Phase II Study of Ofatumumab in Combination with High Dose Methylprednisolone Followed by Ofatumumab and Lenalidomide Consolidative Therapy for the Treatment of Untreated CLL/SLL The HiLOG Trial

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Protocol Title: Phase II Study of Ofatumumab in Combination with High Dose Methylprednisolone followed by Ofatumumab and Lenalidomide consolidative therapy for the treatment of Untreated CLL/SLL: The HiLOG trial.

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PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Principal Investigator:

Signature of Investigator	Date
Printed Name of Investigator	

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

Supporters:	**Celgene Corporation** **Novartis**
Study Location:	H. Lee Moffitt Cancer Center & Research Institute
Principal Investigator:	Celeste Bello, MD
Study Coordinator:	Elyce Turba

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1 Protocol Synopsis

PROTOCOL TITLE: Phase II Study of Ofatumumab in Combination with High Dose Methylprednisolone followed by Ofatumumab and Lenalidomide consolidative therapy for the treatment of untreated CLL/SLL: The HiLOG trial.	
DATE PROTOCOL FINAL:	June 20, 2011
INDICATION:	Untreated CLL/SLL
STUDY PHASE:	Phase II

BACKGROUND AND RATIONALE: Chronic lymphocytic leukemia (CLL), the most common leukemia in the Western countries, is characterized by a progressive accumulation of functionally incompetent monoclonal B lymphocytes. CLL is considered to be identical (same disease at different stages) to the mature B-cell small lymphocytic lymphoma (SLL).[1] CLL is typically considered a disease of the elderly, with a median age at diagnosis of 72 years.[2, 3] The disease remains non curable by current treatment options with the possible exception of allogeneic hematopoietic stem cell transplantation. In addition, the vast majority of patients diagnosed with CLL are older than 65 and many times have significant co-morbidities. This makes it difficult for most patients with CLL to tolerate traditional chemotherapy regimens due to the associated toxicities. A non-chemotherapeutic regimen that provides high efficacy with less toxicity than conventional regimens would be desirable in this population. We are proposing a combination regimen consisting of high dose methylprednisolone combined with ofatumumab, followed by consolidative therapy with lenalidomide in combination with ofatumumab. (See Table 1 for dosing and details of treatment regimen). The rationale for exploring this combination regimen is based on the following previously published trials:

Results of a phase II study combining Rituximab, an anti CD20 monoclonal antibody, with high dose methylprednisolone as a salvage regimen for the treatment of patients with fludarabine refractory CLL showed an overall response rate (ORR) of 93% with a complete remission rate (CR) of 36%. The regimen was well tolerated, and serious adverse events were rare. All patients were able to complete the scheduled treatment without delays or dosage reductions. [4] Another recent paper from the same group

showed similar efficacy in the front line setting using a reduced dose of steroids. They showed an ORR of 96% with a CR rate of 32%. [5]

Ofatumumab (Arzerra®) is a human monoclonal antibody that targets a unique small-loop epitope on CD20 and elicits potent *in vitro* complement-dependent cytotoxicity, even in malignant B cells with low levels of CD20 expression. Ofatumumab is currently approved by the FDA for fludarabine and alemtuzumab refractory CLL. It is also under development by Novartis for the treatment of untreated, relapsed or refractory B-cell follicular lymphoma, for the treatment of untreated CLL, for the treatment of active rheumatoid arthritis, and other autoimmune diseases.

Ofatumumab has been studied in patients with fludarabine and alemtuzumab refractory CLL (FA-ref) or refractory to fludarabine with bulky (>5cm) lymphadenopathy (BF-ref). [6] Ofatumumab was given weekly x 8 doses followed by monthly infusions x 4. Results of a planned interim analysis included 138 treated patients with FA-ref (n = 59) and BF-ref (n = 79) CLL. The overall response rates (primary end point) were 58% [corrected] and 47% in the FA-ref and BF-ref groups, respectively. Complete resolution of constitutional symptoms and improved performance status occurred in 57% and 48% of patients, respectively. Median progression-free survival and overall survival times were 5.7 and 13.7 months in the FA-ref group, respectively, and 5.9 and 15.4 months in the BF-ref group, respectively. The most common adverse events during treatment were infusion reactions and infections, which were primarily, grade 1 or 2 events. Hematologic events during treatment included anemia and neutropenia. These encouraging results in patients with refractory CLL warrant further investigation of ofatumumab in combination with other agents, and as maintenance for the treatment of patients with CLL.

Lenalidomide is a novel immunomodulating anticancer agent that was designed to enhance immunologic and anticancer properties while potentially decreasing neurotoxic and teratogenic adverse effects of the parent compound thalidomide. Its exact antitumor mechanism remains elusive. However, its antitumor activity seems to be mediated through its ability to modulate production of various key survival cytokines such as TNF-

α, IL-6, IL-8 and VEGF in the tumor microenvironment. Lenalidomide has also been shown to affect other components of the tumor microenvironment, including the immune cellular compartment. Preclinical studies demonstrated that lenalidomide enhances NK-cell mediated and monocyte-mediated tumor cell ADCC for a variety of rituximab treated NHL cell lines in vitro. [(7)] A Phase II trial of single agent lenalidomide in patients with relapsed or refractory CLL revealed an ORR of 47% with a CR rate of 9%. [(8)] Another phase II trial of single agent lenalidomide for the treatment of relapsed or refractory CLL revealed an ORR of 32% with 7% CR, 25% stable disease. The most common toxicity was myelosuppression, and the median daily dose of lenalidomide tolerated was 10 mg. [(9)] More recently two combination trials of lenalidomide and rituximab have been reported in abstract form from our center [(10)] and the MDACC. [(11)] Both of these studies evaluated patients with relapsed disease and showed an overall response rate of 60%.

Our hypothesis is that ofatumumab will produce higher rates of CR in this setting. The consolidation with lenalidomide is based on the fact that this drug has activity in CLL but is not immunosuppressive. In addition, there is evidence that lenalidomide can improve the immune system of patients with CLL as well as increase the rates of CR in this population. The reason for incorporating lenalidomide after debulking patients with high dose steroids and ofatumumab is based on the experience with lenalidomide as a single agent in the relapsed and front line setting. In this setting tumor lysis syndrome and tumor flare were observed. We believe that this sequence of drugs will carry less toxicity and will be better tolerated.

