drug administration)	Cycle 1				Cycle 2		All other cycles	At Progression[18]	Discontinuation From Study Drug	Follow-Up Phase	Post-Progression Radiation[19]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 1			Every 3 months	
Record prior medications, treatments	X											
Record prior anti-cancer therapies	X											
Physical examination, vital signs, weight	X					X		X[13]	X	X		X
ECOG performance status	X					X		X[13]	X	X		X
CT/PET[14] or CT of the chest & abdomen / pelvis (as clinically indicated)	X[1]	*Repeat every 8 weeks while receiving treatment*[7]								X		X[20]
Bone scan [2] (as clinically indicated)	X[2]											
Bone marrow Biopsy and aspirate	X[8]											
Colonoscopy and Bx (as clinically indicated)	X[8]											
CT or MRI of the brain (as clinically indicated)	X[3]											
ECG	X											
Hematology (Blood counts)	X		X	X	X	X		X[13]	X	X		X
Serum chemistry and tumor lysis labs[4] (Note: TSH measured as clinically indicated)	X	X/X	X/X	X/X	X/X	X		X[4, 13]	X	X[4]		X
Immune profile[10]	X	X/X		X/X				X[10]	X	X		X[22]
Peripheral blood PCR for t(14,18)[16] (as clinically indicated)	X							X[16]	X			X
Pregnancy test [5]	X[6]		X	X	X	X[6]		X[6,13]		X[6]		
HIV test[17]	X											
Hepatitis B tests	X											
Register patient into Revlimid	X											

Procedure	Screening ≤ 28days from Baseline (First day study drug administration)	Cycle 1				Cycle 2		All other cycles	At Progression[18]	Discontinuation From Study Drug	Follow-Up Phase	Post-Progression Radiation[19]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 1			Every 3 months	
REMS™ program												
Baseline lesion assessment	X											
Allopurinol for tumor lysis prophylaxis [15]	X [15]	X	X	X	X							
Prescribe lenalidomide via Revlimid REMS™ [11]		X[11]				X[11]		X[11]		X		
Rituximab administration [9]				X	X	X [9]	X[9]					
Response assessment [7]						X [7,8]		X [7,8]		X [7,8]		X[21]
Record adverse events [12]				X	X	X	X	X		X[12]		X
Record concomitant therapies/procedures				X	X	X	X	X		X		X
Perform drug accountability						X		X				X
Obtain Follow-Up anti-cancer treatments											X	
Obtain Follow-Up survival information											X	
The patient will be offered local XRT[18]										X		

Study visits and procedures may be scheduled +/- 3 days window except for screening and cycle one.

[1] CT/PET will performed at screening, every 8 weeks while on treatment and at the end of treatment. After 50 cycles, scans will be done only at investigator discretion.

[2] If subject had previously positive bone scan or if symptoms suggest metastases.

[3] If symptoms raise suspicion of CNS lesions.

[4] To include Total protein, albumin, calcium, Alk Phos, LDH, SGPT, SGOT, Bun, Cr, glucose, Na, K, Cl, Co2 uric acid, total Bili. Tumor lysis labs: Basic Metabolic Panel, LDH, and uric acid, phosphorus all to be monitored twice a week for the 1st cycle. Thyroid Stimulating Hormone (TSH) at Screening, end of Cycle 3 and every three months thereafter.

[5] 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).

[6] Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to initiation of lenalidomide. Once treatment has started and during dose interruptions, pregnancy testing for females of childbearing potential should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles, at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix I: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods). Pregnancy

Procedure	Screening ≤ 28days from Baseline (First day study drug administration)	Cycle 1				Cycle 2		All other cycles	At Progression[18]	Discontinuation From Study Drug	Follow-Up Phase	Post-Progression Radiation[19]
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 1			Every 3 months	

testing and counseling should be performed if a patient misses her period or if there is any abnormality in her pregnancy test or in her menstrual bleeding.
[7] Complete after every 2 cycles. All PRs and CRs must be confirmed by repeat scans no less than 4 weeks after the criteria for response are first met. Timing of alternate cycle efficacy assessments will be reset following a confirmation or response assessment. After CR is confirmed scans may be repeated every four cycles. If the subject is in remission for more than 1 year then follow-up will be every four months unless there are clinical indications.
[8]Repeat all evaluations necessary to document known (+ at baseline) or suspected sites of disease.
[9]Rituximab administration four weekly doses days 15, 22 of cycle 1 and days 1 and 8 of cycle 2. To be repeated for 4 weekly doses if no CR attained post cycle 4.
[10] For patient providing consent. Blood samples for companion study to assess immune profiles will be obtained within 1 week prior to starting treatment, on days 15, 30, 60 and 120, and then at the end of treatment or when treatment is discontinued for any reason. See section 11.5
[11] Lenalidomide must be prescribed through and in compliance with the Revlimid REMS™ program. 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 UC Davis pharmacy or participating site's pharmacy that will dispose the drug to the patient. Any unused Revlimid® (lenalidomide) should be returned to the pharmacy for disposition in accordance with the Revlimid REMS™ program
[12] An additional safety assessment will be done 30 days (+/- 2 days) following the last dose of study drug.
[13] Results must be available prior to initiation of cycle, thus procedures should be ordered to ensure results are available on day 1. Procedures may be done up to 3 days before day 1.
[14]If PET/CT is ordered, CT scan must be of "diagnostic" quality in order to allow radiology to provide tumor measurements for response assessment by IWGR criteria.
[15] Tumor lysis prophylaxis with allopurinol starting 24 hours before treatment & then continued daily for the first cycle
[16] Peripheral blood will be tested for quantitative PCR to detect t(14,18) prior to starting the study, as part of the correlative studies for patients providing consent. If positive, this will be repeated if patient achieves a CR with labs every cycle thereafter.
[17] If HIV status is unknown.
[18.] At the time of progression the patient will be offered local radiation therapy and continued treatment with the most recent dose of lenalidomide (section 5.3 and 6.5)
[19] Optional radiation therapy phase at the time of progression. Patients have 4 weeks from the time of progression to start radiation. Lenalidomide will be continued throughout.
[20] CT or PET/CT will be done to document progression and repeated 2 months after completion of radiation therapy. Re-imaging will continue every 2 months until CR or progression
[21] Response assessment will be every 2 months until progression or CR
[22] Additional blood draws for immunologic profiling at day 15, 30 after starting radiation therapy and at the time of progression for patients taking part in the additional radiation therapy cohort. See section 11.5. If the patient progresses within 8 weeks, the blood draw at progression will not be done.

3 Glossary of Abbreviations

AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CR	Complete response
CRF	Case report form
CRu	Complete response unconfirmed
CT	Computed tomography
CTC	Common toxicity criteria
DMC	Data Monitoring Committee
DTIC	Dacarbazine
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMEA	European Agency for Evaluation of Medicinal Products
FDA	Food and Drug Administration
G-CSF	Granulocyte colony stimulating factor, filgrastim (Neupogen)
GM-CSF	Granulocyte/macrophage colony stimulating factor, sargramostim, (Leukine, Prokine)
GCP	Good clinical practice
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IFN	Interferon
IL-2	Interleukin-2
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
IWGRC	International Working Group Response Criteria
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
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
OS	Overall survival
PD	Progressive disease
PR	Partial response
RBC	Red blood cell (count)
RR	Response rate
SAE	Serious adverse event
SD	Stable disease
TCR	Tumor control rate
TPP	Therapeutics Product Program
TSH	Thyroid stimulating hormone
TTP	Time to progression
WBC	White blood cell (count)
WCBP	Women of child bearing potential
WHO	World Health Organization

4 Background and Rationale

4.1 Introduction

Despite the availability of multiple therapeutic modalities and a high response rate to initial therapy, most patients with low grade non-Hodgkin lymphoma (NHL) will develop recurrent or refractory disease and most ultimately die from lymphoma-related complications. Chemotherapy and radiation therapy have clearly provided benefit to patients with these disorders. It is evident, however, that these agents are limited in their potential for cure of patients with indolent lymphoma, and thus new approaches are under investigation. The monoclonal antibody rituximab (directed against the B-cell antigen CD20) has been shown to be useful in the treatment of relapsed patients with low grade NHL for which it received Food and Drug Administration (FDA) approval. In a pivotal trial of 166 patients with relapsed low grade NHL, a response rate of 48% was observed (approximately 60% in the follicular histologies), with a median time to progression (TTP) of 12 months in responders. 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 retreatment, with median TTP of about 18 months after the second administration. Subsequent studies of rituximab have evaluated its utility as a single agent in various other subtypes of NHL, such as diffuse large B-cell and mantle cell, as well as in combination with numerous chemotherapy regimens. Rituximab has been widely adopted by oncologists as a well-tolerated and active agent in NHL, and most lymphoma patients receive it at some point in their course either as a single agent, or in combination with chemotherapy.

Current research directions include ways of enhancing the activity of rituximab. In addition to chemotherapy, numerous “biologic” agents are under development and are being evaluated in combination with rituximab in order to explore the possibility of synergistic activity. These include cytokines (interferon, IL-2, GM-CSF), other antibodies (epratuzumab or anti-CD22, anti-CD80, and Hu1D10 or anti-HLA-DR) and Bcl-2 antisense. Phase I or II trials with these agents in combination with rituximab have been developed, and in some cases have demonstrated promising initial results. These combination regimens are particularly attractive to patients and clinicians who wish to avoid toxicities more typically associated with chemotherapy, and offer alternative mechanisms of action against chemotherapy-resistant disease.

One agent which has been shown to augment the activity of rituximab in NHL is lenalidomide (Revlimid®). It is a potent thalidomide derivative with immunomodulatory activity including stimulation of T cell proliferation as well as production of IL-2 and interferon-gamma in addition to other cytokines. Phase I trials with doses up to 50 mg/day have been conducted in multiple myeloma and myelodysplastic syndrome (MDS). The maximum tolerated dose has been determined to be in the range of 25 mg/day administered orally, with dose-limiting toxicity principally myelosuppression. Grade 1-2 scalp pruritus, diarrhea and urticaria have also been noted, while symptoms of constipation, somnolence and neuropathy as associated

with thalidomide are generally not observed. This dose has achieved concentrations associated with modulation of cytokine production *in vitro*, and has provided clinical responses in both myeloma and MDS. Regimens with 21 days of treatment cycled every 28 days have been associated with less myelosuppression. Lenalidomide has activity against lymphoid cell lines *in vitro*, and xenograft studies using Raji lymphoma cell lines in SCID mice have demonstrated that the addition of lenalidomide to rituximab augments anti-tumor effects. These preclinical studies provide evidence that the combination of lenalidomide and rituximab warrants further evaluation in NHL. The favorable toxicity profile of rituximab does not overlap with lenalidomide, and suggests that they can be safely employed together (with appropriate dose modification guidelines for lenalidomide, if necessary). Preclinical studies, as well as several clinical trials in B cell malignancies, suggest that not only may lenalidomide augment the activity of rituximab. Given the importance of rituximab and the promise of rituximab-based combinations in indolent lymphoma, rational assessment of these regimens in a series of studies is a priority. We have an ongoing clinical trial studying the combination of lenalidomide and rituximab in relapsed/ refractory indolent NHL. In this a Phase II trial, and the combination appears to be safe and active with an acceptable side effect profile. The preliminary results from this study have been encouraging and hence this therapy is being tested as upfront treatment of indolent NHL.

