Protocol Title: A Phase II Study of Revlimid in Combination with Rituximab as Initial Treatment for Patients with Indolent Non-Hodgkin's Lymphoma

STUDY DRUG	**Lenalidomide (Revlimid®)**
PROTOCOL NUMBER:	**2008-0042**
	Celgene Protocol Number:
	(RV-LYM-PI-0247)
DATE FINAL:	***12/05/2011***
AMENDMENT:	**10.0**

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Principal Investigator:

Signature of Investigator Date

Printed Name of Investigator

Felipe Samaniego, M.D.

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.

STUDY PERSONNEL

Supporter:	**Celgene Corporation** **86 Morris Ave,** **Summit, NJ 07901** **1-800-903-9000**
Study Location:	MD Anderson Cancer Center, Houston Texas
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Co-Principal Investigator:	Nathan Fowler, M.D.
Study Coordinator:	Linda Lacerte, R.N.

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1. Protocol Synopsis

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<tr><td>STUDY DRUG:</td><td>Revlimid®, lenalidomide</td></tr>
<tr><td>INDICATION:</td><td>Indolent non-Hodgkin’s lymphoma</td></tr>
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<tr><td colspan="2">BACKGROUND AND RATIONALE:
Current therapy for indolent non-Hodgkin’s lymphoma show high overall response rates but with some toxicity. A common regimen uses fludarabine, mitoxanterone, decadron and rituximab which produces over 90% overall response rate but with 20% prolonged bone marrow toxicity and myelodysplastic syndrome. To improve on these results, we plan to treat subjects with combination with rituximab which targets tumor cells and the immunomodulator analog lenalidomide that targets both the tumor cell and the cancer cell environment. This combination shows synergy in killing of lymphoma cells and minimal overlapping toxicity.</td></tr>
<tr><td colspan="2">STUDY OBJECTIVES:
<u>Primary:</u>
To evaluate the overall response rate of lenalidomide in combination with rituximab in previously untreated indolent non-Hodgkin’s lymphoma
<u>Secondary:</u>
To evaluate the toxicity of lenalidomide in combination with Rituximab in previously untreated indolent non-Hodgkin’s lymphoma.</td></tr>
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Primary: To determine the number of CR, PR, and progression-free survival.
Secondary: Determine the type, frequency, severity, and relationship of adverse events to lenalidomide and rituximab.</td></tr>
<tr><td>STUDY DURATION: 1 year</td><td>TOTAL SAMPLE SIZE: 155</td></tr>
<tr><td>DOSING REGIMEN(S):
Schedule A:
Lenalidomide 20 mg po daily, with escalation up to 25 mg on days 1-21 of 28 day cycle for patients with follicular and marginal zone lymphoma. Rituximab 375mg/m2 IV x1 on day 1 of every cycle Total 6 cycles.
-and-
Lenalidomide 10 mg po daily, with escalation up to 25 mg on days 1-21 of 28 day cycle for patients with a diagnosis of small lymphomocyctic lymphoma. Rituximab 375mg/m2 IV x1 on day 1of every cycle Total 6</td><td>STUDY DRUG SUPPLIES:
For study participants, Celgene Corporation will provide lenalidomide at no charge through the RevAssist® program.</td></tr>
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cycles. Patients with evidence of tumor response after 6 cycles can remain on treatment for a total of 12 months. **Schedule B:** Lenalidomide 20 mg po daily, with escalation up to 25 mg on days 2-22 of 28 day cycle for patients with follicular lymphoma for cycles 1-6. Lenalidomide 10mg po daily for days 2-22 for cycles 7-12. Rituximab 375mg/m2 IV x1 on day 1,8,15 and 22 of cycle 1 and on day 1 of every subsequent cycle. Total 12 cycles. -and- Lenalidomide 10 mg po daily, with escalation up to 25 mg on days 2-22 of 28 day cycle for patients with small lymphocytic lymphoma for cycles 1-6. Lenalidomide 10mg po daily for days 2-22 for cycles 7-12. Rituximab 375mg/m2 IV x1 on day 1,8,15 and 22 of cycle 1 and on day 1 of every subsequent cycle. Total 12 cycles.	

2. Schedule of Study Assessments

Procedure 8*	Screening ≤ 30days from Baseline (First day study drug administration)	Cycle 1				All Cycles *	After Cycles 3, 6, 9,12	Discontinuation From Study Drug	Follow-Up Phase
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 1		Every 3[6] months
Record prior medications, treatments	X								
Record prior anti-cancer therapies	X								
HIV and Hepatitis B/C screening	x								
Physical examination, vital signs, weight	X					X		X	
ECOG performance status	X					X		X	
CT of the chest & abdomen / pelvis, neck, PET CT. [8*]	X						X	X	X [6]
Chest x-ray	X						X	X	
Bilateral bone marrow Bx, BM cytogenetics. On Follicular lymphoma histology do BM and blood PCR for Bcl-2 rearrangement. On SLL/CLL do ZAP70, CD38 staining and somatic mutation analysis on BM and tumor tissue.	X [2]						X[2]	X[2]	
Register patient into RevAssist® program[1]	X								
Prescribe lenalidomide via RevAssist® [1]	X					X			
Rituximab infusion [12]		X*	x	x	x	X*			
Hematology Test: hematocrit, platelet count, WBC count with differential, Absolute neutrophil count (ANC) and absolute lymphocyte count (ALC). [9, 11]	X		x		X	X		X	

Serum chemistry: Blood chemistries should include sodium, potassium, chloride, CO2, blood urea nitrogen (BUN), creatinine, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), calcium, phosphorus, and magnesium. [5]	X		X		X	X		X	
Pregnancy test [3,4]	X[4]	X	X	X	X	X[4]		X[4]	
Tumor lesions assessment	X						X	X	
Response assessment using IWG criteria							X	X	
Record adverse events		X	x	x	x	X		X	
Record concomitant therapies/procedures						X		X	
Obtain Follow-Up anti-cancer treatments									X [6]
Obtain Follow-Up survival information									X [6]
Immune Studies [13]		x				x			

* Variations of +/- 3 days of the schedule are permitted

[1] Lenalidomide must be prescribed through and in compliance with Celgene's RevAssist® program. Prescriptions must be filled within 7 days.

[2] Repeat BM evaluation to confirm morphologic and genetic markers of disease. Zap 70 and CD38 staining will be done if tissue is available. Repeat BM biopsy is at investigators discretion once documentation of absence of morphologic disease and by PCR for BCL2 (if BCL2 was positive at screening) is obtained. Screening bone marrow biopsy can be obtained up to 60 days prior to study entry.

[3] 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).