Table 1. HiLOG Clinical Study Dosing Schema

Week	Study Day	HDMP	Ofatumumab	Lenalidomide
1	Cycle 1 Day 1	1000 mg/m^2	300 mg	
2	Cycle 1 Day 8	1000 mg/m^2	2000 mg	
3	Cycle 1 Day 15	1000 mg/m^2	2000 mg	
4	Cycle 1 Day 22	1000 mg/m^2	2000 mg	
5	Cycle 2 Day 1	1000 mg/m^2	2000 mg	
6	Cycle 2 Day 8			
7	Cycle 2 Day 15	1000 mg/m^2	2000 mg	
8	Cycle 2 Day 22			
9	Cycle 3 Day 1	1000 mg/m^2	2000 mg	
10	Cycle 3 Day 8			

11	Cycle 3 Day 15	1000 mg/m^2	2000 mg	
12	Cycle 3 Day 22			
13	Cycle 4 Day 1			5-10 mg pd Days 1-28 as per Cr Cl
17	Cycle 5 Day 1			5-10 mg pd Days 1-28 as per Cr Cl
21	Cycle 6 Day 1		2000 mg	5-10 mg pd Days 1-28 as per Cr Cl
25	Cycle 7 Day 1			5-10 mg pd Days 1-28 as per Cr Cl
29	Cycle 8 Day 1		2000 mg	5-10 mg pd Days 1-28 as per Cr Cl
33	Cycle 9 Day 1			5-10 mg pd Days 1-28 as per Cr Cl
37	Cycle 10 Day 1		2000 mg	5-10 mg pd Days 1-28 as per Cr Cl
41	Cycle 11 Day 1			5-10 mg pd Days 1-28 as per Cr Cl
45	Cycle 12 Day 1		2000 mg	5-10 mg pd Days 1-28 as per Cr Cl

STUDY OBJECTIVES:

Primary:

1. To estimate the response rate for the combination of ofatumumab with high dose methylprednisolone followed by consolidative therapy with lenalidomide and ofatumumab for patients with previously untreated CLL/SLL with indication criteria to initiate treatment (See Appendix E: Criteria for Treatment).

Secondary:

To collect preliminary efficacy data on:

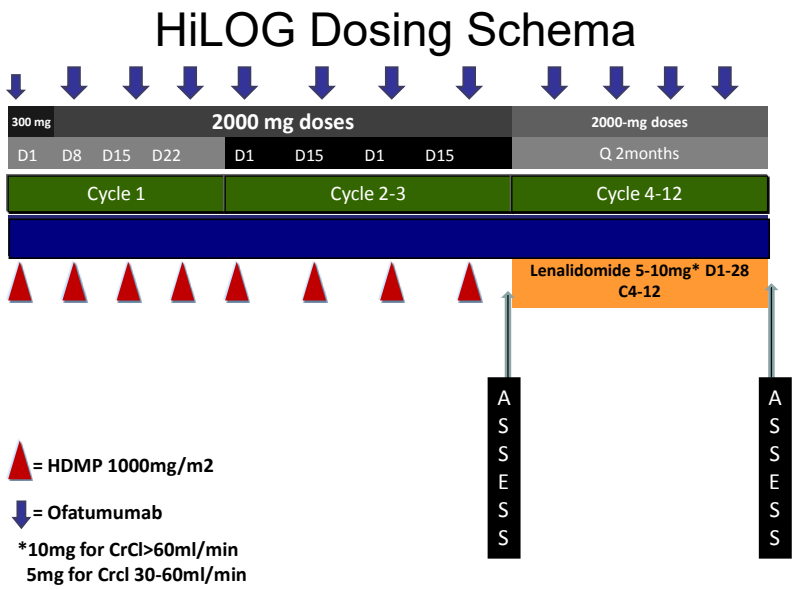
1. Progression/relapse free survival.
2. Overall survival.

STUDY DESIGN:

This is a phase II, single institution, and non-randomized study of patients with untreated CLL/SLL, utilizing a two-stage trial design. The primary endpoint for this trial is the combined complete and partial response rate (at 3 months, after the end of cycle 3) to the protocol therapy. We anticipate this trial will have a CR+PR response rate of at least 80%.

A two-stage design is employed for this trial. The null/unacceptable CR+PR response rate is ≤60% while the anticipated true response rate to the protocol treatment is at least 80% for each disease cohort. At the first stage, 26 patients will be accrued to the trial. If 15 or fewer of these patients respond, then the trial will be terminated early and the response rate to the protocol treatment will be deemed unacceptable (≤60%). Otherwise, if more than 15 patients respond during the first stage, an additional 19 patients will be enrolled to this trial during stage 2 for a total of 45 patients. If 32 or fewer of these 45 patients respond to the protocol treatment at the end of stage 2, no further investigation of the protocol treatment is considered warranted. On the other hand, if more than 32 patients out of the 45 enrolled patients respond, the protocol treatment will be considered promising. If the true response rate is ≤60%, the probability of ending the trial at stage 1 is 0.48. If, however, the true response rate is at least 80%, then the probability of ending the trial at stage 1 is only 0.01. This two-stage design has an overall alpha level of 0.045 and a power of 0.90.

For the purpose of interim analysis at the end of stage 1, the objective response will be measured by the end of 3 months (or end of cycle 3) from the start of the protocol treatment prior to the initiation of the combination of ofatumumab with lenalidomide. The accrual will not be suspended while waiting for the results of the interim analysis unless the observed objective response rate among those patients whose objective response data are available is below 55%.



STUDY ENDPOINTS

Primary:

- Objective response (CR+PR) rate

Secondary:

- Progression/relapse free survival.
- Overall survival.

STUDY DURATION: 2 years	**TOTAL SAMPLE SIZE:** up to 45
DOSING REGIMEN(S): Refer to dosing schema table for dosing of each drug	**DRUG SUPPLIES:** For study participants Novartis will provide ofatumumab, and Celgene Corporation will provide lenalidomide at no charge through the REMS® program.