Lenalidomide belongs to a proprietary class of Celgene compounds called IMiDs®. IMiDs®, of which thalidomide is the parent compound, have both immunomodulatory and anti-angiogenic properties which could confer antitumor and antimetastatic effects. Lenalidomide has been demonstrated to possess anti-angiogenic activity through inhibition of bFGF, VEGF and TNF-alpha induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF [1]. Lenalidomide stimulates T cell proliferation, and the production of IL-2, IL-10 and IFN-gamma, inhibits IL-1 beta and IL-6 and modulates IL-12 production [2].[0] Upregulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity [3]. In laboratory models, lenalidomide can enhance T- and NK-cell synapse formation with tumor B cells to enhance immune-mediated cytotoxicity. Lenalidomide has also been shown to reverse the impaired ability of T cells to form immunological synapses, a process that appears to be defective in lymphomas and leukemias. Lenalidomide also exerts antiproliferative activity via upregulation of tumor-suppressor genes (including p21 and SPARC) that results in G1 cell-cycle arrest, caspase activation, and apoptosis. To date, lenalidomide has been evaluated in multiple malignant cell types, both solid and hematologic tumors. Significant activity has been demonstrated in multiple myeloma and myelodysplastic syndrome. There are some early clinical studies confirming the activity of lenalidomide in other hematologic malignancies including non-Hodgkin's lymphoma[4].

Rituximab is a monoclonal antibody directed towards CD20, a receptor found on B-cells. It has shown clinical activity, both as a single agent and in combination with chemotherapy, in multiple B-cell based malignancies. Rituximab binds to the antigen on the cell surface (activating complement-dependent cytotoxicity) and to human Fc receptors which mediates cell killing through an antibody-dependent cellular toxicity.

Radiotherapy is commonly employed in both the definitive and palliative management of indolent lymphoma. Stage I/II indolent NHL may be treated with modest doses of radiotherapy alone or with rituximab with curative intent [5, 6], which palliative radiotherapy is frequently used in advanced symptomatic indolent NHL with high rates of response. Due to the exquisite sensitive of indolent NHL to radiotherapy, modest doses ranging from 4-30 Gy with conventional fractionation are successfully used [7, 8]. Depending on the field toxicity from local radiotherapy for indolent NHL is typically quite minimal [8].

4.2 Correlative Studies

The biological effects of the thalidomide derivatives, lenalidomide and CC-4047 (IMiDs®) have been shown to be up to 10,000 times more potent than thalidomide. The biological effects of IMiDs® are presumed to be mediated by: (1) activation of some components of the innate (e.g., NK cells) or adoptive immune system (e.g., T-cells), (2) modification of the cytokine micro-environment of the tumor bed, or (3) inhibition of angiogenesis. Laboratory studies using lenalidomide demonstrated inhibition of DNA synthesis of NHL cell lines). In addition, treatment of lymphoma-bearing SCID mice with a combination of rituximab + IMiDs® demonstrated augmented/synergistic anti-tumor activity compared to monotherapy of either agent alone. This synergistic activity has been hypothesized to be attributed to NK cell activation and expansion as well as changes in the cytokine milieu. Based on this hypothesis we propose to assay PBMC and plasma samples pre-, during and post- therapy by various immune assays (please see correlative studies section 11.6) in an attempt to correlate anti-tumor activity to lenalidomide associated immunomodulatory effects.

Additionally, peripheral blood samples will be tested for quantitative polymerase chain reaction (q-PCR) analysis for t(14;18) (q32;q21) translocation, which juxtaposes the bcl-2 oncogene on chromosome 18 and the JH segment of the immunoglobulin heavy chain (IgH) genes on chromosome 14. This is found frequently in follicular lymphomas and has been shown to predict treatment response and long-term clinical outcome of patients with FL. [9]

4.3 Clinical experience with lenalidomide in solid tumors

Twenty patients with varying types of solid tumors (13 with malignant melanoma, 2 each with carcinoma of the pancreas and non-small-cell lung cancer [NSCLC], 1 each with renal carcinoma, breast carcinoma, and carcinoid-unknown primary) were enrolled in a Phase 1 study of lenalidomide conducted at the St. George Hospital, London, UK. This was a non-randomized, open-label with-in patient dose-escalation design, where patients started on 5 mg/day for 7 days and then increased their dose every 7 days to 10 mg/day, 25 mg/day, and 50 mg/day for a total of 4 weeks on therapy [10].

Investigators at the NCI have enrolled 20 patients, including 18 patients with recurrent high-grade gliomas and 2 with other refractory CNS malignancies (1 recurrent atypical meningioma and 1 multiple recurrent spinal hemangioblastomas) into a phase I trial of lenalidomide given on Days 1 through 21 every 28 days. Treatment has been well tolerated with 1 grade 2 myelosuppression as the only toxicity > grade 1 [11].

In an ongoing phase I trial in patients with refractory metastatic cancer conducted through the NCI, 12 patients with metastatic androgen independent prostate cancer have been enrolled. Lenalidomide was administered in daily doses of 5mg (3 patients), 10mg (3 patients) and 20mg (6 patients). Dose limiting toxicity was seen at 20mg/day (1 grade 3 thrombosis and 1 grade 3 hypotension). Stable PSA values for at least 8 weeks were observed in 6 patients [12].

In a phase III, multi-center, randomized parallel group study comparing two dose regimens of lenalidomide, 293 patients with malignant melanoma were enrolled. Subjects were randomized to receive treatment with lenalidomide at a dose of 5 mg per day orally for 28 days or to 25 mg per day orally for 21 days with a 7 day rest (28 day cycle). Treatment continued until the patient developed disease progression or intolerable adverse events occurred. Interim analysis failed to show an advantage of one regimen over the other with respect to survival. Analyses of response rates are pending. The toxicity profile was similar in both dose groups and the most frequent adverse events were fatigue, seen in 32% of patients, followed by nausea and diarrhea, seen in 24% and 20% of patients respectively. Neutropenia and thrombocytopenia were seen in 2.4% and 2.0% of patients respectively. Grade 3 and 4 toxicities were seen infrequently (<15%).

A second phase III randomized trial compared a lenalidomide dose of 25 mg daily orally for 21 days with a 7 day rest (28 day cycle) to placebo in patients with metastatic melanoma. Three hundred and five patients enrolled on this study and a preplanned interim analysis failed to demonstrate a survival advantage. Response rates are being analyzed. The toxicity profile was favorable and similar to the previous phase III study [13].

4.4 Clinical experience in multiple myeloma with lenalidomide

In 2 phase I studies in multiple myeloma, a total of 41 patients have been treated with lenalidomide. In one study at the University of Arkansas, 15 patients who relapsed or were refractory to high dose melphalan therapy with stem cell transplant were treated for 4 weeks in an open-label safety study and were permitted to continue therapy in an extension phase of the trial. Patient cohorts were treated at the following daily doses: 5mg, 10mg, 25mg, and 50mg [(12)]. In a similar study at the Dana Farber Cancer Institute, 27 patients with rapidly advancing refractory multiple myeloma were enrolled [14].

Anti-myeloma activity was observed in each of these 2 phase I studies. Decreases in neutrophil and platelet counts were the dose-limiting toxicities associated with lenalidomide. The maximum tolerated dose (MTD) was not reached within 28 days. Due to dose modifications associated with myelosuppression observed beyond Day 28 at the 25mg and 50mg daily dose levels, the dose schedule most widely used in future studies has been lenalidomide 25 mg on Days 1-21, repeated every 28 days.

Pharmacokinetic analyses were performed on 15 multiple myeloma patients treated in the phase I studies. Absorption was found to be rapid on both Day 1 and Day 28 with time to maximum blood levels ranging from 0.7 to 2.0 hours at all dose levels (5mg, 10mg, 25mg, and 50mg). Plasma lenalidomide declined in a monophasic manner with elimination half-life ranging from 2.8 to 6.1 hours on both Day 1 and 28 at all 4 doses. No plasma accumulation was observed with multiple daily dosing. Peak and overall plasma concentrations were dose proportional over the dosing range of 5mg to 50mg [15].

A multicenter, randomized, phase II trial compared 2 syncopated dose schedules of lenalidomide used alone or in combination with dexamethasone in the treatment of relapsed or refractory multiple myeloma. All patients were treated on Days 1-21 of a 28-day cycle. Patients treated with 15mg BID experienced more myelosuppression and dose reductions compared with patients treated with 30mg daily. Anti-myeloma activity was observed with each dose and schedule of single agent lenalidomide. The addition of dexamethasone to lenalidomide yielded responses in some patients who had not responded to lenalidomide alone [16].

A recent phase II trial utilizing lenalidomide plus dexamethasone for newly diagnosed multiple myeloma patients was recently reported by the Mayo Clinic. Lenalidomide was given orally 25 mg daily on days 1-21 of a 28-day cycle. Dexamethasone was given orally 40 mg daily on days 1-4, 9-12, 17-20 of each cycle. Objective response was defined as a decrease in serum monoclonal protein by 50% or greater and a decrease in urine M protein by at least 90% or to a level less than 200 mg/24 hours, confirmed by two consecutive determinations at least 4 weeks apart. Thirty-one of 34 patients achieved an objective response, including 2 (6%) achieving complete response (CR), and 11 (32%) meeting criteria for both very good partial response and near complete response, resulting in an overall objective response rate of 91%. Of the 3 remaining patients not achieving an objective response, two had minor response (MR) and one stable disease. Forty-seven percent of patients experienced grade 3 or higher non-hematologic toxicity, most commonly fatigue (15%), muscle weakness (6%), anxiety (6%), pneumonitis (6%) and rash (6%). Rev/Dex is a highly active regimen with manageable side-effects in the treatment of newly diagnosed myeloma [17].

A phase I/II trial of Liposomal doxorubicin (Doxil®), vincristine, dexamethasone (DVd) and lenalidomide in heavily pretreated relapsed/refractory multiple myeloma patients is ongoing. The MTD of lenalidomide was 10mg on Days 1-21 in combination with Doxil® 40mg/m2 IVPB on Day 1, vincristine 2mg IVP on Day 1 and dexamethasone 40mg PO on Days 1-4 cycled every 28 days. All patients received amoxicillin, acyclovir and aspirin 81mg prophylactically. The dose limiting toxicity with lenalidomide 15mg on Days 1-21 in combination with DVd was sepsis/septic shock [18]. Additional phase I trials of lenalidomide with chemotherapy in advanced malignancies are in progress.