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

[5] Thyroid Stimulating Hormone (TSH) will be drawn prior to cycles 4, 7,10, and at treatment discontinuation
[6] Follow-up – Patients will be evaluated every 3 months for one year, every 6 months for 1 year and then yearly with CT of neck, thorax, abdomen and pelvis and other studies as recommend by the treating physician.
[7] Patient evaluation and predose labs can occur up to 3 days prior to starting each cycle. If possible, patients should be seen at least 24 hours prior to each cycle.
[8] If a patient is allergic to IV contrast, non-contrast PET/CT images can be used for tumor evaluation, response assessment. If patient has a history of PET negative disease, repeat PET is not required prior to study entry.
[9] If not reported on patients CBC, patient's ANC and ALC can be calculated from absolute neutrophil percent and absolute lymphocyte percent.
[10] In the absence of a history of blood transfusion or intravenous drug use in the past 6 months, patients can have hepatitis B/C and HIV testing up to 8 weeks prior to study entry.
[11] Hematology testing will occur on day 1 and day 14 (+/- 4 days) of cycles 2-12.
[12] Schedule A: Rituximab will be given weekly on day 1 of each cycle in schedule A. Schedule B: Rituximab will be given on days 1,8,15,22 on cycle 1, and on day 1 of subsequent cycles.
[13] On patients on schedule "B", draw blood for quantitative and qualitative immune subset anaylsis on day 1 of cycle 1 (allowed up to 48 hours prior to treatment), day 1 prior to treatment on cycle 2, day 15 of cycle 2, and on day 28 (+/- 3 days) of cycle 6. WBC gene expression testing on day 1 of cycle 1 (allowed up to 48 hours prior to treatment) and on day 15 of cycle 2.

3. Background and Rationale

Introduction

Lenalidomide, belongs to Celgene Corporation's proprietary class of IMiD™ compounds called IMiDs™. IMiDs™,compounds 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)] In addition, lenalidomide has a variety of immunomodulatory effects. 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)] Upregulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity. [(3)]

Although the exact antitumor mechanism of action of lenalidomide is unknown, a number of mechanisms are postulated to be responsible for lenalidomide's activity against multiple myeloma. Lenalidomide has been shown to increase T cell proliferation, which leads to an increase in IL-2 and IFN-gamma secretion. The increased level of these circulating cytokines augment natural killer cell number and function, and enhance natural killer cell activity to yield an increase in multiple myeloma cell lysis.[(4)] In addition, lenalidomide has direct activity against multiple myeloma and induces apoptosis or G1growth arrest in multiple myeloma cell lines and in multiple myeloma cells of patients resistant to melphalan, doxorubicin and dexamethasone.[(5)]

Clinical experience in solid tumors with lenalidomide

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. [(6)]

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. [(7)]

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. [8]

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.[16]

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. [9] In a similar study at the Dana Farber Cancer Institute, 27 patients with rapidly advancing refractory multiple myeloma were enrolled. [11]

Anti-mutliple 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. [(12)]

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. [(13)]

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. [(14)]

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.[(14)] Additional phase I trials of lenalidomide with chemotherapy in advanced malignancies are in progress.

Celgene Corporation sponsored 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. [16] 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. These studies led to the FDA approval of lenalidomide in combination with dexamethasone for the treatment of multiple myeloma in patients that have received at least one prior therapy.

Clinical experience in myelodysplastic syndromes (MDS), chronic lymphocytic leukemia and lymphoma with lenalidomide

An exploratory trial in 43 MDS patients with transfusion dependent or symptomatic anemia was conducted at the University of Arizona. [19] 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%).

Celgene Corporation sponsored a multicenter trial (MDS-003) of 148 MDS patients with a clonal interstitial deletion involving chromosome 5q31.1. Lenalidomide was given at a dose of 10mg on Days 1-21, repeated every 28 days, to 44 patients, and at a dose of 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. [17]

Another Celgene sponsored trial (MDS-002) in patients with low to intermediate-1 risk MDS enrolled 215 patients, of whom, 166 were documented to have low to intermediate-1 risk MDS. 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. [16]

Lenalidomide in CLL and lymphoma

In a multicenter phase II study of Lenalidomide in relapsed/refractory aggressive non-Hodgkin's lymphoma, subjects with at least 1 prior treatment regimen received 25 mg lenalidomide daily on Days 1-21 of a 28 day cycle for 52 weeks. Response and progression were evaluated using the IWLRC methodology. The median age of the 22 response-evaluable subjects was 65 (46-83) and 13 were female. Histology was diffuse large B-cell [DLBCL] (n=12) follicular center lymphoma grade 3 [FL] (n=13), mantle cell lymphoma [MCL] (n=5) and transformed [TSF] (n=2). Median time from diagnosis to lenalidomide monotherapy was 2.3 (0.7-7) years and median number of prior treatment regimens per subject was 2 (1-6). Seven subjects (32%) exhibited an objective response (2 complete responses unconfirmed (Cru) and 5 partial responses (PR)), 6 had stale disease (SD) for a tumor control rate (TCR) of 59%, and 9 progressive disease (PD). Responses were produced in each of the aggressive histologic subtypes studied: DLBCL (3/12), FL (1/3), MCL (2/5) and TSF (1/2). Grade 3 or 4 adverse events occurred in 18 of 31 (58%) subjects receiving drug. These were predominantly Grade 3 hematological events (neutropenia, thrombocytopenia) with only 4 subjects (13%) experiencing a Grade 4 adverse reaction. These preliminary results relapse/refractory aggressive NHL indicate that lenaliodomide monotherapy is active with manageable side effects. [19]

A. Ferrajoli, et. al., at MD Anderson in a phase II study at MD Anderson of CLL patients who had received at least one purine analog-based regimen, were given lenalidomide 10 mg daily for 28 days followed by titration upward by 5 mg increments every 28 days to a maximum dose of 25 mg daily. 22 patients have received treatment for at least 3 months and are therefore evaluable for response. The median age was 64 years (range 49-82) and

the median number of prior treatments was 4 (1-15). β2m was 4.1 mg/dL (1.6-10.1). 12 patients (55%) had Rai stage III or IV disease. 8 patients (36%) were refractory to fludarabine and 7 patients (32%) to alkylating agents. Responses according to NCI-WG criteria assessed after 3 months of treatment showed that 7 patients (32%) achieved a response [1 CR (5%), 1 nodular PR (5%), 5 PR (23%)]. 9 patients (41%) attained stable disease or clinical improvement and are continuing on treatment, and 6 patients 27% progressed, including one early death that occurred on day 22 secondary to mucormycosis. Fatigue was reported in 59% (G3 in 5%), nausea in 45%, pruritus in 31% and diarrhea in 22% (G3 in 5%). Myelosuppression occurred in 55% of the patients (32% ≥ G3 neutropenia and/or thrombocytopenia). Infectious complications were observed in 6 patients. [20]