2 Schedule of Study Assessments *

	All visits/assessments may be scheduled ± 3 business days											
Procedure	Screening [12] **≤ 28 days from Baseline (First day drug administration)**	**Cycle 1**	**Cycles 2 - 3**	**Cycle 4 [13]**					**Cycles 5-12**	**Lenalidomide Maintenance Therapy**	**Discontinuation From Protocol Therapy [15]**	**Follow-Up Phase**
		Days 1, 8, 15, and 22	**Days 1, and 15**	**Day 1**	**Day 3 or 4 at investigator discretion**	**Day 8**	**Day 15**	**Day 22**	**Day 1 and 15**			
Study drug administration**		X	X	X					X	X		
Record prior medications, treatments	X											
Record prior anti-cancer therapies	X											
Physical examination, vital signs, weight	X	X[10]	X[10]	X[10]					X[10]			
ECOG performance status	X	X[10]	X[10]	X[10]					X[10]			
ECG	X											
Assess lymphadenopathy, spleen / liver[1]		X[1]	X[1]	X[1]		X[1]	X[1]		X[1]			
Peripheral blood for , ZAP 70, β-2 microglobulin, and IgHV mutational status [2]	X											
Research samples[2]	X			X								
Baseline lesion assessment	X			X								
Bone marrow[3]	X			X					X	X		X[3]
CT of the neck, chest, abdomen & pelvis[4]	X			X					X	X		X[4]
Hematology[5]	X	X	X	X[5]		X[5]	X[5]	X[5]	X[5]	X[14]		
Serum chemistry[6]	X	X	X	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[14]		
Hepatitis B and C serology, HBV DNA PCR[7]	X[7]											
Pregnancy testing[8]	X			X		X	X	X	X	X		
Register patient into REMS® program	X											

Prescribe lenalidomide via REMS® [11]				X					X			
Record adverse events[9]		X	X	X					X	X[14]		
Record concomitant therapies/procedures		X	X	X					X			
Obtain Follow-Up anti-cancer treatments												X
Obtain Follow-Up survival information												X

* 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.

** See Table 1 for detailed study drug administration schedule.

[1] Physical examination of lymphadenopathy, the spleen and liver will be performed on Days 1 and 15 of Cycle 1 to access for tumor flare reaction, and on Day 1 of subsequent cycles to assess response.

[2] Peripheral blood for,ZAP 70 IgV_H mutational status, beta-2 microglobulin analyses will be done only at screening. If ZAP 70, IgVh and beta-2 microglobulin was performed within 6 months of screening date, it is not necessary to repeat at screening. Research samples for storage will be drawn during screening, day 1 of cycle 4, day 1 of Maintenance Therapy or discontinuation from protocol therapy if earlier than the end of cycle 12.

[3] Bone marrow studies will be performed for all subjects at baseline, at the end of cycle 3 (day 21-28 prior to cycle 4), after completion of cycle 12 and every 6 months afterwards during lenalidomide maintenance therapy for two years. Bone marrow studies at any other time point will be performed at the physician's discretion.

[4] CT of the neck, chest, abdomen & pelvis will be performed at screening, for response assessment at the end of cycle 3 (day 21-28 prior to cycle 4), after the end of cycle 12 (7-10 days after discontinuation of lenalidomide) and every 6 months afterwards during lenalidomide maintenance therapy for two years. After any other time point, CT scans will be performed at the physician's discretion.

[5] Hematology – CBC with differential WBC and platelet counts. Hematology profiles are required weekly during Cycle 4 (which corresponds to Cycle 1 of lenalidomide-containing therapy), and during any cycle in which the dose of lenalidomide is escalated or re-escalated. For subjects who are on a stable lenalidomide dose (without dose escalation or interruption of the planned dosing schedule) for ≥ 1 cycle of treatment, hematology profiles are required on Days 1 and 15 of the cycle.

[6] Chemistry includes sodium, potassium, chloride, CO2, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST/SGOT, ALT/SGPT, LDH, and uric acid. At a minimum, for tumor lysis syndrome (TLS) monitoring purposes, subjects will have chemistry assessments weekly during at least the first 2 cycles of lenalidomide-containing treatment. Chemistry assessments on Day 3 or 4 of Cycle 1 of lenalidomide-containing treatment are at the investigator's discretion. In addition, because the risk for TLS may be elevated when lenalidomide is re-started after treatment interruptions or when the lenalidomide dose is escalated, in any cycle in which the lenalidomide dose is escalated or re-escalated or treatment is interrupted for more than 1 week, subjects may need to have weekly chemistry assessments performed for at least 4 consecutive weeks as well as an additional chemistry assessment on day 3 or 4 during the first week of escalating, re-escalating or re-initiating lenalidomide therapy. If TLS occurs, subjects will have additional chemistry assessments weekly for at least 4 consecutive weeks as well as on Day 3 or Day 4 following re-initiation of lenalidomide. For subjects who do not experience any abnormalities in serum chemistry assessments for 2 consecutive cycles while on a stable lenalidomide dose (without dose escalation or interruption of the planned dosing schedule) throughout these 2 cycles, the timing of chemistry assessments may be reduced to Day 1 and Day 15 in subsequent cycles. See section 5.6.1.1 for TLS prophylaxis instructions. To include Thyroid Stimulating Hormone (TSH) at Screening, at treatment discontinuation, and whenever clinically indicated. T3 and T4 levels may be assessed as clinically indicated.

[7] Hepatitis B Virus DNA by PCR will be tested at screening. If it is positive then it will be tested every 2 weeks during cycle1, every 4 weeks during cycles 2 ad 3, and then every 2 to 3 months thereafter.

[8] Pregnancy test 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). Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (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 lenalidomide 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 lenalidomide 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).
[9] Adverse event data entry will be captured on day 1 of each cycle. An additional safety assessment will be done 28 days (+/- 2 days) following the last dose of protocol therapy.
[10] If physical examination, vital signs, weight and ECOG performance status were done within 7 days of Day 1, they do not need to be repeated on Day 1. During cycle 1 the physical examination will be done on day 1 and day 15. On subsequent cycles it will be done on day 1 only.
[11] Lenalidomide must be prescribed through and in compliance with the REMS® program of Celgene Corporation. Prescriptions must be filled within 7 days. Consideration should be given to prescribing lenalidomide 5 to 7 days in advance of Day 1 of each cycle to allow time for required patient and prescriber surveys, and drug shipment to patient. Any unused Revlimid® (lenalidomide) should be returned to the patient for disposition in accordance with the REMS® program.
[12] Any required screening tests that have been performed as standard of care prior to consent and are within 28 days of starting study treatment may be used for screening and do not need to be repeated. A bone marrow biopsy performed within 6 weeks of starting study treatment does not need to be repeated during screening.
[13] Cycle 4 may begin up to 14 days after cycle 3 bone marrow biopsy to allow for results of response assessments to be available.
[14] CBC and CMP only every 4 weeks. See Section 5.8. Any grade 3 or 4 cytopenia will be recorded as an adverse event during Maintenance Therapy. No other adverse events will be recorded during Maintenance Therapy
[15] Upon discontinuation of study therapy, any diagnostic testing will be at the discretion of the physician.