There have been 2 multicenter, randomized, double-blinded, placebo-controlled phase III trials [1 U.S. (MM-009) and 1 international (MM-010)] in patients with relapsed or refractory multiple myeloma [19]. More than 350 patients were enrolled into each of these studies. All patients had to be considered sensitive to dexamethasone and were treated with dexamethasone 40mg qd, Days 1-4, 9-12 and 17-20. In addition to receiving dexamethasone, patients were randomized to lenalidomide 25mg qd or placebo, Days 1-21. Cycles were repeated every 28 days. After 4 cycles, there was a predetermined reduction of the dexamethasone dose to 40mg qd, Days 1-4 repeated every 28 days. In both studies, a pre-specified interim analysis conducted by an Independent Data Monitoring Committee demonstrated that subjects receiving the combination of lenalidomide (Len) plus dexamethasone (Dex) had significantly longer times to progression and higher response rates than those treated with single-agent dexamethasone**.**

	MM-009 Len/Dex	MM-010 Len/Dex	MM-009 Placebo/Dex	MM-010 Placebo/Dex	
CR+PR (%)	61.2	58.0	22.8	21.7	P < 0.001
CR (%)	26.5	13.6	4.1	4.0	
PR (%)	34.7	44.3	18.7	17.7	
SD (%)	28.2	33.5	57.9	64.6	
PD (%)	2.9	2.8	12.3	7.4	
Median TTP (mos)	15.0	13.3	5.1	5.1	P <0.000001

4.5 Clinical experience in myelodysplastic syndromes (MDS) with lenalidomide

An exploratory trial in 43 MDS patients with transfusion dependent or symptomatic anemia was conducted at the University of Arizona [20]. Patients received lenalidomide at doses of 25mg or 10mg per day, or of 10mg on Days 1-21, repeated every 28 days. All patients had had no response to erythropoietin or had a high endogenous erythropoietin level. Response rates were similar across the 3 dose schedules used. Responses were observed in 24 patients overall (56%) including 21 patients with a major response and 20 patients with sustained transfusion independence. Patients with a major response reached a median hemoglobin level of 13.2 grams per deciliter, with a corresponding 5.3 grams per deciliter median increase from baseline. After a median follow-up of 81 weeks, the median duration of major response had not been reached and was more than 48 weeks. Of 20 patients with karyotypic abnormalities, 10 (50%) patients had a complete cytogenetic remission. The response rate was highest in patients with a clonal interstitial deletion involving chromosome 5q31.1 (10 out of 12, 83%). Neutropenia and thrombocytopenia were the most common adverse events, and resulted in dose delays or reductions in 25 patients (58%).

A multi-center trial (MDS-003) of 148 MDS patients with a clonal interstitial deletion involving chromosome 5q31.1 where lenalidomide was given: 10mg on Days 1-21 repeated every 28 days to 44 patients and 10mg daily to the other 104 patients. Transfusion independence was achieved in 93 patients (64%), with a median hemoglobin increase of 3.9g/dl. Cytogenetic response was achieved in 76% of transfusion independent patients with 55% achieving a cytogenetic complete response. Pathologic complete response was documented in 32 out of 110 (29%) evaluable patients. With a median follow-up of 9.3 months, the median response duration had not been reached. Neutropenia (39%) and thrombocytopenia (35%) were the most common adverse events requiring dose delays or reductions [21].

Another trial (MDS-002) studied patients with low to intermediate-1 risk MDS. 215 patients, of whom, 166 were documented to have low to intermediate-1 risk MDS were enrolled. Among the patients with documented low to intermediate-1 risk MDS, 84 patients (51%) responded to treatment. Transfusion independence was achieved in 54 patients (33%) and 30 patients (18%) achieved a minor response, defined as a 50% or greater decrease in blood transfusion requirement. The median duration of transfusion-independence was 41 weeks. The median baseline hemoglobin level was 8.0g/dl, which increased by 3.2g/dl in responding patients. Among 20 patients evaluable for cytogenetic response, 9 patients (45%) experienced a cytogenetic remission [22].

REVLIMID® (lenalidomide) is now indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities and in combination with dexamethasone for patients with multiple myeloma that have received at least one prior therapy.

4.6 Clinical experience of thalidomide and lenalidomide in other hematologic malignancies

Hernandez-Ilizaliturri et al showed in early pre-clinical trials the activity of thalidomide derivaties in other NHL. Treatment of NHL cells with lenalidomide resulted in a 40-70% growth inhibition when compared with controls [4]. In vitro studies in severe combined immunodeficient mice showed some synergistic activity between lenalidomide and rituximab compared to rituximab monotherapy-treated animals. Kaufmann et al treated 16 patients with relapsed/refractory mantle cell lymphoma with rituximab in combination with thalidomide. 13 patients (81%) showed an objective response with 5 CRs and median progression free survival of 20.4 months.[23] These two studies outline the potential therapeutic roles IMiDs® have in this patient population.

Clinical experience of lenalidomide in Non Hodgkin's Lymphomas

Aggressive NHL

NHL-003 study by Czuczman et al evaluated the role of lenalidomide as monotherapy in 217 patients with relapsed/refractory aggressive Non-Hodgkin's Lymphoma. Among these, 50% patients had Diffuse large B cell Lymphoma, 26% Mantle Cell Lymphoma, 9% Follicular Lymphoma Grade III, and 15% transformed lymphoma. The ORR for all 217 patients was 35%, with 13% complete response, 22% partial response, and 21% had stable disease. Responses were observed in all histological types. Median progression-free survival for all patients was 3.5 months and the median duration of response for the 77 responders was 11.6 months. The primary side effect of lenalidomide was reversible myelosuppression [24].

Indolent NHL

Witzig et al reported a phase II study of lenalidomide (25 mg/d for 21 of 28 days) in patients with relapsed or refractory indolent NHL. Among 27 assessable patients with a median of three

(range, one to 17) prior therapies, the ORR was 26% (n = 7) including two CRs, whereas the overall clinical benefit (stable disease or better response) was observed in 59% of the patients. A large, randomized, multicenter clinical trial conducted by the Cancer and Leukemia Group B (CALGB) is investigating the clinical benefit of lenalidomide versus lenalidomide/rituximab in patients with relapsed follicular NHL [25].

We at UC Davis have studied the combination of lenalidomide and rituximab in relapsed/ refractory indolent NHL, and it appears to be safe and active with an acceptable side effect profile. 16 patients have been enrolled as of December 2009. 10 of the 16 patients were considered heavily pre-treated, and 7 rituximab refractory. Overall response rate in a preliminary analysis was remarkable at 75%, with 31% CR and 44% PR. The toxicity profile was safe, with the most common grade 3 and 4 events being fatigue, neutropenia and lymphopenia. The protocol was amended after two patients developed tumor lysis syndrome, to include tumor lysis prophylaxis with allopurinol and reducing the initial dose of lenalidomide from 25 to 20 mg. No additional patients developed tumor lysis after this modification.

Fowler et al also recently presented their data on front-line therapy of indolent B-cell non-hodgkins lymphoma with a combination of lenalidomide and rituximab. Patients received lenalidomide at a dose of 20 mg orally on days 1-21 and rituximab 375 mg/m2 IV on day 1 of each cycle, for up to 6 cycles of therapy. Among the 28 patients enrolled, overall response rate was 86%, with a complete response in 75%. The combination was well tolerated with the most common grade 3 and 4 adverse events being myalgia, neutropenia and rash [26].

Mantle-Cell Lymphoma

Kaufman et al first reported the clinical efficacy of thalidomide combined with rituximab in patients with relapsed/refractory mantle-cell lymphoma (MCL). The ORR and CR rate in this study was 81% and 31%, respectively with a median progression-free survival of 20.4 months [23]. On the basis of these findings, a phase I clinical trial of lenalidomide (5 to 25 mg) in combination with rituximab was initiated for MCL. The MTD was 20 mg/d, 21 of 28 days. Overall response rate of 41% was reported. Zaja et al studied lenalidomide in combination with dexamethasone, with a 50% overall response rate [27]. Wang et al reported an overall response rate of 53% for the combination of lenalidomide with rituximab. These studies also demonstrated a favorable toxicity profile for lenalidomide and the combinations.

4.7 Clinical Rationale for Combination of Lenalidomide and Radiotherapy in Indolent NHL

Recent preclinical and early clinical data suggest radiotherapy may act as a potent immunostimulatory agent in the appropriate setting, and may be a promising partner therapy for systemic immunotherapy agents such as lenalidomide. Radiotherapy may exert immunostimulatory effects via multiple mechanisms, including tumor vasculature normalization [28], improved T-cell homing to tumors [28], destruction of immunosuppressive stromal cells [29], induction of immune mediated tumor cell death [30], and tumor antigen exposure in the presence of immune modulation, among others. Small case series and case reports in melanoma patients describe impressive systemic abscopal (*ab-scopus* – away from

the target) responses distant from the radiation target lesion in patients irradiated after failing therapy with the immunotherapy agent ipilimumab, an inhibitor of the immune checkpoint CTLA-4. Grimaldi et al describe 21 patients who progressed through ipilimumab treatment and subsequently underwent palliative radiotherapy to any site [31]. The authors identified a remarkable 52% systemic response rate, with a median time to response of 1 month. Other case reports have suggested similar phenomena in melanoma patients receiving palliative radiation following failure to respond to immunotherapy [32, 33].

The specific interplay between lenalidomide and radiotherapy and the potential for radiation-induced augmentation of systemic anti-tumor response is not well-studied. However, several case reports detailing heavily pre-treated lymphoma and myeloma patients with impressive systemic responses following treatment with lenalidomide and local radiation support possible synergism between these modalities [34, 35]. Additionally, several preliminary clinical trials have provided preliminary evidence of synergistic anti-tumor responses when combining immunotherapy and local radiation for lymphoma patients. Investigators from Stanford University enrolled 15 patients with low grade B cell lymphoma and delivered low dose local radiotherapy (4 Gy in 2 fractions) with concurrent intratumoral injection of C-G enriched, synthetic oligodeoxynucleotide (CpG) TLR9 agonist PF-3512676 [36]. Systemic responses were identified in 6 patients, including one complete response. Similarly, Kim et al evaluated the same approach in 15 patients with mycosis fungoides, with 5 systemic responses identified [37]. Investigators at the Oslo University Hospital completed a 14 patient pilot trial enrolling stage III/IV follicular lymphoma patients. Treatment consisted of low-dose intratumoral rituximab injections with immature autologous dendritic cells and granulocyte-macrophage colony-stimulating factor with a single dose of 8 Gy to the injected site. This regimen was completed to 3 separate sites for each patient: weeks 1, 3, and 5. A 34% objective clinical response rate was identified, with 2 durable complete remissions [38].

4.8 Adverse Events

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

Second new cancers

According to researchers, patients with cancer have a higher risk of developing a second new cancer when compared to people without cancer. In clinical studies of newly diagnosed multiple myeloma, a higher number of second cancers were reported in patients treated with induction therapy (treatment as first step to reducing number of cancer cells) and/or bone marrow transplant then lenalidomide for a long period of time compared to patients treated with induction therapy and/or bone marrow transplant then placebo (a capsule containing no

lenalidomide). Patients should make their doctors aware of their medical history and any concerns they may have regarding their own increased risk of other cancers.

Complete and updated adverse events are available in the Investigational Drug Brochure and the IND Safety Letters.

The most frequent adverse events associated with rituximab include: infusion-related toxicities (fevers/chills, rigors, hypertension/hypotension, bronchospasm, angioedema, nausea/vomiting, myalgias, and rigors), cytopenias (neutropenia with a mean duration of 13 days, leucopenia, lymphopenia with a mean duration of 14 days), and generalized weakness. Rare reports of hepatitis B reactivation have been associated with rituximab.

4.9 Rationale for Treatment in this Setting

The rationale for combining lenalidomide and rituximab originates from the hypothesis that enhancement of host immune effector mechanisms may augment the clinical efficacy of rituximab without significantly increasing toxicity. Recent studies as above have shown this to be effective and safe in patients with relapsed/refractory as well as upfront treatment of indolent non-Hodgkin's lymphoma.

5 Study Objectives and Endpoints

5.1 Objectives

5.1.1 Primary objectives

- To determine the response rates to treatment with the combination of lenalidomide and rituximab in patients with previously untreated indolent NHL.