In a multicenter phase II study of lenalidomide in relapsed/refractory indolent non-Hodgkin's lymphoma T. Witzig, et al treat subjects with 25 mg lenalidomide daily on Days 1-21 every 28 days and continue therapy for 52 weeks. The median age of the 15 response-evaluable subjects was 64 (54-82) and 5 were female. Histology was small lymphocytic lymphoma (SLL) (n=8), follicular center lymphoma grades 1, 2 (FL) (n=5) and nodal marginal B-cell lymphoma (NML) (n=2). Median time from diagnosis to lenalidomide monotherapy was 7.6 (3-14) years and median number of prior treatment regimens per subject was 3 (1-17). Using the IWLRC methodology, two subjects (13%) exhibited an objective partial response (PR) at four months. Both responses, one FL and one NML, occurred in subjects with substantial tumor burden. The 4-month time-to-response for these indolent NHL subjects was longer than the time-to-response in aggressive NHL subjects (n=7) following lenalidomide monotherapy. Seven patients had stable disease (SD) for a tumor control rate (TCR) of 60% and 6 had progressive disease (PD). Grade 3 or 4 adverse events occurred in 9 (39%) subjects. These were predominantly Grade 3 hematological events (neutropenia, thrombocytopenia) with only 3 subjects (13%) experiencing a Grade 4 adverse reaction (all neutropenia). Lenalidomide monotherapy in indolent NHL showed evidence of activity with an acceptable safety profile. [21]

Lenalidomide in combination therapy in lymphoma.

In a phase I/II study of Lenalidomide in combination with Rituximab in relapsed/refractory mantle cell lymphoma with 1-4 prior therapies, M. Wang, et.al., at MD Anderson, subjects were given Lenalidomide daily for 21 days followed by 7 days of rest and Rituximab 375 mg/m^2 weekly for 4 weeks. A standard phase I dose escalation was used to determine MTD with Lenalidomide dose levels at 10 mg, 15 mg, 20 mg, and 25 mg. Dose-limiting toxicity (DLT) was defined as grade 3 or 4 non-hematologic or

grade 4 hematologic toxicity. Seven evaluable (4 patients at 10 mg and 3 at 15 mg). Median age was 73, range 56-84; median prior lines of therapy were 3, range 1-4. Each cohort has 3 patients. No DLT has been encountered with a maximum Lenalidomide dose up to 20 mg. The number of cycles given ranged from 1 to 5 cycles. There were no grade 3 or 4 toxicities during cycle 1. Grade 1 non-hematologic toxic events included fatigue in 4, stomatitis in 3, pruritis in 3, and myalgias in 2. There was 1 episode of grade 2 anemia. The MTD has not been reached. Two patients had stable disease at cycle 3 and cycle 5, respectively. Four patients had progressive disease and were taken off the study. The combination provided stable disease in an aggressive lymphoma subtype with minimal toxicity. [(22)]

Preliminary results from this study have shown favorable response rates. In the first 13 patients evaluable for response, the overall response rate has been 85% with a complete response rate of 77%. The complete and overall response rate in patients with follicular lymphoma (n=7) has been 100%.

INDICATIONS AND USAGE:

Revlimid® (lenalidomide) is 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. Revlimid® is also approved in combination with dexamethasone for the treatment of patients with multiple myeloma that have received at least one prior therapy.

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, cellulites, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified, tumor lysis syndrome and fractures. Lenalidomide may cause breakdown products of the cancer cells to enter the blood stream, which may lead to heart rate abnormalities, kidney failure, muscle twitching, and/or muscle cramps.

The US rituximab product label lists as the most serious adverse reactions: infusion reactions, tumor lysis syndrome, mucocutaneous reactions, hypersensitivity reactions, progressive multifocal leukoencephalopathy, hepatitis B virus (HBV) reactivation, cardiac arrhythmias and angina, infections, and renal failure.

Mild to moderate infusion reactions consisting of fever and chills and rigors occurred in the majority of subjects during the first infusion. Other frequent infusion reaction symptoms included nausea, pruritus, angioedema, asthenia, hypotension, headache, bronchospasm, throat irritation, rhinitis, urticaria, rash, vomiting, myalgia, dizziness, and hypertension.

The most common respiratory AEs were increased cough, rhinitis, bronchospasm, dyspnea, and sinusitis. In addition, immune/autoimmune events have been reported including uveitis, optic neuritis, pleuritis, serum sickness with polyarticular arthritis, and vasculitis with rash.

Less common AEs reported from clinical studies included agitation, anorexia, arthritis, conjunctivitis, depression, dyspepsia, edema, hypokinesia, hypertonia, hypesthesia, hypoglycemia, injection site pain, insomnia, lacrimation disorder, malaise, nervousness, neuritis, neuropathy, paresthesia, somnolence, vertigo, and weight decrease.

Severe rash has been reported following lenalidomide use. Although this rash is usually mild and resolves, there have been reported cases of severe reactions, and in some cases this has lead to death.

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

Rationale for Treatment in this Setting

Current therapy for indolent non-Hodgkin's lymphoma: The optimal treatment of indolent non-Hodgkin's lymphoma has not been determined. While indolent non-Hodgkin's lymphoma responds to many drugs, there is no best combination that offers efficacy with minimal toxicity. Combination chemotherapy such as fludarabine novanterone decadron and rituximab provide greater than 95% response rates; however, long term myelosuppression can be observed in 20% and secondary cancer occur in 5%. There is a need for better options. Rituximab consistently improves response rates in non-Hodgkin's lymphoma. The immunomodulator lenalidomide targets the cancer cell environment. Rituxan appears a rational combination with expected synergistic activity and minimal overlapping toxicity.

4. Study Objectives and Endpoints

Objectives

Primary objectives

To evaluate the overall response rate of lenalidomide in combination with rituximab in previously untreated indolent non-Hodgkin's lymphoma

Secondary study objectives

To evaluate the toxicity of lenalidomide in combination with Rituximab in previously untreated indolent non-Hodgkin's lymphoma

Endpoints

Primary Endpoint

To determine the number of CR, and PR.

Secondary Endpoints

Determine the type, frequency, severity, and relationship of adverse events to lenalidomide and rituximab.

5. Investigational Plan

Overall design

Patients will be stratified into 3 subgroups based upon their diagnosis. The three groups are defined as follicular lymphoma, marginal zone lymphoma, and small lymphocytic lymphoma (SLL). Up to 30 patients will be enrolled in the marginal zone lymphoma group, 45 patients small lymphocytic group (30 schedule A, and 15 Schedule B), and 80 patients (50 schedule A, 30 schedule B) will be enrolled in the follicular lymphoma group. Groups will continue to screen and enroll patients until maximum accrual is reached or evidence of unacceptable toxicity or lack of response is observed (see section 10; biostatistical analysis, for stopping rules).