3 Background and Rationale

3.1 Introduction: Chronic lymphocytic leukemia / Small lymphocytic lymphoma

Chronic lymphocytic leukemia (CLL), a monoclonal B-cell malignancy with a low level of proliferation, is characterized by a progressive accumulation of mature-appearing but functionally incompetent, malignant B lymphocytes. CLL is the most common form of leukemia diagnosed in the Western countries. [(1)] It accounts for over 15,000 new diagnoses (almost 40% of all leukemias) and over 4,000 deaths per year in the United States. CLL is a disease of the elderly with a median age at diagnosis of 72 years and more than two-thirds of patients are over 65 years of age. [(2, 3)]

The cells are characterized by having mature B-cell markers such as CD19, CD20, and CD22 but also express CD5 which is a T-cell marker. [(2)] The spectrum of this disease varies from a simple lymphocytosis to splenomegaly and/or cytopenias. Some patients have an indolent course while others have a more accelerated course. In either case, the disease relapses frequently once treatment is initiated, and there is considerable morbidity from the disease and the treatments themselves. [(12)]

Several predictive factors have been identified in CLL In addition to clinical staging, traditional prognostic factors for identifying high risk of disease progression have included elevated serum levels of beta-2 microglobulin, soluble CD23, diffuse bone marrow infiltration, short lymphocyte doubling time, and high levels of zeta-associated protein (ZAP-70) on the surface of malignant cells. [(13, 14)] More recently, the presence of certain cytogenetic abnormalities identified by fluorescence in situ hybridization (FISH) analysis and mutational status of immunoglobulin heavy chain (IgHV) have become a more meaningful predictor of disease progression and duration of response to therapy. [(15)]

CLL remains non curable by current treatment options with the possible exception of allogeneic hematopoietic stem cell transplantation. Previously, when the need for treatment was established, chlorambucil with or without corticosteroids was often used as

first line treatment and purine analogues such as fludarabine as second line treatment. However, first line treatment in most centers is either fludarabine combined with cyclophosphamide or these 2 compounds combined with rituximab. Other treatment options include combination chemotherapy or alemtuzumab. Previously, rituximab has been administered as monotherapy, but due to the low response rates this treatment is now abandoned. Despite having a first line combination regimen of fludarabine, cyclophosphamide and rituximab with an excellent complete response rate of 44%, these patients do relapse and require further treatments. Patients without a complete response also progress and require further therapy. Considering that the vast majority of patients diagnosed with CLL are older than 65 years of age, there is a need to search for a non-chemotherapeutic regimen that provides high efficacy with less toxicity than conventional regimens. We are proposing a combination regimen consisting of high dose methylprednisolone combined with ofatumumab, followed by consolidative therapy with lenalidomide in combination with ofatumumab (See Section 1 Table 1 for dosing schema and details of regimen).

3.2 Ofatumumab

Ofatumumab (Arzerra®) is a human monoclonal antibody that targets a unique small-loop epitope on CD20 and elicits potent *in vitro* complement-dependent cytotoxicity, even in malignant B cells with low levels of CD20 expression. Ofatumumab is currently approved by the FDA for fludarabine and alemtuzumab refractory CLL. It is also under development by Novartis for the treatment of untreated, relapsed or refractory B-cell follicular lymphoma, for the treatment of untreated CLL, for the treatment of active rheumatoid arthritis, and other autoimmune diseases.

3.2.1 Ofatumumab Indications

Ofatumumab was approved by the FDA on October 27th, 2009 for the treatment of patients with CLL whose cancer is no longer being controlled by other forms of chemotherapy. It has also shown potential in treating follicular non-Hodgkin's lymphoma

(FL), diffuse large B cell lymphoma, rheumatoid arthritis (RA) and relapsing remitting multiple sclerosis.

3.2.2 Ofatumumab Adverse Events

During clinical trials of ofatumumab in FL, CLL and RA subjects, adverse events occurring during the infusions of trial drug have been reported. The following reactions should be regarded as expected infusion-related adverse reactions in connection with the use of ofatumumab probably as a consequence of B cell depletion and cytokine release: pruritus, dyspnea, bronchospasm, throat irritation, cough, pharyngolaryngeal pain, flushing, hyperhidrosis, nausea and vomiting, abdominal pain, hypotension, rash/urticaria, influenza-like-illness, fatigue, fever, chills, headache, dizziness, myalgia and arthralgia.

The incidence of infusion-related symptoms was highest during the first infusion and decreased substantially with subsequent infusions. Implementation of pre-medication before infusions has reduced the number as well as the severity of infusion related adverse events. One serious case of cytokine release complicated with laryngeal edema and one case of anaphylactoid-like reaction have been observed; both events were fully reversible after cessation of the infusion and proper treatment. It should be noted that none of these subjects received premedication with prednisolone.

During the ongoing study in subjects with CLL refractory to alemtuzumab and fludarabine, infusion related adverse events have been reported in approximately 30% of subjects. Only 2-3 % were serious adverse events. All subjects received pre-medication with prednisolone, acetaminophen and antihistamine. In the completed CLL trial 402 in patients with relapsed or refractory CLL, 15% of the subjects had serious infections. In the ongoing CLL 406 trial in subjects refractory to both alemtuzumab and fludarabine an increased frequency of serious infections (25-30%) have been reported.

Subjects who are HBsAg negative, anti-HBc positive and HBV DNA negative may be included in the study but must undergo HBV DNA monitoring. Consult with a physician experienced in care & management of subjects with hepatitis B to manage/treat subjects who are anti-HBc positive. Initiate anti-viral therapy if required. If a subject's HBV DNA becomes positive during the study, notify the NOVARTIS medical monitor. For subjects who have not completed planned ofatumumab therapy, discuss with the medical monitor the risks and benefits of continuing or discontinuing ofatumumab before appropriate treatment decisions are made for that individual subject.