5.1.2 Secondary study objectives

- Time to disease progression, safety, tolerability, duration of response, and overall survival.
- To assess changes in serum cytokines as well as cellular immune phenotypic and functional changes before and after treatment, and correlate these changes with response.
- Examine immune correlates after local radiotherapy

5.2 Endpoints

5.2.1 Primary Endpoint

- Complete response (CR), near complete response (CRu), or partial response (PR), stable disease (SD) of 4 months

5.2.2 Secondary Endpoints

- Time to disease progression

- Tolerability (type, frequency, severity and relationship of adverse events to study treatment based on the NCI criteria)
- Duration of response from the start of therapy
- Overall survival
- Serum cytokine levels
- Tumor Control Rate

Investigational Plan

5.3 Overall design

The study is a phase II clinical trial with all patients to be accrued at UCD Cancer Center and other participating centers. All patients who are eligible will receive both lenalidomide and rituximab.

- Lenalidomide will be started at 20 mg daily, days 1 – 21 of a 28 day cycle.
- A total of 30 patients will be evaluated in this study.
- Rituximab 375 mg/m2/wk x 4 weeks, to begin on day 15 of cycle 1. After 4 cycles of therapy if a patient has not achieved a CR, the patient will be given a second course of Rituximab, on days 1, 8, 15 and 22 of cycle 5.

Patients who progress through this combination will be offered optional participation in a radiotherapy cohort. Up to 10 patients who consent will continue lenalidomide and receive local radiotherapy to a single target lesion.

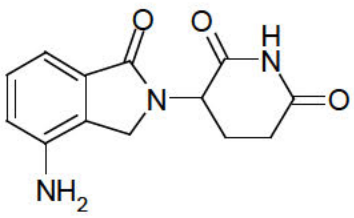
- Lenalidomide will be continued at the patient's most recent dose daily, days 1 – 21 of a 28 day cycle.
- Radiotherapy will be delivered to a single involved site to a dose of 20 Gy over 5 daily fractions of 4 Gy each, day 1-5, using electron or photon beams with a conventional linear accelerator.

Investigational Drugs

5.3.1 DESCRIPTION of 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 an 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.

REVLIMID® (lenalidomide) is available in 5 mg and 25 mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

5.3.1.1 CLINICAL PHARMACOLOGY

Mechanism of Action:

The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory and antiangiogenic 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.

5.3.1.2 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.

Pharmacokinetic Parameters:

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.

5.3.1.3 Supplier(s)

Celgene Corporation will supply Revlimid®, lenalidomide to study participants at no charge through Celgene's Revlimid Risk Evaluation and Mitigation Strategy™ (REMS) (formerly known as RevAssist® Program). .

5.3.1.4 Dosage form

Lenalidomide will be supplied as 5 mg capsules for oral administration.

5.3.1.5 Packaging

Lenalidomide will be shipped directly to patients or to the clinic site for IND studies. Bottles will contain a sufficient number of capsules for one cycle of dosing**.**

5.3.1.6 Labeling

Lenalidomide investigational supplies are dispensed to the patients in individual bottles of capsules. Each bottle will identify the contents as study medication and bear Celgene's name, quantity contained, and the standard caution statement as follows: Caution: New drug - Limited by Federal law to investigational use.

The study drug label must be clearly visible. For appropriate drug accountability, it is recommended that each bottle be marked with the institutional or Celgene protocol number (RV-NHL-PI-0448) upon receipt. Additional labels must not cover the Celgene label. Additional labels must not cover the Celgene label.

5.3.1.7 Receipt of study drug

The Investigator or designee is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The Investigator will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene or its representative.

5.3.1.8 Storage

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access.

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

5.3.1.9 Unused study drug supplies

Any unused Revlimid® (lenalidomide) should be returned as instructed through the Revlimid REMS™ program.

5.3.1.10 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 of Celgene Corporation. Per standard Revlimid REMS™ program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the Revlimid REMS™ program. Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site for IND studies. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle**.

Further information about the Revlimid REMS® **program is available at www.celgeneriskmanagement.com.**

5.3.1.11 Pregnancy Testing

Females must follow pregnancy testing requirements as outlined in the Revlimid REMS® program.

5.3.2 DESCRIPTION of Rituximab

Rituxan® (rituximab) is a monoclonal antibody directed against the CD20 antigen on B-lymphocytes. CD20 regulates cell cycle initiation; and, possibly, functions as a calcium channel.

5.3.2.1 CLINICAL PHARMACOLOGY

Mechanism of Action:

Rituximab binds to the antigen on the cell surface, activating complement-dependent cytotoxicity; and to human Fc receptors, mediating cell killing through an antibody-dependent cellular toxicity.

5.3.2.2 Pharmacokinetics and Drug Metabolism:

Absorption:

Rituximab is administered intravenously.

Pharmacokinetic Parameters:

Metabolism and Excretion:

Rituximab remains detectable in the serum for 3-6 months after completion of treatment with B-cell recovery beginning about 6 months following completion of treatment. Median B-cell levels return to normal by 12 months after completion of therapy. Once infused, absorption is

immediate and results in rapid and sustained depletion of circulating and tissue-based B cells. The half-life of rituximab at doses >100 mg/m2 is 4.4 days (range of 1.6-10.5 days). At doses of 375 mg/m2, the half life is 50 hours following the first dose to 174 hours following the fourth dose). The mechanism of clearance for rituximab is uncertain although phagocytosis and catabolism in the reticuloendothelial system is suspected.

5.3.2.3 Supplier(s)

Genentech Pharmaceuticals, Inc. Commercial rituximab for intravenous administration will be obtained from the UC Davis Cancer Center pharmacy or participating site's pharmacy and billed to the patient or a third party payer.

5.3.2.4 Dosage form

Rituximab is supplied as a sterile, colorless, preservative-free liquid concentrate for intravenous (IV) administration. Rituximab is supplied at a concentration of 10 mg/ml in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for IV administration in 9 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dehydrate, 0.7 mg/mL polysorbate 80, and sterile water for injection. The pH is adjusted to 6.5.

5.3.2.5 Storage

Unopened vials may be stored refrigerated. When diluted for infusion, the solutions are stable at 2-8 degrees C (36-46 degrees F) for 24 hours and at room temperature for an additional 12 hours.

5.4 Screening and Eligibility

The Investigator is responsible for keeping a record of all subjects who sign an Informed Consent Form for entry into the study. All subjects will be screened for eligibility. Screening procedures are outlined in Section 2, Schedule of Study Assessments and unless otherwise specified, must take place within 28 days prior to initiation of therapy. Screening pregnancy tests for women of child-bearing potential must occur 10-14 days and again ≤ 24 hours from initiation of therapy.

Approximately 30 subjects with previously untreated indolent Non-Hodgkin's Lymphoma will be screened for enrollment and must meet the eligibility criteria below.

5.4.1 Inclusion Criteria

Subjects must meet the following inclusion criteria to be eligible for the study. (All responses to inclusion criteria should be YES)

1. All patients must be informed of the investigative nature of the clinical trial and give written informed consent in accordance with institutional and federal guidelines.
2. Age ≥18 years at the time of signing the informed consent form.
3. Able to adhere to the study visit schedule and other protocol requirements.
4. Previously untreated, histologically confirmed indolent lymphoma including follicle cell lymphoma, WHO classification, grade I or II, and marginal zone lymphoma. Bone

marrow biopsies as the sole means of diagnosis are not acceptable, but they may be submitted in conjunction with nodal biopsies. Fine needle aspirates are not acceptable.

5. At least one measurable lesion according to the International Working Group Response criteria for lymphomas. There must be measurable lymphadenopathy to follow with serial exam and/or imaging.
6. Submission of original biopsy for review by hematopathologist at local institution.
7. ECOG performance status of 0 -2 at study entry. (see appendix II)
8. No major organ dysfunction with laboratory test results within these ranges:
   - Absolute neutrophil count ≥ 1000 /uL
   - Platelet count ≥ 75 x 10^9/L
   - Total bilirubin ≤ 2.0 mg/dL.
   - HIV negative
   - Subjects must have calculated creatinine clearance ≥ 30ml/min by Cockcroft-Gault formula. See section below, "Dosing Regimen", regarding lenalidomide dose adjustment for calculated creatinine clearance ≥ 30ml/min and < 60ml/min.
9. Life expectancy of greater than 3 months.
10. All study participants must be registered into the mandatory Revlimid REMS ™ program, and be willing and able to comply with the requirements of Revlimid REMS™
11. Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program. 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 and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days as required by Revlimid REMS™) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. 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.

[†] 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).

12. Disease free of prior malignancies for ≥ 4 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix or breast.
13. Able to take aspirin (81 or 325 mg) daily as prophylactic anticoagulation. (Patient's intolerant to ASA may use low molecular weight heparin).
14. Must be able to swallow lenalidomide capsules.

Inclusion Criteria for Radiotherapy Cohort

- Enrolled on UCDCC#224 and progress through protocol therapy
- At least two measurable sites of disease according to the International Working Group Response criteria for lymphomas. There must be measurable lymphadenopathy to follow with serial exam and/or imaging, and one lesion must be suitable for local radiotherapy, with an additional lesion(s) to follow for response assessment.

5.4.2 Exclusion criteria

1. Any prior treatment for Non-Hodgkin's Lymphoma.
2. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.
3. Pregnant or breast-feeding females. (Lactating females must agree not to breast feed while taking lenalidomide).
4. 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.
5. Use of any other experimental drug or therapy within 28 days of baseline.
6. Known hypersensitivity to thalidomide or rituximab.
7. The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide or similar drugs.
8. Any prior use of lenalidomide.
9. Concurrent use of other anti-cancer agents or treatments.
10. Known positive for HIV
11. Known active hepatitis, type A, B or C. Patients who are seropositive because of hepatitis B virus vaccine are eligible.
12. Evidence for CNS metastatic disease
13. Subjects with ≥ Grade 2 neuropathy

14. For Radiotherapy cohort, prior radiotherapy to the planned target lesion (prior radiotherapy to other sites of disease is permitted at investigator discretion)
15. For the radiotherapy cohort, CNS disease at the time of progression

5.5 Visit schedule and assessments

Screening Assessments and all on study scheduled visits and assessments are outlined in Section 2 Table of Study Assessments.

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.

At treatment discontinuation, subjects will undergo off study evaluations per the Schedule of Assessments, Section 2. In addition, a safety assessment will be done approximately 30 days post the last dose of study drug. Follow-Up contact with the subjects should occur at a minimum of 4 weeks.

If the subject is in remission for more than 1 year then follow-up will be every four months unless there are clinical indications.

6 Treatment assignments

All patients will receive the treatment regimen outlined below.

6.1 Treatment Schedule

Lenalidomide capsules will be taken orally in the morning each day on days 1 - 21, followed by 7 days of no therapy of each 28-day cycle. Rituximab will be given by intravenous infusion weekly for 4 weeks beginning on day 15 of treatment start, thus on days 15, 22 of cycle 1 and days 1 and 8 of cycle 2.

Following cycle one, therapy with lenalidomide will continue in 28-day cycles, until there is disease progression, unacceptable toxicity or the patient chooses to withdraw from therapy. Lenalidomide may be discontinued after twelve cycles if complete response demonstrated, per physician and patient discretion. Additional course of rituximab will be administered if CR not attained after cycle 4, to be administered during cycle 5 on days 1, 8, 15 and 22. The patient must see the study physician before the next cycle may begin. There will be a +/-3 day window for study visits and procedures after completion of cycle one.

Dosing regimen

The planned maximum dose of lenalidomide for investigation is 20 mg daily, days 1- 21 of a 28 day cycle. Dosing will be in the morning at approximately the same time each day. Lenalidomide may be taken orally either with a full or an empty stomach.

Due to the uncertain amount of re-absorption of lenalidomide, there will be no re-dose for lenalidomide if the patient vomits the pills.

Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened.

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.