Schedule A: Lenalidomide will be administered orally at 20 mg total daily dose on days 1 to 21 of a 28 day cycle in patients with follicular and marginal zone lymphoma. Following cycle 3, if patients fail to show a response (partial or complete) the dose will be increased to 25mg/day. Patients with a diagnosis of small lymphocytic lymphoma (SLL) will begin at a dose of 10 mg total daily on days 1 to 21 of a 28 day cycle. This dose will be escalated by 5mg every 28 days up to 20mg if no toxicity is encountered. If no response is observed by cycle 3, the dose will be increased to 25 mg. (see dose modification for lenalidomide table). A single 375 mg/m2 intravenous dose of rituximab will be given at day 1 of every cycle.

Schedule B: Lenalidomide will be administered orally at 20 mg total daily dose on days 2 to 22 of a 28 day cycle in patients with follicular lymphoma. Following cycle 3, if patients fail to show a response (partial or complete) the dose will be increased to

25mg/day. Patients with a diagnosis of small lymphocytic lymphoma (SLL) will begin at a dose of 10 mg total daily on days 2 to 22 of a 28 day cycle. This dose will be escalated by 5mg every 28 days up to 20mg if no toxicity is encountered. If no response is observed by cycle 3, the dose will be increased to 25 mg. (see dose modification for lenalidomide table). A single 375 mg/m2 intravenous dose of rituximab will be given at day 1, 8,15, and 22 of cycle 1 and on day 1 of every subsequent cycle. In the absence of progression or toxicity, patients will remain on treatment for a total of 12 months. If patients attain a complete response following cycle 6 or 9, lenalidomide will be reduced to 10mg daily for the remaining cycles with the same dosing schedule of rituximab and lenalidomide as described above."

Patients that have documented clinical benefit and no evidence of progression of disease can remain on treatment for a total of 12 months. Treatment will be continued at the cycle 6 dose level with the same dosing schedule of rituximab and lenalidomide as described above.

Several phase II studies have shown activity with lenalidomide in CLL. Higher doses (25mg) have been associated with increased toxicity in the form of an increased incidence of tumor flare and tumor lysis syndrome (TLS).27,28 Tumor flare has also been correlated with response and may be associated with lenalidomide efficacy. 29 However, lower doses (10mg) appear to be better tolerated and have been associated with fewer cases of tumor flare. Ferrajoli et al treated 35 patients with CLL with a starting dose of 10mg daily for 28 days with a dose escalation to 25mg as tolerated. There were no cases of tumor lysis reported, and only 12% of patients developed tumor flare. The median dose level was 10mg. 30 In another phase II trial with lenalidomide in CLL, 2 out of the first 25 patients experienced TLS at the initial starting dose level (25mg). The study was modified to begin at a lower starting dose and none of the 16 patients who started on the 10mg dose level experienced tumor lysis. The incidence of tumor flare was unchanged, but the severity of reactions decreased significantly.31

Response to therapy will be assessed after 3 cycles and after 6 cycles of chemotherapy. In patients that continue on with extended dosing beyond cycle 6, response will also be evaluated after 9 and 12 cycles of chemotherapy. If after 3 cycles of therapy, there is stable disease without progression, as defined by IWG criteria, the lenalidomide dose will be increased for a total daily dose of 25mg, or 5 mg above the current dose in patients with SLL. If there is evidence of progression of disease, the patient will discontinue study medication.

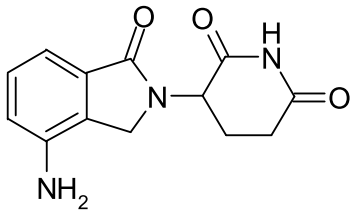
The rationale for schedule B is derived from studies in both CLL and multiple myeloma suggest a clinical benefit (response rate and PFS) with extended dosing of lenalidomide. In schedule B, the dose of lenalidomide will be reduced in responding patients on cycles 7-12 to minimize potential myelosupression with increased exposure. In addition, significant infusion reactions to rituximab have been noted to occur beyond cycle 2. Although etiology of the infusion reactions is unknown, the severity of the reaction may be potentiated by concurrent dosing of lenalidomide. Ancedotal experience suggests that starting lenalidomide on day 2 of treatment (rituximab on day 1) may lessen the observed toxicity. Dose intensification of rituximab (weekly dosing) will occur in cycle 1 to increase mean serum concentration early in treatment.

Investigational Drug

Lenalidomide Description

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. The 5 mg capsule shell contains gelatin, titanium dioxide and black ink. The 10 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink.

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.

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.

Supplier(s)

Celgene Corporation will supply Revlimid® (lenalidomide) to study participants at no charge through the RevAssist® program. All physicians who prescribe lenalidomide for research subjects enrolled into this trial and all research subjects enrolled into this trial must be registered in and must comply with all requirements of Celgene's RevAssist® program.

Dosage form

Lenalidomide will be supplied as capsules for oral administration. The tablets are available in 5, 10, 15, and 25 mg capsule strengths.

Packaging

Lenalidomide will be shipped directly to the patient. Bottles will contain a sufficient number of capsules for one cycle of dosing.

Storage

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

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 RevAssist® program. Per standard RevAssist® requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of Celgene's RevAssist® program. Prescriptions must be filled within 7 days. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle**.

Unused study drug supplies

Patients should follow instructions for the return of study medication per the RevAssist® program. The RevAssist® Program will be used to return unused Revlimid by calling 1888 423 5436 who will collect the drug.

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 30 days prior to initiation of therapy.

Approximately 110 of subjects with indolent non-Hodgkins lymphoma will be screened for enrollment and must meet the eligibility criteria below. Bone marrow biopsy can be performed up to 60 days prior to study entry.

Inclusion Criteria

Subjects must meet the following inclusion/exclusion criteria to be eligible for the study.

Inclusion criteria

1. Understand and voluntarily sign an informed consent form.
2. Age ≥ 18 at the time of signing the informed consent form**.**
3. Able to adhere to the study visit schedule and other protocol requirements.
4. Untreated indolent non-Hodgkin's lymphoma stage III-IV including small lymphocytic lymphoma, marginal zone lymphoma, grade 1 or 2 follicular lymphoma (prior radiation for localized disease allowed).
5. At least one measurable lesion according to the International workshop standardized response criteria for non-Hodgkin's lymphomas (IWG) greater than 1.5cm.
6. ECOG performance status of ≤ 2 at study entry
7. Laboratory test results within these ranges:
   - Absolute neutrophil count ≥ 1.5 x 10^9/L[††]
   - Platelet count ≥ 100 x 10^9/L
   - Serum creatinine ≤ 2.0 mg/dL
   - Total bilirubin ≤ 1.5 mg/dL
   - AST (SGOT) and ALT (SGPT) ≤ 2 x ULN or ≤ 5 x ULN if hepatic metastases are present.
8. Disease free of prior malignancies for >/= 5 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma "insitu" of the cervix or breast, or localized prostate cancer treated with curative intent.
9. All study participants must be registered into the mandatory RevAssist® program, and be willing and able to comply with the requirements of RevAssist®.
10. Females of childbearing potential (FCBP)[†] must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior

[†] 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).
[††] Patients can enroll with ANC < 1.5 x 10^9 /L or PLT count less than 100 x10^9/L if cytopenia is due to extensive bone marrow involvement of disease as determined by the treating physician.

to and again within 24 hours of prescribing lenalidomide 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 4 weeks 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 female of child bearing potential even if they have had a successful vasectomy. See Appendix I: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control

For patients with bulky disease (tumors >5cm) must be able to take aspirin (81mg or 325 mg) daily as prophylactic anticoagulation (patients intolerant to ASA may use warfarin or low molecular weight heparin.