One case of Progressive Multifocal Leukoencephalopathy (PML) has been reported in a very ill CLL subject previously treated with alemtuzumab and fludarabine and with a very low CD4 cell count. Leukopenia, including neutropenia, anemia, and thrombocytopenia have been reported in CLL subjects. These events are most likely related to the patients' baseline disease; however, a causal relationship to ofatumumab cannot be excluded.

3.3 High Dose Methylprednisolone

Methylprednisolone is a corticosteroid that has been on the market for several years and is available in generic form.

Results of a phase II study combining Rituximab, an anti CD20 monoclonal antibody, with high dose methylprednisolone as salvage regimen for the treatment of patient with fludarabine refractory CLL showed an overall response rate (ORR) of 93% with a complete remission rate (CR) of 36%. The regimen was well tolerated and serious adverse events were rare. All patients were able to complete the scheduled treatment without delays or dosage reductions. [(4)] Another recent paper from the same group showed a similar efficacy in the front line setting using a reduced dose of steroids. They showed an ORR of 96% with a CR rate of 32%. [(5)]

3.3.1 Methylprednisolone Adverse Effects

The following adverse events have been reported with the use of methylprednisolone and are common to most corticosteroids: arrhythmias, bradycardia, cardiac arrest, cardiomegaly, circulatory collapse, congestive heart failure, edema, fat embolism, hypertension in premature infants, myocardial rupture (post MI), syncope, tachycardia, thromboembolism, vasculitis, delirium, depression, emotional instability, euphoria, hallucinations, headache, intracranial pressure increased, insomnia, malaise, mood swings, nervousness, neuritis, personality changes, psychic disorders, pseudotumor cerebri (usually following discontinuation), seizure, vertigo, acne, allergic dermatitis, alopecia, dry scaly skin, ecchymoses, edema, erythema, hirsutism, hyper-/hypopigmentation, hypertrichosis, impaired wound healing, petechiae, rash, skin atrophy, sterile abscess, skin test reaction impaired, striae, urticaria, adrenal suppression, amenorrhea, carbohydrate intolerance increased, Cushing's syndrome, diabetes mellitus, fluid retention, glucose intolerance, hyperglycemia, hyperlipidemia, hypokalemia, hypokalemic alkalosis, menstrual irregularities, negative nitrogen balance, pituitary-adrenal axis suppression, protein catabolism, sodium and water retention, abdominal distention, appetite increased, gastrointestinal hemorrhage, gastrointestinal perforation, nausea, pancreatitis, peptic ulcer, perforation of the small and large intestine, ulcerative esophagitis, vomiting, weight gain, leukocytosis (transient), hepatomegaly, increased transaminases, arthralgia, arthropathy, aseptic necrosis (femoral and humoral heads), fractures, muscle mass loss, muscle weakness, myopathy (particularly in conjunction with neuromuscular disease or neuromuscular-blocking agents), neuropathy, osteoporosis, parasthesia, tendon rupture, vertebral compression fractures, weakness, cataracts, exophthalmoses, glaucoma, intraocular pressure increased, glycosuria, pulmonary edema, abnormal fat disposition, anaphylactoid reaction, anaphylaxis, angioedema, avascular necrosis, diaphoresis, hiccups, hypersensitivity reactions, infections, secondary malignancy

3.4 Lenalidomide

Lenalidomide (Revlimid®) is a proprietary IMiD® compound of Celgene Corporation. IMiD® 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-α induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF [16]. In addition, lenalidomide has a variety of immunomodulatory effects. Lenalidomide stimulates T cell proliferation, stimulates the production of IL-2, IL-10 and IFN-gamma, inhibits IL-1 beta and IL-6, and modulates IL-12 production.[17] Up regulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity. [18]

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-γ 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. [19] 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. [20]

Lenalidomide Indications and Usage:

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.

Lenalidomide 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, 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 and fractures. Tumor flare reactions (TFR) have been reported frequently in CLL patients treated with lenalidomide. Tumor lysis syndrome (TLS) has been reported in CLL patients treated with lenalidomide. Precautions must be taken to prevent TLS including proper selection of patients with regard to renal function, correction of electrolyte abnormalities, and TLS prophylaxis and monitoring.

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

3.5 Rationale for Combination Regimen in CLL/SLL

The rationale for exploring this combination regimen is based on the following previously published trials. Results of a phase II study combining Rituximab, an anti CD20 monoclonal antibody, with high dose methylprednisolone as salvage regimen for the treatment of patient with fludarabine refractory CLL showed an overall response rate (ORR) of 93% with a complete remission rate (CR) of 36%. The regimen was well tolerated and serious adverse events were rare. All patients were able to complete the scheduled treatment without delays or dosage reductions. [(4)]

Ofatumumab single agent has been studied in patients with fludarabine and alemtuzumab refractory CLL (FA-ref) or refractory to fludarabine with bulky (>5cm) lymphadenopathy (BF-ref). [(6)] Ofatumumab was given weekly x 8 doses followed by monthly infusions x 4. Results of a planned interim analysis included 138 treated patients with FA-ref (n = 59) and BF-ref (n = 79) CLL. The overall response rates (primary end point) were 58% [corrected] and 47% in the FA-ref and BF-ref groups, respectively. Complete resolution of constitutional symptoms and improved performance status occurred in 57% and 48%

of patients, respectively. Median progression-free survival and overall survival times were 5.7 and 13.7 months in the FA-ref group, respectively, and 5.9 and 15.4 months in the BF-ref group, respectively. The most common adverse events during treatment were infusion reactions and infections, which were primarily, grade 1 or 2 events. Hematologic events during treatment included anemia and neutropenia. These encouraging results in patients with refractory CLL warrant further investigation of ofatumumab in combination with other agents and as maintenance for the treatment of patients with CLL.

A Phase II trial of single agent lenalidomide in patients with relapsed or refractory CLL revealed an ORR of 47% with a CR rate of 9%. [(8)] Another phase II trial of single agent lenalidomide for the treatment of relapsed or refractory CLL revealed an ORR of 32% with 7% CR, 25% stable disease. The most common toxicity was myelosuppression, and the median daily dose of lenalidomide tolerated was 10 mg. [(9)] More recently two combination trials of lenalidomide and rituximab have been reported in abstract form from our center [(10)] and MDACC.[(11)] Both these studies evaluated patients in the relapsed setting and had an overall response rate of 60%.