Prophylactic anti-coagulation is required during lenalidomide treatment. See Section 6.5.1.2.

Rituximab 375 mg/m2/week will be administered by IV infusion starting on day 15 from start of treatment and will continue weekly for 4 weeks (a total of four doses). The course of rituximab will be repeated if CR not attained after cycle 4. It will be administered at 375 mg/m2 weekly during cycle 5 on days 1, 8, 15 and 22.

For patients with peripheral blood involvement (leukemic presentation) as defined for this purpose as >20,000 lymphocytes per mm^3 as determined by flow cytometry studies, the initiation of rituximab should be delayed until the lymphocyte count drops to <20,000/mm^3 in the peripheral blood. For such patients, or for those with high tumor burden, despite lymphocyte count <20,000 cells/mm^3 (as determined by the principal investigator), the infusion of rituximab may be divided as outlined below:

- Day 1 – Rituximab 50 mg/m^2
- Day 2 – If no cytokine release phenomenon is noted on Day 1 of rituximab and the peripheral blood white cell counts have decreased to < 20,000 cells/mm^3 or <25% of baseline WBC counts, then the dose of rituximab can be increased to 325 mg/m^2 on Day 2 at the PI discretion.

A similar 2-day split dose approach may be taken for rituximab infusion on subsequent dose of rituximab in patients with high tumor burden or high peripheral blood WBC counts as determined by the PI prior to each infusion of rituximab.

Pre-medication consisting of acetaminophen and diphendydramine should be considered before each infusion of rituximab to attenuate potential infusion reactions. Since transient hypotension may occur during rituximab infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to rituximab infusion.

Rituximab First Infusion: The rituximab solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted with other drugs. If hypersensitivity or infusion related events do not occur, the infusion can be escalated to 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If hypersensitivity or an infusion-related event develops, the infusion should be temporarily slowed or interrupted. The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

Subsequent Rituximab Infusions: Subsequent rituximab infusions can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minute intervals, to a maximum of 400 mg/hr as tolerated.

Route of Administration

Rituximab is administered intravenously. To prevent infusion related or hypersensitivity events, rituximab is not to be administered as an intravenous push or bolus.

Please refer to rituximab package insert for details concerning drug storage, preparation and administration guidelines.

Subjects experiencing adverse events may need study treatment modifications (See section 6.4).

6.2 Special Handling Instructions

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

6.3 Record of administration

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

To monitor treatment compliance, reconciliation of lenalidomide capsules will be done at each visit. Subject diaries will be provided to assist in the collection of dosing information to monitor compliance.

6.4 Dose Continuation, Modification and Interruption

Subjects will be evaluated for AEs at each visit with the NCI CTCAE v4.0 (Appendix III: NCI CTCAE v4.0) used as a guide for the grading of severity. Refer to Sections 6.5.1, 6.5.2 and 6.5.3 for full instruction on initiation of a new cycle of therapy and dose modifications during a cycle of therapy.

6.4.1 Lenalidomide Dose Reduction Steps

Lenalidomide will be initiated at a dose of 20 mg daily for 21 days on a 28 day cycle, except patients with renal insufficiency, who will start at a lower dose, as above.

Rituximab: There will be no dose reduction for rituximab. The rate of administration may be slowed or divided as needed based on tolerability. Patients with unacceptable hypersensitivity to rituximab will not receive further rituximab therapy.

6.4.2 Instruction 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 ≥ 800/μL;
- The platelet count is ≥ 50,000/μL;
- Any lenalidomide or rituximab-related rash, allergic reaction/hypersensitivity or sinus bradycardia/ other cardiac arrhythmia adverse event that may have occurred has resolved to ≤ grade 1 severity;
- Any other lenalidomide-related adverse event that may have occurred has 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 lenalidomide 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.

Dose Reduction Steps

Dose level	Lenalidomide	Rituximab
0	20 mg (days 1-21/28 day cycle)	375 mg/m2 weekly x4
-1	15 mg (days 1-21/28 day cycle)	--
-2	10 mg (days 1-21/28 day cycle)	--
-3	5 mg (days 1-21/28 day cycle)	--

6.4.3 Instructions for dose modifications or interruption of lenalidomide during a cycle.

Table 2: Dose Modification for Lenalidomide

NCI CTC Toxicity Grade	Day 2-14 of Cycle	≥Day 15 of Cycle
Grade 3 neutropenia associated with fever (temperature ≥ 38.5° C) or Grade 4 neutropenia	• Hold (interrupt dose). • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 prior to Day 21, restart at next lower dose level and continue the cycle until Day 21.	• Omit lenalidomide for remainder of cycle .
	NOTE: If neutropenia is the only toxicity for which a dose reduction is required. G-CSF may be used and the dose maintained for the next cycle at the investigators discretion	
Thrombocytopenia ≥Grade 4 (platelet count < 25,000/mm³)	• Hold (interrupt dose). • Follow CBC weekly. • If thrombocytopenia resolves to ≤ grade 2 prior to Day 21, restart at next lower dose level and continue the cycle until Day 21.	• Omit lenalidomide for remainder of cycle • Hold ASA or other anticoagulant
Thrombocytopenia, Grade 3 (platelet count 25,000 to 50,000/mm³)	• Hold ASA or other anticoagulant	• Hold ASA or other anticoagulant
Non-blistering rash Grade 3	• If Grade 3 hold (interrupt) dose. Follow weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21.	• Omit lenalidomide for remainder of cycle.
Grade 4	• Discontinue lenalidomide study drug.	• Discontinue lenalidomide study drug.
Desquamating (blistering) rash- any Grade	• Discontinue lenalidomide study drug.	• Discontinue lenalidomide study drug.
Erythema multiforme ≥ Grade 3	• Discontinue lenalidomide study drug.	• Discontinue lenalidomide study drug.
Sinus bradycardia/ other cardiac arrhythmia Grade 2	• Hold (interrupt) dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21.	• Omit lenalidomide for the remainder of the cycle.
≥ Grade 3	• Discontinue lenalidomide study drug.	• Discontinue lenalidomide study drug.

Table 2: Dose Modification for Lenalidomide		
NCI CTC Toxicity Grade	**Day 2-14 of Cycle**	**≥Day 15 of Cycle**
Allergic reaction or hypersensitivity **Grade 2-3**	• Hold (interrupt) dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21.	• Omit lenalidomide for the remainder of the cycle.
Grade 4	• Discontinue lenalidomide study drug.	• Discontinue lenalidomide study drug
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. See Anticoagulation Consideration (Section 6.5.1.2)
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	• 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 21.	• Omit lenalidomide for remainder of cycle. • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level.

6.4.4 Treatment compliance

At all times, when dispensing study drug, research center personnel will review the instructions, printed on the packaging, with subjects. Subjects will be asked to maintain a diary to record the drug administration.

6.5 Radiation Therapy

6.5.1 Selection of a target lesion

All patients should have at least 2 measurable sites of disease (one target lesion and one or more lesions for response assessment). The target lesion for radiation should measure a minimum of 1 cm and a maximum of 8 cm in greatest diameter. The lesion least likely to result in normal tissue toxicity should generally be selected for treatment at investigator discretion. Suitable targets include lymph nodes and extranodal tumor deposits. CNS disease is NOT a suitable target and patients with CNS involvement are not eligible for enrollment.

6.5.2 Treatment planning/target volumes

GTV: Will include visible target lesion as identified by diagnostic and/or treatment planning CT or PET and clinical exam

PTV: An additional margin of 5-10 mm will be added to account for setup error at treating physician discretion.

*If clinical setup is used, a 1.*5 cm *block margin on clinically apparent disease should be applied*

6.5.3 Dose specifications

All patients will receive a dose of 20 Gy delivered in 5 daily fractions of 4 Gy each. At least 95% of the GTV should receive the full prescription dose of 20 Gy. Coverage may be estimated in the case of clinical set-up.

6.5.4 Technical parameters

Radiation will be delivered with megavoltage equipment at photon energies ≥ 6 MV or with electron fields ≥4 MeV. Cobalt-60 and proton beams are not permitted. Any beam arrangement that allows for optimal coverage of the target lesion and minimizes dose to surrounding structures is permitted.

6.5.5 Immobilization and simulation

Patients will be positioned reproducibly with a customized thermoplastic immobilization cast or a molded foam cradle as needed or stabilization. CT simulation is encouraged, but clinical set-up is permitted for superficial lesions that can be easily demarcated without CT simulation.

6.5.6 Normal critical structures and dose constraints

Normal critical structures located within 5 cm of the PTV should be delineated and dose should be tracked, including but not limited to: Spinal cord, lungs (right and left), heart, esophagus, liver, small bowel, large bowel, bladder, rectum, brain, orbits (right and left), brainstem. As the prescription dose is such that normal tissue tolerance is generally not expected

6.5.7 Treatment Verification and Image Guidance

At the start of treatment, electronic portal imaging should be used to verify treatment fields. More frequent imaging is permitted but not required.

6.5.8 Radiation Adverse Events

Adverse Events will be categorized and graded based on the Common Toxicity Criteria for adverse events Version 4.0 (CTCAE version 4.0).

Radiotherapy should be discontinued for Grade 4 in-field toxicity

6.6 Concomitant therapy

All medications (prescription and non-prescription), treatments, and therapies taken from the first day of study drug through the end of the study, must be recorded on the source documents.

6.6.1 Recommended concomitant therapy

The use of filgrastim (G-CSF) for subjects in this study is permitted when used to treat neutropenia. Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, and antiemetics when appropriate.

Use of steroids is allowed in emergencies including the management of infusion reactions to rituximab.

6.6.1.2 Anticoagulation Consideration

Lenalidomide likely 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. Based on data with thalidomide it has been hypothesized that when lenalidomide is combined with other agents such as steroids (e.g. dexamethasone, prednisone), anthracyclines (Doxil, adriamycin) and erythropoeitin the risk of thrombosis may be increased.

The use of aspirin (81 or 325 mg) or some other form of prophylaxis as deemed appropriate is required. 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 at the discretion of the PI. Hold anticoagulation for platelet count < 50,000 mm^3.

6.6.1.3 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. Concomitant use of other anti-lymphoma therapy, including steroids (except for the treatment of hypersensitivity reactions), while the subject is on study drug is prohibited.

6.7 Discontinuation of Study Treatment

Treatment will continue until evidence of disease progression or the occurrence of any of the following events.

Treatment with study drug is to be discontinued when any of the following occurs:

- Lack of therapeutic effect/progressive disease as defined in section 8.0
- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug.
- Major violation of the study protocol.
- Withdrawal of consent
- Lost to follow up
- Death
- Suspected pregnancy
- Treatment may also be discontinued after a total of twelve cycles of treatment if a patient achieves and maintains a complete response. This will be decided by the treating physician.

6.8 Follow-Up

Subjects who discontinue treatment for any reason will be followed for disease progression and overall survival. At treatment discontinuation, subjects will undergo a safety assessment approximately 30 days post the last dose of study drug. In addition off study evaluations per the Schedule of Assessments, Section 2 will be done. If the subject is in remission for more than 1 year then follow-up will be every four months unless there are clinical indications.

Patients will be followed for survival every three months.

6.9 On Study Evaluations

All study evaluations outlined in schedule 2 of Assessments will be completed during study for assessments of response and toxicity.

Study visits and procedures may be scheduled +/- 3 days window except for screening and cycle one.

CT scans should include neck if necessary

If in CR by radiologic evaluation, bone marrow biopsy and PET scan, colonoscopy or endoscopy with random biopsy may be necessary to confirm CR.