Exclusion criteria

1. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.
2. Pregnant or breast feeding females.
3. 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.
4. Use of any chemotherapy or experimental therapy within 28 days of enrollment.
5. Known hypersensitivity to thalidomide.
6. The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide or similar drugs.
7. Any prior use of lenalidomide.
8. Concurrent use of other anti-cancer agents or experimental treatments.
9. Known positive for HIV or infectious hepatitis type B or C. [¥]

[¥] Hepatitis B core antibody can be positive if Hep B surface antigen is negative and no HBV DNA in blood, indicating a cleared infection.

Visit schedule and assessments

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

All timepoints outlined in the Schedule of Assessments allow variation of +/- 3 days. Due to the drug delivery from an outside facility, clinicians should allow up to 72 hours from patient assessment/evaluation to the start of each cycle.

Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.

In addition to the required pregnancy testing, the Investigator must confirm with FCBP that she is continuing to use two reliable methods of birth control at each visit.

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 28 days post the last dose of study drug.

Drug Administration

Rituxan 375 mg/m2 iv, infused per the MD Anderson Chemotherapy Order Sheet, will be given on day 1 of cycles 1-12 in schedule A, and day 1, 8,15, and 22 of cycle 1 and on day 1 of every subsequent cycle in schedule B. Rituxan will be obtained commercially, and will not be supplied by the sponsor. Rituxan should be administered by IV infusion, per the MD Anderson pharmacy guidelines for rituximab infusion.

The amount of drug to be administered will be based on BSA. Body surface area will be calculated using a standard nomogram on Cycle 1, Day 1 and at subsequent visits if the subject experiences a >5% change in body weight from the weight used for the most recent BSA calculation.

Schedule A: The planned dose of lenalidomide for patients with follicular lymphoma and marginal zone lymphoma is 20 mg/day, orally on days 1 – 21 followed by 7 days rest (28 day cycle). Following cycle 3, if patients fail to show a response (partial or complete) the dose will be increased to 25mg/day.

Schedule B: Lenalidomide will be administered orally at 20 mg total daily dose on days 2 to 22 of a 28 day cycle in patients with follicular lymphoma. Following cycle 3, if patients fail to show a response (partial or complete) the dose will be increased to

25mg/day. Patients with a diagnosis of small lymphocytic lymphoma (SLL) will begin at a dose of 10 mg total daily on days 2 to 22 of a 28 day cycle. This dose will be escalated by 5mg every 28 days up to 20mg if no toxicity is encountered. If no response is observed by cycle 3, the dose will be increased to 25 mg. (see dose modification for lenalidomide table). A single 375 mg/m2 intravenous dose of rituximab will be given at day 1, 8,15, and 22 of cycle 1 and on day 1 of every subsequent cycle. In the absence of progression or toxicity, patients will remain on treatment for a total of 12 months. If patients attain a complete response following cycle 6 or 9, lenalidomide will be reduced to 10mg daily for the remaining cycles with the same dosing schedule of rituximab and lenalidomide as described above.
Dosing will be at approximately the same time each day.The planned dose of lenalidomide for patients with SLL is 10 mg/day, orally on days 1 – 21 followed by 7 days rest (28 day cycle). If no toxicities are encountered, the dose of lenalidomide in patients with SLL will be increased by 5 mg with each cycle up to 20mg/day. Following cycle 3, if patients fail to show a response (partial or complete) the dose will be increased to 25mg/day. Only one cycle of study drug will be supplied to the patient each cycle.(for dose modification guidelines, see Table 2: Dose modification for Lenalidomide) Only one cycle of study drug will be supplied to the patient each cycle.

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

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

Subjects experiencing adverse events may need study treatment modifications. See Table 2.

Special Handling Instructions

Women of childbearing potential should not handle or administer the clinical dosage forms unless they are wearing gloves.

Dose Continuation, Modification and *Interruption*

Subjects will be evaluated for AEs at each visit with the NCI CTCAE v3.0, see below for full instruction on initiation of a new cycle of therapy and dose modifications during a cycle of therapy.

Lenalidomide Dose Adjustment Steps

Table 1 outlines lenalidomide dose adjustment steps

Table 1: LENALIDOMIDE Dose Adjustment Steps	
Starting Dose	**20 mg daily for 21 days every 28 days**
Dose Level +1	25 mg daily for 21 days every 28 days
Dose Level –1	15 mg daily for 21 days every 28 days
Dose Level –2	10 mg daily for 21 days every 28 days
Dose Level –3	5 mg daily for 21 days every 28 days

Table 2: LENALIDOMIDE Dose Adjustment Steps in SLL	
Starting Dose	10 mg daily for 21 days every 28 days
Dose level +1	15 mg daily for 21 days every 28 days
Dose level +2	20 mg daily for 21 days every 28 days
Dose level +3	25 mg daily for 21 days every 28 days
Dose level -1	5 mg daily for 21 days every 28 days
Dose level -2	5 mg daily for 14 days every 28 days
Dose level -3	Hold therapy

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 ≥ 1,000/μL;
- The platelet count is ≥ 50,000/μL;
- Any lenalidomide-related 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 more than 7 days due to toxicity newly**

encountered on the scheduled Day 1, then the new cycle will be started with a one-level dose reduction.

Instructions for dose modifications or interruption 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 ≥ 38.5º C) or Grade 4 neutropenia	• Hold (interrupt dose). • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 restart at next lower dose level and continue the cycle until Day 21.	• Omit lenalidomide for remainder of cycle 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 3 (platelet count < 50,000/mm³)	• Hold (interrupt dose). • Follow CBC weekly. • If thrombocytopenia resolves to ≤ grade 2 restart at next lower dose level and continue the cycle until Day 21.	• Omit lenalidomide for remainder of cycle
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.
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

Table 2: Dose Modification for Lenalidomide		
NCI CTC Toxicity Grade	**Day 2-14 of Cycle**	**≥Day 15 of Cycle**
Venous thrombosis/embolism ≥ Grade 3	• Hold (interrupt) dose and start anticoagulation; restart at investigator's discretion (maintain dose level).	• Omit lenalidomide for remainder of cycle. Anticoagulation measures as described in Conncomitant therapy section below.
other non-hematologic toxicity assessed as Lenalidomide-related ≥ Grade 3	• Hold (interrupt) dose. Follow at least weekly. • If the toxicity 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.
Hyperthyroidism or hypothyroidism	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide next cycle (decrease dose by one dose level).	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide next cycle (decrease dose by one dose level).