Our hypothesis is that ofatumumab will produce higher rates of CR when combined with lenalidomide and high dose steroids. The consolidation with lenalidomide is based on the fact that this drug has activity in CLL but is not immunosuppressive. In addition, there is evidence that lenalidomide can improve the immune system of patients with CLL as well as increase the rates of CR in this population. The reason for incorporating lenalidomide after debulking patients with high dose steroids and ofatumumab is based on the experience with lenalidomide as a single agent in the relapsed and front line setting. In this setting tumor lysis syndrome and tumor flare were observed. We believe that this sequence of drugs will carry less toxicity and will be better tolerated.

4 Study Objectives and Endpoints

4.1 Objectives

4.1.1 Primary objective

- To estimate the response rate for the combination of ofatumumab with high dose methylprednisolone followed by consolidative therapy with lenalidomide and ofatumumab for patients with CLL/SLL previously untreated with indication criteria to initiate treatment.

4.1.2 Secondary study objective

To collect preliminary efficacy data on:

- Progression/relapse free survival.
- Overall survival.

4.2 Endpoints

4.2.1 Primary Endpoint

- Objective response (CR+PR) rate

4.2.2 Secondary Endpoints

- Progression/relapse free survival.
- Overall survival.

5 Investigational Plan

5.1 Overall design

This is a phase II study, single institution, non randomized study involving patients with previously untreated CLL/SLL receiving a combination treatment of ofatumumab and

high dose methylprednisolone, followed by ofatumumab and lenalidomide consolidative therapy.

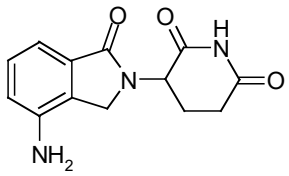
The study has 2 stages (see study schema in section 1). Stage 1 is an induction phase and incorporates cycles 1-3 (see table1 for drug dosing). Stage 2 is a maintenance phase and incorporates cycles 4-12. After stage 1 (cycle 3) all patients will be assessed for response (see section 7, Response criteria). Patients with a CR, PR, or SD will then proceed to the 2nd stage of treatment (cycles 4-12). Patients with disease progression will be removed from the study. Patients continuing on the study will then be reassessed at the end of treatment.

5.2 Protocol Therapy

5.2.1 Lenalidomide

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

Chemical Structure of Lenalidomide



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

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

Lenalidomide is off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon

atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

5.2.1.1 Clinical Pharmacology

Mechanism of Action:

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

5.2.1.2 Pharmacokinetics and Drug Metabolism:

Absorption:

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

Pharmacokinetic 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). No plasma accumulation was observed with multiple daily dosing. 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. Peak and overall plasma concentrations were dose proportional over the dosing range of 5mg to 50mg. Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

Pharmacokinetic Parameters:

Distribution:

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

Metabolism and Excretion:

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

5.2.1.3 Supplier(s)

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

5.2.1.4 Dosage form

Lenalidomide will be supplied as capsules for oral administration.

5.2.1.5 Packaging

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

5.2.1.6 Storage

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

5.2.1.7 Prescribing Information

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the REMS® program of Celgene Corporation. Per standard REMS® requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the REMS® program. Prescriptions must be filled within 7 days. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

5.2.2 Ofatumumab

Ofatumumab (ARZERRA) is an IgG1κ human monoclonal antibody (mAb) that specifically recognizes epitopes on the human CD20 molecule on B cells. The antibody is generated via transgenic mouse and hybridoma technology and produced in a recombinant murine cell line (NS0) using standard mammalian cell cultivation and purification technologies.

Ofatumumab represents a novel anti-CD20 mAb, as it binds to a CD20 epitope distinct from the epitope recognized by rituximab. Ofatumumab is superior in CDC and its ability to kill rituximab resistant tumors as compared to rituximab. Based on the data from the non-clinical investigations of ofatumumab it is suggested that ofatumumab may deplete B cells for a longer period of time than rituximab, which may lead to a longer duration of treatment response and could potentially result in less dose needed. Ofatumumab is a human mAb with an anticipated very low immunogenicity. Therefore, subjects are not expected to produce human anti-human antibodies (HAHA) to the same degree as to the human anti-chimeric antibodies (HACA) seen in some subjects following rituximab treatment.

5.2.2.2 Clinical Pharmacology

Mechanism of Action:

Ofatumumab binds specifically to epitopes which encompass the amino acid residues 163 and 166 in the second extracellular loop of CD20. Ofatumumab induces cross linking of CD20 molecules and relocation of these CD20 molecules to the so-called lipid rafts. The translocation of CD20 into lipid rafts is considered important for induction of cell signaling and more effective complement activation. Differences in antibody function between various anti-CD20 antibodies might be explained by their distinct ability to induce relocation of the CD20 molecules within the lipid rafts. The binding of ofatumumab induces cell death, primarily through CDC and ADCC and not by apoptosis. Thus, depletion of B cells by ofatumumab treatment may provide clinical benefits to subjects with CD20-expressing cell tumors. In the treatment of FL and CLL, the goal is to achieve a complete B-cell depletion in blood and to induce an objective tumor response in lymph nodes.

In patients with CLL refractory to fludarabine and alemtuzumab, the median decrease in circulating CD19-positive B cells was 91% (n = 50) with the 8^{th} infusion and 85% (n = 32) with the 12^{th} infusion. The time to recovery of lymphocytes to normal levels has not been determined.

5.2.2.2 Pharmacokinetic and Drug Metabolism

Pharmacokinetic data were obtained from 146 patients with refractory CLL who received a 300-mg initial dose followed by 7 weekly and 4 monthly infusions of 2,000 mg. The C_{max} and $AUC_{(0-\infty)}$ after the 8^{th} infusion in Study 1 were approximately 40% and 60% higher than after the 4^{th} infusion in Study 2. The mean volume of distribution at steady-state (V_{ss}) values ranged from 1.7 to 5.1 L.