After CR has been confirmed by a repeat scan, the restaging scans will be obtained every four cycles, unless deemed clinically necessary by treating physician.

7 Adverse events

7.0 Serious Adverse Event (SAE) Definition

A serious adverse event is one that at any dose (including overdose):

- ☐ Results in death
- ☐ Is life-threatening[1]
- ☐ Requires inpatient hospitalization or prolongation of existing hospitalization
- ☐ Results in persistent or significant disability or incapacity[2]
- ☐ Is a congenital anomaly or birth defect
- ☐ Is an important medical event[3]

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[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.

7.1 Adverse Event Reporting

Toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (http://evs.nci.nih.gov/ftp1/CTCAE/About.html). All appropriate treatment areas have access to a copy of the CTCAE Version 4.0. 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.

Second primary malignancies are considered events of interest and should be included as part of the assessment of adverse events throughout the course of the study. Investigators are to report any second primary malignancies as serious adverse events regardless of causal relationship to lenalidomide, occurring at any time for the duration of the study For all subjects who develop second primary malignancies, sites will be required to submit all diagnostic reports (eg pathology, cytogenetics, flow cytometry results) from the indication diagnostic confirmation samples submitted at screening and all reports for the tumor samples from the SPM diagnosis. For SPMs diagnosed at another institution (outside the investigational site), sites are to make every effort to obtain these reports for the SPM confirmation.

Pregnancies

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

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

other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form,

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the *in utero* exposure to the study drug should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

Male Subjects

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

7.1.1 Celgene Drug Safety Contact Information

Celgene Corporation
Global Drug Safety and Risk Management
86 Morris Avenue
Summit, NJ 07901
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

7.2 Investigator Reporting Responsibilities

The conduct of the study will comply with all FDA safety reporting requirements.

IND Annual Reports

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Celgene Corporation as a supporter of this study as follows.

Celgene Corporation
Attn: Medical Affairs Operations
86 Morris Avenue
Summit, NJ 07901

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to study drug (probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present. The investigator is responsible for reporting adverse events to Celgene as described below.

7.2.1 Expedited Reporting by Investigator to Celgene

Serious adverse events (SAE) are defined above. The investigator should inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (RV-NHL-PI-0488) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

Participating study sites must report SAEs to Celgene as described and within 24 hours of awareness. Participating sites should also report SAEs to the primary study site.

7.2.2 Report of Adverse Events to the Institutional Review Board

The Principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

7.2.3 Investigator Reporting to the FDA

Serious adverse events (SAEs) that are **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) by telephone or fax. Fatal or life threatening SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 7 calendar days after awareness of the event. All other SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 15 calendar days after awareness of the event. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

Participating study sites should NOT report SAEs to the FDA. Rather, participating sites should report SAEs to Celgene and the primary study site, and the primary site will be responsible for reporting to FDA.

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.

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all AE information, including correspondence with Celgene and the IRB/EC, on file (see Section 12.4 for records retention information).

8 Response Criteria

Responses will be assessed by Revised Working Group Response Criteria for Malignant Lymphoma (Cheson et al, JCO Vol 25, No 5 (February 10), 2007: pp. 579-586), as follows:

8.1 Complete Response (CR):

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

2a. Typically FDG-avid lymphoma: in patients with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

2b. Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT 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 long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤ 1.0cmin their short axis after treatment.

2. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

3. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

8.2 Complete Response Unconfirmed (CRu):

The use of the above definition for CR and that below for PR eliminates the category of CRu.

8.3 Partial Response (PR)

1. At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

2. No increase should be observed in the size of other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.

4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

6. No new sites of disease should be observed.

7. Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.

8. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used. In patients with follicular lymphomaor mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

8.4 Stable disease (SD):

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).

2. Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post treatment CT or PET.

3. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

8.5 Relapsed Disease (after CR)/Progressive Disease (after PR, SD)

Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes ≤1.0 ≤1.0cm will not be considered as abnormal for relapse or progressive disease.

1. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

2. At least a 50%increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0cm must increase by ≥ 50% and to a size of 1.5x1.5 cm or more than 1.5 cm in the long axis.

3. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

4. Lesions should be PET positive if observed in a typical FDG avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (<1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

8.6 Progressive disease (PD) in PR patients or nonresponders

- ≥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.

Summary of response criteria:

Response Category	Definition	Nodal Mass	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immuno-histochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greates transverse diameter); no increase in size of liver or spleen	Irrelevant
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET		

Response Category	Definition	Nodal Mass	Spleen, Liver	Bone Marrow
		(b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapse/PD	Any new lesion or increase by _≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) >1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, Or ≥ 50% increase in longest diameter of a previously identified node >1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50 increase from nadir in the SPD of any previous lesions	New or recurrent involvement

8.7 Duration of Overall Response:

The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

8.7.1 Duration of Stable Disease:

Stable disease is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

8.7.2 Time to Progression:

Time to progression will be measured as the time from when the patient started treatment to the time the patient is first recorded as having disease progression, or the date of death if the patient dies due to causes other than disease progression.

8.7.3 Time to Treatment Failure:

Time to treatment failure will be measured as the time from when the patient started treatment to the time the patient is withdrawn due to: adverse events, progressive disease/insufficient therapeutic response, death, failure to return, and refused treatment/did not cooperate/withdrew consent. The date of last dose of treatment will be used as the date of event in the case that PD was not recorded earlier.

8.7.4 Survival:

Survival will be measured as the time from start of treatment to the date of death or the last date the patient was known to be alive.

9 Data Management

9.1 Analyses and Reporting

Data will be analyzed and reported after all 30 patients have enrolled in the clinical trial and have received 2 cycles of treatment. All subsequent data collected will be analyzed and reported in a follow-up clinical report.

9.2 Data and Safety Monitoring

In addition to the requirements for adverse event reporting as outlined in section 7.2, this protocol is also subject to the UC Davis Cancer Center's (UCDCC) Data and Safety Monitoring Plan. The UCDCC is committed to pursuing high-quality patient-oriented clinical research and has established mechanisms to ensure both scientific rigor and patient safety in the conduct of clinical research studies. The UCDCC relies on a multi-tiered committee system that reviews and monitors all cancer clinical trials and ensures the safety of its participants, in compliance with institutional and federal requirements on adverse event (AE) reporting, verification of data accuracy, and adherence to protocol eligibility requirements, treatment guidelines, and related matters. The Scientific Review Committee (SRC) assumes overall

oversight of cancer studies, with assistance and input from two independent, but interacting, committees: the Quality Assurance Committee and the Data Safety Monitoring Committee. A multi-level review system strengthens the ability of the UCDCC to fulfill its mission in conducting high quality clinical cancer research.

As per University of California Davis Cancer Center (UCDCC) Clinical Trials Support Unit (CTSU) SOP AM 506: Protocol Specific Meetings, the principal investigator (PI) and clinical research coordinator (CRC) meet at least monthly for ongoing study information, to discuss patient data and adverse events and to determine if dose escalation is warranted, when applicable. Representatives from all participating centers will be included via conference call, as well as representatives from the drug provider or financial sponsor if necessary. The call will update participants on the current status of the trial, any serious adverse events encountered will be discussed, and appropriate action taken. In between these regularly scheduled conference calls, investigators will be informed of any serious adverse events via email.

According to the UCDCC Data and Safety Monitoring Plan (DSMP), any new serious adverse events related to the drugs being used on this trial are reviewed monthly by the UCDCC Data and Safety Monitoring Committee (DSMC) and any applicable changes to the study are recommended to the PI, if necessary.

The UCDCC Scientific Review Committee (SRC) determines if a UCDCC Data and Safety Monitoring Board (DSMB) is required. If required, the DSMC will appoint a DSMB. The DSMB is responsible for reviewing study accrual logs, adverse event information and dose escalation meeting minutes (where applicable) to ensure subject safety and compliance with protocol defined guidelines.

10 Study monitoring and auditing

10.1 Investigator responsibilities

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations.

Investigators must enter study data onto CRFs or other data collection system. The Investigator will permit study-related monitoring visits and audits by Celgene or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), 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 monitoring visits 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.

11 Biostatistical Analysis

11.1 Overview

This is a Phase II trial designed to assess the efficacy and toxicity of the combination of lenalidomide with rituximab in patients previously untreated follicular NHL.

11.2 Datasets to be analyzed

The primary study endpoint is response to therapy (defined as a CR, nCR, or PR of 4 months). The secondary end points (time to progression, tolerability, duration of response and overall survival will be measured from the time of entry into the clinical trial.

Toxicity information recorded will include the type, severity, time of onset, time of resolution, and the probable association with the study regimen. Tables will be constructed to summarize the observed incidence by severity and type of toxicity.

11.3 Statistical Methodology

30 patients will be treated with rituximab and lenalidomide at indicated dose levels. Objective response (CR +PR) will be monitored using Simon's optimal 2-stage design. This study design is optimal in that sense that it minimizes the expected sample size among competing designs. The OR rate of rituximab naïve follicular lymphoma patients treated with rituximab alone is approximately 60%. A 20% increase in the objective response rate with the addition of lenalidomide to 80% in this treatment naïve patient population would justify evaluation of this regimen in larger, more definitive trials. We assume a one-sided type I error rate of 5% and desire at least 80% power to conclude that this regimen elicits and objective response rate significantly greater than 60% if the true response rate of this regimen is 60% or higher. Under these assumptions, if 11 or fewer OR's are observed in the first 26 patients, the principal investigator may conclude that regimen is insufficiently active to warrant further study. Otherwise, accrual will continue to a total of 30 patients. If 15 or more OR's are observed in 30 patients, this regimen will be deemed sufficiently active to warrant further study. Given the relatively small sample size the additional study in patients receiving radiation therapy would be considered exploratory. Any documented response would be considered "significant" and warrant further study.

Analysis Plan:
Continuous variables (e.g., age, hematology values) will be summarized using the mean (s.d.) or median (range). Frequency tables will be used to summarize categorical variables. Logistic regression will be used to assess the impact of patient characteristics (e.g., low/high LDH) on the objective response rate. The distribution of time-to-event endpoints (e.g., CR duration, overall survival) will be estimated using the method of Kaplan and Meier. Comparison of time-to-event endpoints by important subgroups of patients will be made using the logrank test. Cox (proportional hazards) regression will be used to evaluate multivariable predictive models of time-to-event outcomes.

11.4 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 drugs and had this confirmed, will not be evaluated for safety.

The severity of the toxicities will be graded according to the NCI CTCAE v4.0 whenever possible.

11.5 Sample Procurement for Immunologic Assessment

If a patient has consented and agreed to allow their blood to be used for research studies, 7-10 mL of whole blood in one purple top tube, 8mL in one BD vacutaner CPT cell preparation tube, and 7-10 mL in a serum separator tube will be acquired at the following timepoints: prior to treatment, and at day 15, 30, 60, and 120 and at the completion of treatment. Samples will be held on ice, centrifuged at 2500 RPM for 10 min, separated as soon as possible, and aliquoted into one (Preferably two) vials containing 0.1 – 0.5 mL serum each and two vials with the cellular contents. The cellular material obtained from the CPT tubes by removing the top layer (according to the manufacturers recommendations) and will be mixed with an equal part of freezing solution (30% DMSO + 70% fetal calf serum). The tubes will be labeled with a non-patient identifying ID number with the date of collection, protocol number, and source and intended use of the material (i.e., plasma sample for cytokine assays). Sample volumes between 0.05 and 0.1 mL are acceptable, but the laboratory will not be able to repeat the analysis or further dilute the sample, if necessary. Samples will be frozen at -70°C batched and archived. Immune assessment will be done as described below. If there are any questions with sample procurement please page the study PI (Joseph Tuscano) [redacted]

11.6 CORRELATIVE STUDIES.

In this Phase II clinical trial the immunological affects of the combination of Lenalidomide and Rituximab in patients with previously untreated indolent NHL will be explored.