† If patient had low baseline platelets due to prior to study entry, dose reduction not required.

Dose Escalation

In schedule B, all patients in a complete response will reduce lenalidomide to 10mg daily on cycles 7-12.

If after 3 cycles of therapy, there is stable disease without evidence of progression as defined by IWG criteria, the lenalidomide dose will be increased to 25 mg per day (dose level +1) or 5 mg above the current dose in patients with SLL. The initiation of the next cycle will only be initiated if there is no evidence of toxicity as outlined above in the Instructions for Initiation of a New Cycle.

Treatment compliance

Subjects will be asked to maintain a diary to record the drug administration.

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.

Discontinuation of Study Treatment

In Schedule A, treatment will continue until six cycles or the occurrence, if it is determined by the treating physician that the patient will derive clinical benefit from

extended dosing. **In schedule B**, all patients will continue until 12 cycles 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
- 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

Follow-Up

Subjects who discontinue treatment for any reason, will be followed for 6 months. Subjects will undergo a safety assessment approximately 28 days post the last dose of study drug. In addition, off study evaluations, such as recording subsequent therapy, per the Schedule of Assessments will be done. Following completion of chemotherapy, patients will be evaluated every 3 months for one year, every 6 months for 1 year and then yearly with CT of neck, thorax, abdomen and pelvis and other studies as recommend by the treating physician.

Correlative Studies:

The mechanism of action, as well as the effect on the target microenvironment of the combination of lenalidomide and rituximab is poorly understood. In vitro, lenalidomide has been shown to increase recruitment and activation of immune effector cells and potentially repair T cell recognition and killing of malignant cells. By measuring levels of immune effector cells in accessible lesions, and comparing these with pre-treatment biopsies, we will learn about potential mechanisms of action of lenalidomide in untreated NHL.

Using peripheral blood samples, we will measure the number and function of immune effector cell subsets on day 1 of cycle 1 (allowed up to 48 hours prior to treatment), day 1 prior to treatment on cycle 2, day 15 of cycle 2, and on day 28 (+/- 3 days) of cycle 6. We will also measure gene expression on PBMCs prior to treatment on day 1 (allowed up to 48 hours prior to treatment) and on day #15 of cycle 2.

An elective core needle biopsy of an accessible tumor will be obtained with the patient's consent on day 18 of cycle 1. The tumor composition will be examined for infiltration and levels of non-malignant B-cells, activated NK cells, and T-cell subsets.

6. Adverse events

MD Anderson (Sponsor) Reporting Requirements for Serious Adverse Events and Dose Limiting Toxicities:

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]

Suspected positive Pregnancy

[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.

Adverse Drug Reaction Reporting

Toxicity will be scored using CTCAE Version 3.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP homepage (HTTP://CTEP.INFO.NIH.GOV). All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0. 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.

Serious Adverse Events Reporting: The principle investigator has the obligation to report all serious adverse events to the University of Texas M. D. Anderson Cancer Center (MDACC) IRB via the Office of Protocol Research and to Celgene within 24 hours.

In IND studies, all serious adverse events must be reported to the FDA by the investigator through the Office of Research Education & Regulatory Management (ORERM) as required by 21 CFR 312.32. These reports are to be filed utilizing the University of Texas M. D. Anderson Cancer Center Adverse Event Reporting Form. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences.
All other serious adverse events not requiring expedited reporting should be reported to MDACC IRB and ORERM within 5 business days.

All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 24 hours of knowledge regardless of the attribution. SAEs beyond 4 weeks after the end of study drug administration will be reported if thought to be drug related.

NOTE: Instructions concerning procedures and reporting for pregnancies below.

Pregnancies

Pregnancies occurring while the subject is on lenalidomide or within 4 weeks after the subject's last dose of lenalidomide are considered expedited reportable events. If the subject is on lenalidomide, it is to be discontinued immediately and the subject is to be instructed to return any unused portion of lenalidomide to the Investigator. The pregnancy must be reported by the investigator to MDACC IRB and ORERM AND to Celgene Corporation Worldwide Drug Safety Surveillance (WWDSS) within 24 hours of the Investigator's knowledge of the pregnancy by phone and facsimile using the SAE Form.

The Investigator will follow the subject until completion of the pregnancy, and must notify Celgene Corporation Worldwide Drug Safety Surveillance (WWDSS) of the outcome as specified below. The Investigator will provide this information as a follow-up to the initial SAE.

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

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

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

Celgene Drug Safety Contact Information:

Celgene Corporation
Worldwide Drug Safety Surveillance (WWDSS)
86 Morris Avenue
Summit, N.J. 07901

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

Investigator Reporting Responsibilities

The conduct of the study will comply with all FDA safety reporting requirements. Serious Adverse Events Reporting: The principle investigator has the obligation to report all serious adverse events to the University of Texas M. D. Anderson Cancer Center (MDACC) IRB via the Office of Protocol Research and also to Celgene within 24 hours.

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 with MD Anderson's ORERM, who will then forward to FDA. An additional copy should be placed in the study's Regulatory Binder and a copy must be sent to Celgene Corporation as a supporter of this study as follows.

Celgene Corporation
Attn: Medical Development
86 Morris Avenue
Summit, NJ 07901
Tel: (908) 673-9000

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.

Expedited reporting by investigator to Celgene

Serious adverse events (SAE) are defined above. The investigator should inform Celgene of any SAE within 24 hours of being aware of the event. The date of awareness should be noted on the report. This must be documented on an MD Anderson SAE form. This form must be completed and supplied to MDACC IRB, ORERM and Celgene within 24 hours/1 business day at the latest on the following working day. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and 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 MD Anderson SAE form. A final report to document resolution of the SAE is required. The Celgene protocol number (RV-LYM-PI-0247 should be included on SAE reports 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.

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.

Sponsor Reporting to the FDA

Adverse drug reactions that are **Serious, Unlisted/unexpected, and at least possibly associated to the drug,** and that have not previously been reported in the Investigators

brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) in writing by each investigator/physician engaged in clinical research. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

The sponsor shall notify the FDA by telephone or by fax of any unexpected fatal or life threatening experience associated with the use of the drug. As soon as possible, but no later than 7 calendar days after the sponsors initial receipt of the information. Each phone call or fax shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND if applicable.

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.

7. Response Criteria

Baseline lesion assessments will be measured. At least 1 lesion greater than 1.5 cm must be documented during screening as per Section 2, Schedule of Study Assessments.

Efficacy assessments are scheduled to occur per the Schedule of Study Assessments, Section 2. Assessments for response will be done at approximately day 1 of every cycle. Response will also be done using CT scans, PET-CT and bone marrow biopsy after 3, 6, 9 and cycle 12.

Response and progression will be evaluated in this study using the International workshop standardized response criteria for non-Hodgkin's lymphomas (IWG) (23).