Ofatumumab is eliminated through both a target-independent route and a B cell-mediated route. Ofatumumab exhibited dose-dependent clearance in the dose range of 100 to 2,000 mg. Due to the depletion of B cells, the clearance of ofatumumab decreased substantially after subsequent infusions compared to the first infusion. The mean clearance between

the 4th and 12th infusions was approximately 0.01 L/hr and exhibited large inter-subject variability with CV% greater than 50%. The mean $t_{1/2}$ between the 4th and 12th infusions was approximately 14 days (range: 2.3 to 61.5 days).

Special Populations: Cross-study analyses were performed on data from patients with a variety of conditions, including 162 patients with CLL, who received multiple infusions of ofatumumab as a single agent at doses ranging from 100 to 2,000 mg. The effects of various covariates (e.g., body size [weight, height, and body surface area], age, gender, baseline creatinine clearance) on ofatumumab pharmacokinetics were assessed in a population pharmacokinetic analysis.

Body Weight: Volume of distribution and clearance increased with body weight. However, this increase was not clinically significant. No dosage adjustment is recommended based on body weight.

Age: Age did not significantly influence ofatumumab pharmacokinetics in patients ranging from 21 to 86 years of age.

Gender: Gender had a modest effect on ofatumumab pharmacokinetics (14% to 25% lower clearance and volume of distribution in female patients compared to male patients) in a cross-study population analysis (41% of the patients in this analysis were male and 59% were female). These effects are not considered clinically important, and no dosage adjustment is recommended.

Renal Impairment: Creatinine clearance at baseline did not have a clinically important effect on ofatumumab pharmacokinetics in patients with calculated creatinine clearance values ranging from 33 to 287 mL/min.

5.2.2.3 Supplier

Novartis will supply ofatumumab to H. Lee Moffitt Cancer Center at no charge to study participants.

5.2.2.4 Ofatumumab Dosage Form

The quantitative composition in acetate formulation is 20 mg/mL. This is available in two volumes, 5 mL / vial (100 mg/vial) and 50 mL/vial (1000 mg/vial).

Ingredient	Quantity/ mL
Ofatumumab	20.0 mg
Sodium Acetate, Trihydrate	6.80 mg
Edetate Disodium, Dihydrate (EDTA)	0.019 mg
Polysorbate 80	0.20 mg
L-Arginine	10.0 mg
Sodium Chloride	2.98 mg
Hydrochloric Acid	to give pH 5.5
Water for Injection	*q.s.* to 1.0 mL

5.2.2.5 Packaging

Ofatumumab will be shipped from Novartis directly to H. Lee Moffitt Cancer Center Pharmacy Department. Novartis will supply commercial ofatumumab to the investigator - presented as either 100 mg – acetate formulation, 20 mg/mL, 5 mL fill vials, or 1000 mg – acetate formulation, 20 mg/mL, 50 mL fill vials.

The investigational medical product, ofatumumab, is a liquid concentrate for solution for intravenous infusion presented in glass vials. Ofatumumab will be dosed as described in dosing schema in section 1.

The ofatumumab infusions will be prepared in 1000 mL NaCl sterile, pyrogen free 0.9% NaCl to yield a 0.3 mg/mL, 1 mg/mL, or 2 mg/mL ofatumumab concentration for infusions of 300 mg, 1000 mg, or 2000 mg, respectively. Ofatumumab vials must be stored at 2-8°C. Protect from light and do not freeze. No special packaging components, other than the outer white cardboard carton in which the vials are placed, will be used to

afford light protection. Ofatumumab open-labeled product will be for intravenous infusion. The site is responsible for labeling individual vials for investigational use. All items required for administration of study medication (e.g., infusion bags, filters, etc.) are to be provided by the site.

Comment [KC1]: Novartis does affix an investigational use label on the box, but not on the individual vials inside the box. So I would keep this sentence in the protocol.

5.2.2.6 Storage

The product should be stored in a refrigerator at a temperature between +2ºC and +8ºC (36° to 46°F). Do not freeze. Vials should be protected from light and may not be utilized after the expiry date printed on label.

5.2.2.7 Preparation of Ofatumumab Infusion

Ofatumumab will be prepared as 1000 mL dilution of ofatumumab in sterile, pyrogen-free 0.9% NaCl. The exact time of dilution into the 0.9% NaCl must be written on the label of the infusion bag. Once diluted into saline, the product is stable for up to 48 hours at ambient temperature. However, the product contains no preservative and should be used as soon as possible after dilution. Preparation of drug solution for intravenous injection by the site pharmacist or designee will be done in accordance with the protocol, and in these dilution instructions. Ofatumumab intravenous solution will be prepared using standard dilution methods and following general aseptic practice standard to preparation of IV medications. Eyes and hands should be protected when handling ofatumumab. For intravenous administration, compatibility of the following components for ofatumumab in clinical studies (i.e., not for commercial product) has been established:

Dosing Components for Ofatumumab in Clinical Studies

Dosing component	Material of construction	Suggested Vendor
1L Saline Bags	Polyvinyl Chloride (PVC)	Baxter
	Polyolefin [polyethylene* (PE)/polypropylene (PP)]	Baxter, B. Braun
Administration Set	PVC	Baxter

	PVC lined with Polyethylene	B. Braun
Filter Extension Set	Sterilizing-grade (0.22 μm) hydrophilic filter	Durapore brand by Millipore
	Lines made of PVC, filter membrane material polyether sulfone	Baxter
	Lines made of PVC lined with Polyethylene, filter membrane material polyether sulfone	Alaris/Cardinal Health

Preparation of the 1000 mL infusion bags should be done on the day of planned infusion.
* polyethylene (IUPAC name: polyethene)

5.2.2.8 Materials for Preparation and Administration of Infusion

The following materials are needed when preparing and administering the infusion:1000 mL sterile pyrogen free 0.9% saline (NaCl) infusion bag(s). The solution can be kept at ambient temperature for a maximum of 48 hours after preparation; however, the product does not contain a preservative and dosing should begin as soon as possible after dose preparation.

Ofatumumab 100 mg and 1000 mg vials (supplied by NOVARTIS)

Needles and syringes (50 mL sterile syringe) supplied by study site

Intravenous (IV) cannula (not required if subject has central venous access) supplied by study site

Infusion pump and infusion tubing set supplied by study site

In-line low protein binding, polyether sulfone filter 0.2 μm (please make sure a spare filter is available in case the filter needs to be changed) supplied by study site Please note that the commercial filters are sterilizing-grade (0.22 μm) hydrophilic Durapore by Millipore.