Rationale:
This clinical study will be a unique opportunity to measure and characterize the baseline immune parameters and immune modulating effects of lenalidomide with or without rituximab in patients with previously untreated indolent NHL. This will allow for a better understanding of the mechanism of action, better prediction of who will respond to treatment, and allow for rational design of future clinical trials with these and/or other biologics.

Objectives:
Comprehensive assessment of immune parameters prior to therapy, after treatment with lenalidomide alone, and after treatment with the combination of lenalidomide and rituximab

Assay timeline:
Baseline, day + 15, +30, +60, and +120, completion of study, progression or withdrawal. Additional blood draws for immunologic profiling for patients taking part in the additional radiation therapy cohort will be done at day 15, 30 after starting radiation therapy and at the

time of progression. If the patient progresses within 8 weeks, the blood draw at progression will not be done.

Given that the protocol requires 2 weeks of lenalidomide alone followed by rituximab, this will allow for assessment of immune parameters at baseline, after treatment with lenalidomide alone, and after combination therapy with lenalidomide and rituximab. Because there have been dramatic responses to lenalidomide alone in the first cohort of patients on the relapsed protocol immune profiling patients before and after rituximab is added is justified.

Methods:

Distribution, phenotype, and frequency of mononuclear cell subsets*:* To examine the overall pattern of mononuclear cell subsets, blood will be collected from patients (see Study Calendar) prior to, during and after therapy. After preparation via standard procedures, the cells will be analyzed using a multi-parameter, Hi-D FACS to determine the frequency and phenotype of mononuclear subsets including: helper T cells, cytotoxic T cells, regulatory T cells, naive T cells, memory T cells, NKT cells, NK cells, dendritic cell subsets and B-cell subsets, Table 1.

Assay of T Cell Proliferation, Cytokine Production and Cytotoxic Lymphocyte (CTL) Activity: CD4 and CD8 T cells will be purified from blood using EasySep (Stem cell Technologies; Vancouver, BC, Canada). Cells ($1x10^5$/well in 200 μL culture media) will be cultured in quadruplicate 96-well U-bottom plates for each condition: culture medium alone or medium supplemented with CD3/CD28 mAb (0.5 μg/ml), or PHA (5 μg/ml). Cells will be incubated for 3-5 days at 37°C, 5% CO_2. Sixteen hours before the end of the incubation, 1 μCi of [^{3}H] thymidine will be added per well. Following harvest of cells, [^{3}H] thymidine incorporation will be measured with a beta counter following dissolution in scintillation fluid.

The culture supernatants will be collected prior to addition of [^{3}H] thymidine and stored at -70°C. The supernatants will be assayed for several cytokines/chemokines (e.g. IL-2, IFN-γ, IL-17, IL-10, IL-4, TNF-α, TGF-β) using the Multiplex Bead-based Luminex® Technology, Cytokine Human 10-Plex Panel (or if batched with other samples, the Cytokine Human 25-Plex Panel) (Invitrogen, Carlsbad, CA), see below.

CTL activity will be assessed by using the ELISpot Assay Kit (R&D Systems, Minneapolis, MN) by measuring IFN-gamma producing CD8+T cells, per the manufacturer's recommendations.

Table 1: Phenotypic markers for analysis of various immune cells

Cell subset		Phenotype marker
T cell	$CD4^+$ helper T cell	$CD3^+CD4^+$
	$CD8^+$ cytotoxic T cell	$CD3^+CD8^+$
	Regulatory T cells	$CD3^+CD4^+CD25^+Foxp3^+$
	Naïve T cell	$CD4^+/CD8^+CD45RA^+CD11a^+$
	Memory T cell	$CD4^+/CD8^+CD45RO^+CD11a^+$
	NK T cell	$CD3^+CD56^+CD16^+$
	iNKT cell	$CD3^+CD56^+CD16^+6B11^+CD1d^+$
NK cell		$CD3^-CD56^+CD16^+$
B cell	B2 cell	$CD19^+IgD^+CD11b^-CD5^-$
	B1a cell	$CD19^+IgM^+CD11b^+CD5^+$
	B1b cell	$CD19^+IgM^+CD11b^+CD5^-$
Dendritic cell	Myeloid DC	$CD11c^+HLADR^+$ lymphomononuclear cell lineage negative
	Plasmacytoid DC (pDC)	$CD123^+$ BCDA2/$BCDA4^+HLADR^+$ lymphomononuclear cell lineage negative

T-reg Cells Function: $CD4^+CD25^+$ $FoxP3^+$T cells will be isolated using magnetic separation with the MACS $CD4^+CD25^+$ isolation kit (Miltenyi Biotec, Auburn, CA) and then cultured with $CD4^+CD25^-$ T cells in plates coated with anti-CD3/CD28 antibodies (5 μg/ml each) in the presence of Lenalidomide, or saline (control) for 3 days. The supernatant will be collected before the addition of [^{3}H] thymidine for measurement IL-10, IL-4, TGF-β, IL-2, TNF-α, and IFN-γ by multi-parameter Hi-D FACS analyses or Multiplex Bead-based Luminex® Technology. Proliferation will be measured after 72h in culture, with [^{3}H] thymidine labeling for the last 16 hours.

Multiplex Bead-based Luminex® Technology: The microbead multiplex detection system developed by Invitrogen) enables detection of numerous cytokines simultaneously in a single reaction container [39]. In this technology, molecular reactions take place on the surface of microscopic plastic beads (2 um). For each reaction, capture molecules (i.e., mono-specific antibodies) are covalently attached to the surface of internally color-coded microbeads. The assigned color-code identifies the reaction in a specific microbead population throughout the test. Multiplex capability involves mixing several populations of microbeads, each with a specific capture molecule, into one reaction vessel at the start of the test. The magnitude of the biomolecular reaction is measured using a reporter molecule which signals the extent of the reaction by attaching to the test molecules captured on the microbeads. To perform a test, the color-coded microbeads, reporter molecules, and sample (e.g., tumor cell lysate) are mixed and then injected into the Luminex flow cytometer where lasers illuminate the colors inside and on the surface of each microbead. This method is rapid, sensitive, and quantitative, and lends itself to high-throughput in an economical fashion [40].

Serum Cytokines: The Luminex assay for immunologic analytes will include 37 different cytokines and growth factors (including IL-1, 2, 4, 5, 6, 7, 10,12, 17, TNF, INF-γ, TGF-beta, GM-CSF, PDGF, and VEGF) (Invitrogen). This test will allow for the ultrasensitive

determination of cytokines in the serum of patients before and during Lenalidomide alone and Lenalidomide in combination with Rituximab.

B-cell Phenotype and Functional Analysis: The B-cell phenotype will also be assessed. Blood mononuclear cells will be prepared with EasySep and stained with antibodies (Zymed, San Francisco, CA) against each set of markers listed in Table 1. Clearly B-cells in these patients are going to be radically different at different stages of the protocol, because the patients will have been on rituximab, which depletes B-cells. This will give us an opportunity to assess Lenalidomide's function before and after rituximab in the same patients. The phenotype of B-cell subsets (Table 1) will be analyzed by FACS.
A B cell functional assay will be performed by measuring IgM production using B cells isolated from blood. $CD19^+$ B cells will be isolated by positive selection using magnetic beads (2). B cell subsets will be sorted by FACS. B cell will be stimulated by LPS or CpG for 3 days, then IgM production will be measured by ELISA [41].

Immunoglobulin Levels: Serum samples will be obtained at various time points to assess for the serum levels of IgM, IgA, and IgG. Immunoglobulin levels will be measured by the clinical lab at UCDMC using standard techniques.

NK, NKT and iNKT cell phenotype and functional assay: Human iNKT cells will be identified using CD1d tetramer and a novel monoclonal antibody (clone 6B11) specific for the CDR3 loop of the human Vα24Jα18 TCR alpha chain which specifically identify iNKT cells. Other antibodies comprise CD3-APC, CD4-PerCP and CD8α-FITC (BD Biosciences, San Jose, CA). For surface staining, cells will be washed with staining buffer (PBS with 2% FCS), and incubated for 30 minutes, on ice in the dark with the relevant antibody combinations. Cells will then be washed twice with staining buffer and analyzed by flow cytometry (BD Coulter). Data will be collected using a FACS ARIA (BD Biosciences) and analyzed by "Flowjo" flow cytometry data analysis software (Tree Star Inc, Ashland, OR).

NK (CD3-CD56+CD16+), NKT (CD3+CD56+CD16+) and iNKT cells will be sorted from blood. The sorted NK/NKT cells will be stimulated with poly IC for 12 and 24 h. iNKT cells will be stimulated with iNKT cell-specific ligand, α-GalCer. Supernatants will be collected to analyze the levels of IFN-gamma, IL-6 and IL-8 using the BD cytometric bead array kit per the manufacturer's recommendations. IFN-gamma and IL-4 will be measured by CBA kit or intracellular staining. Sera cytokine will be measured by CBA kit.

NK Cell Killing Activity: NK cells bind to, and kill K562 cells (a human myelogenous cell line, ATCC) thus forming the basis of this functional killing assay [42]; this flow cytometric assay can detect binding and killing. K562 cells will be grown in RPMI 1640 with 10% fetal calf serum and checked for viability by trypan blue exclusion before use. Sorted NK cells that are obtained before and after treatment initiation will be combined with K562 cells at an effector-target-cell ratio of 20:1. Incubation will proceed for up to 3 hours at 37^oC in 5% CO_2. NK cells will be tested for their killing activity with or without stimulation by IL-2 (1 ng/ml of human rIL-2; Genzyme, Cambridge MA). Spontaneous lysis will be tested at each time point using equivalently cultured K562 cells in the absence of effectors. If we encounter any problems with this assay, a standard ^{51}Cr-release assay will be done, testing groups equivalent

to those described above. NK cells will also be assessed for Rituximab-mediated ADCC by using the human NHL cell line Raji (ATCC) as the target cell. The assay will be done as described above with and without 50ug/ml of Rituximab added.

Response of PBMC to Stimulation with Tetanus Toxoid and Tetanus Specific Antibody Production: The response to tetanus toxoid or PPD will be used to assess the immune response of patients on the study. As in the general population, the patients in this study will have been vaccinated against tetanus at some point in their lives. The response to tetanus toxoid does vary between people with a number of factors such as age, steroid use and other random factors [43, 44], however that is not a problem in this study since pre-study values will act as an internal control. As similar to the other assays assessment will be at baseline and after the first and fourth cycle.

Cellular Proliferation Response to Tetanus Toxoid: The *in vitro* cellular proliferative response will be measured as previously described [43, 44]. Using standard isolation techniques, PBMC (1x 10^5) in 100 µL RPMI 1640 (10% human AB+ sera) will be cultured in 96-well round bottom microtiter plates, in triplicate with either tetanus toxoid (10 µg/ml, Massachusetts Public Health Biological Laboratories; Cambridge, MA) or PPD (10 µg/ml Statens Serum Institute). Phytohemagglutinin (PHA) will be the positive control, and unstimulated cells will be the negative control. Cultures will proceed for 5 days at 37^{o}C and 5% CO_2, then pulsed with 1 µCi/well of ^{3}H-thymidine for 18 hours. Cells will then be harvested; tritiated thymidine uptake determined and reported as the proliferation index.