-and-

Instructions for interpreting response criteria for lesion evaluation and best overall response may be found in Appendix D, International workshop standardized response criteria for non-Hodgkin's lymphomas (IWG).

8. Protocol Amendments/Deviations

Protocol amendments

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

Protocol deviations

When an emergency occurs that requires a deviation from the protocol for a subject, a deviation will be made only for that subject. A decision will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was effected) is to continue in the study. The subject's medical records will completely describe the deviation from the protocol and state the reasons for such deviation. In addition, the Investigator will notify the IRB/EC in writing of such deviation from protocol.

9. Data Management

Analyses and Reporting

Data will be analyzed and reported after all subjects have been assessed for overall response after 3 cycles. . All subsequent data collected will be analyzed and reported in a follow-up clinical report.

Study monitoring and auditing

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 into MDACC's PDMS. The Investigator will permit study-related monitoring visits and audits by MDACC's ORERM, 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 MDACC ORERM and the Celgene representative so that the accuracy and completeness may be checked.

The Investigator will be responsible for reviewing the data and determining the stopping rule.

10. Biostatistical Analysis

Overview

This is an open label, phase II clinical trial to evaluate the efficacy and safety of Lenalidomide given in combination with Ritximab to patients with indolent non-Hodgkin's lymphoma.

Datasets to be analyzed

Statistical Methodology

The trial consists of 4 parallel patient cohorts. Using dose schedule A we will enroll 50 patients with follicular lymphoma (cohort 1) and 30 patients with marginal zone lymphoma (cohort 2). We will enroll 45 patients with small lymphocytic lymphoma (cohort 3). We will also enroll 30 patients with follicular lymphoma patients and treat them with dosing schedule B (cohort 4). This will allow the investigators to better characterize and define possible differences in the response rate and toxicity profiles for each of the study subgroups.

The overall response, denoted as OR (to be assessed at the end of 3 cycles), and toxicity (to be assessed at the end of the first cycle) will be monitored simultaneously for each of the subgroups separately using the Bayesian approach of Thall, Simon, Estey (1995, 1996) as extended by Thall and Sung (1998). Toxicity is defined as any grade 3 or 4 nonhematologic toxicity.

Cohort 1: For the subgroup of patients with follicular lymphoma and treated with dosing schedule A, historical data on similar patients show an overall response rate of 70% and toxicity rate of 20%. However, the information was down-weighted to reflect the same marginal OR and toxicity rates in 10 patients. Independence was assumed between OR and toxicity. It is expected for the current trial that the two-drug combination will improve the OR rate to 80% while the toxicity rate is maintained at 30%. A sample size of 50 patients ensures that, if the trial is not terminated early, a posterior 90% credibility interval for overall response rate will have width of 0.19 at most, under the assumption of an 80% of overall response rate. The probabilities of OR and toxicity for the historical data are modeled by beta distributions (*Beta*(7, 3) and *Beta*(2, 8), respectively). The prior probabilities of OR and toxicity for the experimental regimen are also modeled by beta distributions

(*Beta*(1.4, 0.6) and *Beta*(0.4, 1.6), respectively), which have the same *means* as the corresponding beta distributions for the historical data. Denoting the historical probabilities of overall response rate and toxicity rate by {p(OR,H) , p(TOX,H)}, the following decision criteria will be applied:

1) **Let E correspond to the experimental treatment, stop if Prob{p(OR,H) + δ_{OR} > p(OR,E) | data} > 0.90, where δ_{OR} =0.1**
2) **Stop if Prob{p(TOX,H) + δ_{TOX} < p(TOX,E)| data}>0.90, where δ_{TOX} =0.1**

Patients will be monitored according to the following stopping boundaries for overall response and toxicity.

Number of patients evaluated	Recommend stopping if ≤ OR observed	Recommend stopping if ≥ toxicity observed
5	2	4
10	5	7
15	8	9
20	11	11
25	14	14
30	17	16
35	20	18
40	23	21
45	26	23
50	29	25

The operating characteristics are summarized in the following table (based on simulations from 10,000 trials).

True Toxicity Rate	True OR Rate	Prob(stop the trial early)
0.10	0.60	0.71
	0.70	0.31
	0.80	0.08
	0.90	0.01
0.20	0.60	0.71
	0.70	0.32
	0.80	0.09
	0.90	0.02
0.30	0.60	0.72
	0.70	0.35
	0.80	0.13
	0.90	0.06
0.40	0.60	0.78
	0.70	0.49
	0.80	0.32
	0.90	0.27
0.50	0.60	0.91
	0.70	0.78
	0.80	0.71
	0.90	0.68

Cohort 2: For the subgroup of patients with marginal zone lymphoma and treated with dosing schedule A, historical data on similar patients show an overall response

rate of 70% and toxicity rate of 20%. However, the information was down-weighted to reflect the same marginal OR and toxicity rates in 10 patients. Independence was assumed between OR and toxicity. It is expected for the current trial that the two-drug combination will improve the OR rate to 80% while the toxicity rate is maintained at 30%. A sample size of 30 patients ensures that, if the trial is not terminated early, a posterior 90% credibility interval for overall response rate will have width of 0.23 at most, under the assumption of an 80% of overall response rate. The probabilities of OR and toxicity for the historical data are modeled by beta distributions (*Beta*(7, 3) and *Beta*(2, 8), respectively). The prior probabilities of OR and toxicity for the experimental regimen are also modeled by beta distributions (*Beta*(1.4, 0.6) and *Beta*(0.4, 1.6), respectively), which have the same *means* as the corresponding beta distributions for the historical data. Denoting the historical probabilities of overall response rate and toxicity rate by {p(OR,H) , p(TOX,H)}, the following decision criteria will be applied:

3) **Let E correspond to the experimental treatment, stop if Prob{p(OR,H) + δ_{OR} > p(OR,E) | data} > 0.90, where δ_{OR} =0.1**
4) **Stop if Prob{p(TOX,H) + δ_{TOX} < p(TOX,E)| data}>0.90, where δ_{TOX} =0.1**

Patients will be monitored according to the following stopping boundaries for overall response and toxicity.

Number of patients evaluated	Recommend stopping if ≤ OR observed	Recommend stopping if ≥ toxicity observed
5	2	4
10	5	7
15	8	9
20	11	11
25	14	14
30	17	16

The operating characteristics are summarized in the following table (based on simulations from 10,000 trials).

True Toxicity Rate	True OR Rate	Prob(stop the trial early)
0.10	0.60	0.62
	0.70	0.29
	0.80	0.08
	0.90	0.01
0.20	0.60	0.62
	0.70	0.29
	0.80	0.09
	0.90	0.02
0.30	0.60	0.64
	0.70	0.33
	0.80	0.13
	0.90	0.06
0.40	0.60	0.70
	0.70	0.44
	0.80	0.27
	0.90	0.22
0.50	0.60	0.82

	0.70	**0.66**
	0.80	**0.56**
	0.90	**0.52**

Cohort 3: For the subgroup of patients with small lymphocytic lymphoma, historical data on similar patients show an overall response rate of 50% and toxicity rate of 20%. However, the information was down-weighted to reflect the same marginal OR and toxicity rates in 10 patients. Independence was assumed between OR and toxicity. It is expected for the current trial that the two-drug combination will improve the OR rate to 60% while the toxicity rate is maintained at 30%. A sample size of 45 patients ensures that, if the trial is not terminated early, a posterior 90% credibility interval for overall response rate will have width of 0.23 at most, under the assumption of an 60% of overall response rate. The probabilities of OR and toxicity for the historical data are modeled by beta distributions (*Beta*(5, 5) and *Beta*(2, 8), respectively). The prior probabilities of OR and toxicity for the experimental regimen are also modeled by beta distributions (*Beta*(1, 1) and *Beta*(0.4, 1.6), respectively), which have the same *means* as the corresponding beta distributions for the historical data. Denoting the historical probabilities of overall response rate and toxicity rate by {p(OR,H) , p(TOX,H)}, the following decision criteria will be applied:

5) **Let E correspond to the experimental treatment, stop if Prob{p(OR,H) + δ_{OR} > p(OR,E) | data} > 0.90, where δ_{OR} =0.1**
6) **Stop if Prob{p(TOX,H) + δ_{TOX} < p(TOX,E)| data}>0.90, where δ_{TOX} =0.1**

Patients will be monitored according to the following stopping boundaries for overall response and toxicity.

Number of patients evaluated	Recommend stopping if ≤ OR observed	Recommend stopping if ≥ toxicity observed
5	**1**	**4**
10	**3**	**7**
15	**5**	**9**
20	**7**	**11**
25	**8**	**14**
30	**10**	**16**
35	**12**	**18**
40	**14**	**21**
45	**16**	**23**

The operating characteristics are summarized in the following table (based on simulations from 10,000 trials).

True Toxicity Rate	True OR Rate	Prob(stop the trial early)
0.10	**0.40**	**0.65**
	0.50	**0.32**
	0.60	**0.12**
	0.70	**0.04**
0.20	**0.40**	**0.65**
	0.50	**0.33**

	0.60	**0.13**
	0.70	**0.04**
0.30	**0.40**	**0.67**
	0.50	**0.36**
	0.60	**0.17**
	0.70	**0.09**
0.40	**0.40**	**0.74**
	0.50	**0.49**
	0.60	**0.34**
	0.70	**0.28**
0.50	**0.40**	**0.88**
	0.50	**0.76**
	0.60	**0.69**
	0.70	**0.66**

Cohort 4: For the subgroup of patients with follicular lymphoma and treated with dosing schedule B, historical data on similar patients show an overall response rate of 70% and toxicity rate of 20%. However, the information was down-weighted to reflect the same marginal OR and toxicity rates in 10 patients. Independence was assumed between OR and toxicity. It is expected for the current trial that the two-drug combination will improve the OR rate to 80% while the toxicity rate is maintained at 30%. A sample size of 30 patients ensures that, if the trial is not terminated early, a posterior 90% credibility interval for overall response rate will have width of 0.23 at most, under the assumption of an 80% of overall response rate. The probabilities of OR and toxicity for the historical data are modeled by beta distributions (*Beta*(7, 3) and *Beta*(2, 8), respectively). The prior probabilities of OR and toxicity for the experimental regimen are also modeled by beta distributions (*Beta*(1.4, 0.6) and *Beta*(0.4, 1.6), respectively), which have the same *means* as the corresponding beta distributions for the historical data. Denoting the historical probabilities of overall response rate and toxicity rate by {p(OR,H) , p(TOX,H)}, the following decision criteria will be applied:

1) **Let E correspond to the experimental treatment, stop if Prob{p(OR,H) + δ_{OR} > p(OR,E) | data} > 0.90, where δ_{OR} =0.1**
2) **Stop if Prob{p(TOX,H) + δ_{TOX} < p(TOX,E)| data}>0.90, where δ_{TOX} =0.1**

Patients will be monitored according to the following stopping boundaries for overall response and toxicity.

Number of patients evaluated	Recommend stopping if ≤ OR observed	Recommend stopping if ≥ toxicity observed
5	**2**	**4**
10	**5**	**7**
15	**8**	**9**
20	**11**	**11**
25	**14**	**14**
30	**17**	**16**

The operating characteristics are summarized in the following table (based on simulations from 10,000 trials).

True Toxicity Rate	True OR Rate	Prob(stop the trial early)
0.10	**0.60**	**0.62**
	0.70	**0.29**
	0.80	**0.08**
	0.90	**0.01**
0.20	**0.60**	**0.62**
	0.70	**0.29**
	0.80	**0.09**
	0.90	**0.02**
0.30	**0.60**	**0.64**
	0.70	**0.33**
	0.80	**0.13**
	0.90	**0.06**
0.40	**0.60**	**0.70**
	0.70	**0.44**
	0.80	**0.27**
	0.90	**0.22**
0.50	**0.60**	**0.82**
	0.70	**0.66**
	0.80	**0.56**
	0.90	**0.52**

11.3 Analysis Plan

Data from each of the patient subgroups will be analyzed separately. Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize categorical variables. Logistic regression will be utilized to assess the effect of patient prognostic factors on the response rate and the toxicity rate. The distribution of time-to-event endpoints will be estimated using the method of Kaplan and Meier. Comparison of time-to-event endpoints by important subgroups will be made using the log-rank test. Cox proportional hazard regression will be employed for multivariate analysis on time-to-event outcomes.

11. Regulatory Considerations

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 amendments to the protocol after receipt of IRB/EC approval must be submitted by the Investigator to the IRB/EC for approval. 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.

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.

Subject confidentiality

Affirmed in MDACC informed consent document.

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; SAE reports, 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.

Premature discontinuation of study

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.

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.).

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

Risks Associated with Pregnancy

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. The risks to a fetus are not known. However, because lenalidomide is related to thalidomide, and thalidomide is known to cause severe birth defects, the following requirements must be observed.

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

Females of childbearing potential (FCBP)[†] 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 study drug; 2) while participating in the study; and 3) for at least 28 days after discontinuation from the study. The two methods of reliable contraception must include one highly effective method (i.e. intrauterine device (IUD), hormonal [birth control pills, injections, or implants], tubal ligation, partner's vasectomy) and one additional effective (barrier) method (i.e. latex condom, diaphragm, cervical cap). FCBP must be referred to a qualified provider of contraceptive methods if needed.

Before starting study drug:

Female Subjects:

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

Male Subjects:

- Must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least 28 days

[†] 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).

following discontinuation from the study even if he has undergone a successful vasectomy.

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

All Subjects:

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

Female Subjects:

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

Male Subjects:

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