Antibody Response to Tetanus Toxoid: Tetanus toxoid-specific antibodies will be determined using ELISA as previously described [44]. PBMC from patients will be cultured with tetanus toxoid for 7 days as described above, and then the supernatant from the wells will be harvested. Microtiter plates (96-well) will be coated with tetanus toxoid (2 µg/ml) overnight at 4^{o}C, then washed and blocked with 1% human serum albumin in 0.05 M carbonate buffer. Then serum samples obtained from patients (100 µl) will be added to the wells and incubated for 120 minutes, then washed. Biotinylated goat anti-human IgG or IgM (Zymed) will be diluted and added to the wells. Subsequently, streptavidin-conjugated alkaline phosphatase (Zymed) will be added along with the color substrate (Bio-Rad, Hercules, CA). Optical density will be read at 405 nm in an automatic plate reader.

Monocyte Activation: Monocytes play a critical role in immunity, antigen presentation and regulation. CD80 (B7.1), HLA-DR and TNF-α secretion are markers of monocyte activation. Their activation status will be tested. Monocytes will be obtained and cultured as described previously [45], with or without LPS (1 µg/ml E. coli 055:B5, Sigma, St. Louis, Mo). Cells will be incubated with fluorescein isothiocyanate-conjugated anti-CD80 or anti-HLA-DR (Pharmingen, San Diego, CA) and subjected to FACS for analysis. The secretion of TNF-α will be done by using with the Multiplex Bead-based Luminex system, see above. Samples for TNF-α may be frozen and stored for batch analysis.

RNA sequence analysis: When available, protocol required biopsy material (formalin fixed paraffin embedded or fresh frozen) either at the time of diagnosis, study enrollment, or at relapse will be labeled with a non-patient indemnifying ID number with the date of collection,

protocol number, and source. This material will be provided to Celgene along with relevant non-patient indemnifying clinical data for complete mRNA sequence analysis (RNA SEQ) and will be statistically correlated with clinical outcome. The unused biopsy material will be subsequently returned to UC Davis Medical Center Department of Pathology.

Biopsy specimens will be sent to:

Anita K. Gandhi, Ph.D.
Senior Director
Translational Development & Diagnostics
Celgene Corporation
[redacted]

Return unused biopsy material to:

UC Davis Medical Center Department of Pathology
[redacted]

Statistical Analysis: Statistical analysis of lymphocyte frequency and functions between the groups will be done by unpaired Student's t test. The study design proposed will be interpreted by Dr. Laurel Beckett, Division of Biostatistics, University of California, Davis.

12 Regulatory Considerations

12.1 Institutional Review Board/Ethics Committee approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The Investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

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. The Investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB/EC prior to use.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions.

The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

12.2 Informed consent

The Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and 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.

12.3 Subject confidentiality

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.

12.4 Study records requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; 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 study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing

approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

12.5 Premature discontinuation of study

12.5.1 Single center

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 in any single center. 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.

12.5.2 Study as a whole

Celgene reserves the right to terminate this clinical study at any time for reasonable medical or administrative reasons.

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.).

13 REGISTRATION GUIDELINES

13.1 Study Registration

Registration will be done centrally at UC Davis. To register a patient, the site's data manager must complete the Eligibility Checklist and FAX a copy of this and the informed consent including the Bill of Rights to the Clinical Trials Support Unit/UC Davis Comprehensive Cancer Center [redacted]. If there are any questions, contact CTSU [redacted], or PI Dr. Joseph Tuscano [redacted] After verifying the eligibility; the CTSU Coordinator will register the patient onto the study and assign a patient accession number. See Appendix, ("Registration Procedures for Phase II Trials") for details.

13.2 Protocol Deviations

Study deviations and exceptions are not allowed. However, should the need arise, any deviation or exceptions should be reviewed by the site PI and coordinating center PI before they are enacted. If it does occur, it should be reported to the PI of the study within one week. Any consequences from deviations and exceptions must be reported to the University of California Davis Institutional Review Board as well as to local IRBs.

14 RECORDS TO BE KEPT AND DATA SUBMISSION SCHEDULE

14.1 Confidentiality of Records

The original data collection forms will be stored at the originating institution. The forms will be stored in a secure location.

14.2 Patient Consent Form

An original signed and dated participant Informed Consent document will reside in a secured location within the UCD CTSU or participating site. Copies of the signed and dated Informed Consent document will be provided to the study participant and UCD Health System Information Management for inclusion in the participant's UCD Health System Medical Record or per participating site's institutional policies.

14.3 Quality Assurance and Control

Quality assurance audits of select patients and source documents may be conducted by the UC Davis Cancer Center Quality Assurance Committee as outlined in the UC Davis Cancer Center Data and Safety Monitoring plan.

Quality control will be maintained by the CTSU Quality Assurance team according to CTSU policy.

Quality assurance audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are mailed/sent by from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the sponsor/PI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, Drug Accountability Record forms, patient registration lists, response assessment scans, x-rays, etc. available for the audit.

15 MINORITIES AND GENDER STATEMENT

Recruitment is open to all minorities and both genders. Although distributions may vary by disease type, our recruitment procedures have been developed to enroll patients who are representative of the respective target population.

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Appendix I Lenalidomide 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. 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™. Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) 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 or pregnant female, and that he understands the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a female of childbearing potential or pregnant female.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least

28 days before starting lenalidomide; 2) throughout the entire duration of lenalidomide treatment; 3) during dose interruptions; and 4) for at least 28 days after lenalidomide discontinuation.

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

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

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 lenalidomide

Female Patients:

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. The patient may not receive lenalidomide until the Investigator has verified that the results of these pregnancy tests are negative.

Male Patients:

Must agree to practice complete abstinence or agree to use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following lenalidomide discontinuation

Female Patients:

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

Male Patients:

- Must practice complete abstinence or use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of

lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.

- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.
- Male patients should not donate blood, semen or sperm during therapy or for at least 28 days following discontinuation of lenalidomide.

Additional precautions

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

Appendix II 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 III

Cockcroft-Gault estimation of CrCl:

Cockcroft-Gault estimation of creatinine clearance (CrCl):
(Cockcroft, 1976; Luke 1990)

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

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

Appendix IV

NCI CTC Version 4.0

TOXICITY WILL BE SCORED USING NCI CTCAE VERSION 4.0 FOR TOXICITY AND ADVERSE EVENT REPORTING. A COPY OF THE NCI CTC VERSION 4.0 CAN BE DOWNLOADED FROM THE CTEP HOMEPAGE: (HTTP://CTEP.INFO.NIH.GOV **OR HTTP://EVS.NCI.NIH.GOV/FTP1/CTCAE/ABOUT.HTML). ALL APPROPRIATE TREATMENT AREAS HAVE ACCESS TO A COPY OF THE CTCAE VERSION 4.0**

Appendix V

Rituxan® (Rituximab) Package Insert

This can be obtained at:

http://www.gene.com/gene/products/information/pdf/rituxan-prescribing.pdf

Appendix VI

Revlimid® (Lenalidomide) Package Insert

This can be obtained at:

http://www.revlimid.com/pdf/REVLIMID_PI.pdf

Appendix VII

Registration Procedures for Phase II Trials

REGISTRATION POLICIES

A. Registrations for this protocol must be made through the Clinical Trials Support Unit (CTSU) of the University of California, Davis Cancer Center between the hours of 9am and 3pm (Pacific Time), Monday through Friday (except holidays). Documentation of current IRB approval of this protocol by non-UCD institutions must be on file prior to registration of patients at these institutions.

B. Pre-study laboratory tests, scans, and x-rays, must be completed prior to registration, within the time frame specified in the protocol. The eligibility checklist must be completed. Patients must sign an informed consent prior to registration.

C. If the patient is to be registered the same day as the proposed treatment start date, the UC Davis Protocol Coordinator must be notified [redacted] 24 hrs prior to proposed treatment start date that the site has a patient to register.

D. Patients may be registered up to 72 hrs prior to treatment initiation. The signed consent, completed checklist and reports from all pre-study laboratory tests, scans and x-rays must be faxed to the University of California, Davis Cancer Center Clinical Trials Support Unit in order to register the patient. The UC Davis Protocol Coordinator will review these documents and fax a registration confirmation within 3 hours. **NOTE: Administration of study medication may not be initiated until the registration confirmation has been received.**

E. A patient failing to meet all protocol requirements may not be registered. If you have any questions regarding eligibility, please contact the coordinating site PI or Study Coordinator.

REGISTRATION PROCEDURES

If the patient is be registered the same day as the proposed treatment start date, the UC Davis Protocol Coordinator must be notified by fax 24 hrs prior to proposed treatment start date that the site has a patient to register. Patients may be registered up to 72 hrs prior to treatment initiation. The signed consent, completed checklist and reports from all pre-study laboratory tests, scans and x-rays must be faxed to the University of California, Davis Cancer Center Clinical Trials Support Unit in order to register the patient.

The Protocol Coordinator will verify that the patient is eligible, that pre-study tests have been completed, and that the forms are complete. The Protocol Coordinator will then register the patient, confirm the dose-level and assign a patient accession number. The Protocol Coordinator will fax back a registration confirmation including the patient's dose level and patient accession number within 3 hours.

NOTE: Administration of study medication may not be initiated until the registration confirmation has been received.

Appendix VIII

Data Collection Forms and Submission Schedule

All data will be collected using the UCD Database System (eVELOS) forms. All data forms will be completed, submitted and processed in accordance with UCD CTSU policies. Any and all source documentation should be maintained.

- SUBMIT WITHIN 24 HOURS OF REGISTRATION:
  Patient Registration Form

- SUBMIT WITHIN 14 DAYS OF REGISTRATION:
  In-House Pre-Study Evaluation Form (IH-102)

- SUBMIT WITHIN 7 DAYS OF SCREENING FAILURE:
  Patient Screen Failure Form

- SUBMIT WITH 14 DAYS OF CYCLE COMPLETION:
  Adverse Event/Drug Relationship Form

- SUBMIT WITHIN 14 DAYS OF END OF EACH TREATMENT CYCLE:
  In-House Treatment Cycle Form (IH-201)

- SUBMIT WITHIN 14 DAYS OF EACH RESPONSE ASSESSMENT:
  Tumor Measurement Log

- SUBMIT WITHIN 14 DAYS OF OFF TREATMENT:
  Off Treatment/In Follow-up/Off Study/Expiration Form (IH-301)

- SUBMIT WITHIN 14 DAYS OF KNOWLEDGE OF DEATH IF PATIENT IS STILL ON STUDY OR 30–DAYS IF OFF STUDY:
  Off Treatment/In Follow-up/Off Study/Expiration Form (IH-301)

- SUBMIT WITHIN 2 DAYS OF KNOWLEDGE OF PROTOCOL DEVIATION:
  Clinical Trials Support Unit: Notice of Protocol Deviation

- SUBMIT WITHIN 14 DAYS OF EACH REQUIRED FOLLOW-UP ENCOUNTER:
  Follow-Up Form (IH-302)

- ALL SERIOUS ADVERSE EVENTS MUST BE REPORTED AS OUTLINED IN THE PROTOCOL.

Appendix IX

Correlative Studies (Instructions for Sutter Pacific Medical Foundation):

1. Three tubes of EDTA blood (10-ml each) and One serum tube, collected at the time-points per protocol.
2. Ship to UC Davis overnight, in ambient shipper with cool packs inside (not frozen packs)

[redacted]

[redacted]