5.2.2.9 Dilution of Ofatumumab

- Ensure the correct container number is used.
- Take a 1000 mL infusion bag (sterile pyrogen free 0.9% saline), remove and dispose of the appropriate amount of saline according to Table 2 or Table 3 below
- Draw the required amount of ofatumumab according to Table 2 (100 mg vials) or Table 3 (1000 mg vials) below
- Inject ofatumumab into the saline bag
- Invert the infusion bag slowly 3 times, avoiding formation of any foam
- Label the infusion bag with the completed label

Preparation of Ofatumumab Infusion: 100 mg vials

Dose of Ofatumumab	Infusion bag size	Volume of NaCl to be removed from infusion bag	Volume ofatumumab (number of ofatumumab vials)
300 mg	1000 mL	15 mL	15 mL (3 vials, 5 mL/vial)
1000 mg	1000 mL	50 mL	50 mL (10 vials, 5 mL/vial)
2000 mg	1000 mL	100 mL	100 mL (20 vials, 5 mL/vial)

Preparation of Ofatumumab Infusion: 1000 mg vials

Dose of Ofatumumab	Infusion bag size	Volume of NaCl to be removed from infusion bag	Volume ofatumumab (number of ofatumumab vials)
1000 mg	1000 mL	50 mL	50 mL (1 vial, 50 mL/vial)
2000 mg	1000 mL	100 mL	100 mL (2 vials, 50 mL/vial)

5.2.3.0 Ofatumumab Infusion Set up

Ofatumumab must be administered by i.v. infusion through an in-line filter and through a well-functioning i.v. catheter (i.v. cannula) into a vein in the arm (or other venous access) by an infusion pump.

Please Note: It is mandatory to use an in-line low protein binding 0.2 micron polyether sulfone filter for all IV dosing of ofatumumab drug product.
DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.
Ofatumumab should not be mixed with any other medication. If ofatumumab is to be dosed through an in-dwelling catheter, then, any previous medication should be removed by flushing with normal saline prior to dosing with ofatumumab.
Please note that the infusion site can be used for blood sampling only if there is no risk of contamination of the infusion needle with the saline, infusion solutions, or any other fluid(s). Only a newly inserted needle can be used for the predose blood samples.

- Check subject ID against the label on the infusion bag and ensure the expiry of the solution. The solution must be administered in its entirety to the subject within 48 hours from time of preparation.
- Attach the 1000mL infusion bag to the infusion set (if not done at the pharmacy).
- Attach the in-line filter to the infusion set (closest to the subject; see **Error! Reference source not found.**). **Note: The in-line filter must be used during the entire infusion.**
- Prime the infusion set and filter with ofatumumab (if not done at the pharmacy).
- In case of a problem with the filter (i.e. clogging/blockage), please change, re-prime the new filter, and continue the infusion.
- In case of problem with infusion set, follow local procedures.
- Collect the pre-dose blood samples, if required.

- Check the backflow from the i.v. cannula according to routine practice at site
- Set the pump at the initial infusion rate 12mL/hr for the first infusion and 25mL/hr for the subsequent infusions (if no grade ≥ 3 infusion-associated AEs were observed in the previous infusion)
- Start the infusion using the infusion rates described in drug administration section 5.5.2.

5.3 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. Unless otherwise specified, screening must take place within 28 days prior to initiation of therapy.

Approximately 45 subjects with previously untreated CLL/SLL will be screened for enrollment and must meet the eligibility criteria below.

5.3.1 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 years at the time of signing the informed consent form.
3. Able to adhere to the study visit schedule and other protocol requirements.
4. Patients must have histologically or cytologically confirmed CD5+/CD20+ B-Cell chronic lymphocytic leukemia or small lymphocytic lymphoma. The diagnosis of CLL is based upon the NCCN guidelines. Any outside pathology slides used as inclusion criteria for the patient will be reviewed at this institution to confirm the

diagnosis. The patient must meet all of the following CLL criteria to participate in this study:

- absolute lymphocyte count > 5000/µL
- CD20+ and CD5+
- Bone marrow lymphocytes ≥ 30%
- Or previous confirmed diagnosis of CLL/SLL with less than 5000/µl or less than 30% lymphocytes in BM

5. Patients are eligible if they have stage III or IV disease. Patients with stage 0, I or II disease will be eligible if they have evidence of active disease defined as one or more of the following signs/symptoms: (See also Appendix E: Criteria for Treatment)
    - Documented weight loss of ≥ 10% over a six month period
    - Febrile episodes of 38 degrees Celsius (100.5 degrees F) or greater for greater than 2 weeks without evidence of infection
    - Massive or progressive splenomegaly defined as > 6 cm below the left costal margin
    - Massive (> 10 cm in longest diameter) or progressive lymphadenopathy.
6. Patient has not received any prior treatment for CLL in the past.
7. ECOG performance status of ≤ 2 at study entry (see Appendix B).
8. Laboratory test results within these ranges:
    - Absolute neutrophil count ≥ 1000/mm³
    - Platelet count ≥50,000 /mm³

    (Adequate baseline platelet and neutrophil levels must be present, unless there is clear evidence of extensive bone marrow involvement with tumor infiltration Extensive bone marrow involvement is defined as:
    -Bone marrow lymphocytes ≥ 30%

- Renal function assessed by calculated creatinine clearance ≥ 30ml/min by Cockcroft-Gault formula. (see Appendix: Cockcroft-Gault estimation of CrCl)
- Total bilirubin ≤ 1.5 x ULN
- AST (SGOT) and ALT (SGPT) ≤ 2.5 x ULN.
- Alkaline phosphatase <2.5 x ULN

9. Disease free of prior malignancies for ≥ 5 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix or breast.
10. All study participants must be registered into the mandatory REMS® program, and be willing and able to comply with the requirements of REMS®.
11. Females of childbearing potential (FCBP)[†] must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. See Appendix A: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

[†] A female of childbearing potential 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).

12. Able to take aspirin (81 or 325 mg) daily as prophylactic anticoagulation (patients intolerant to ASA may use warfarin or low molecular weight heparin).

5.3.2 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. (Lactating females must agree not to breast feed while taking lenalidomide).
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. Evidence of laboratory TLS by Cairo-Bishop Definition of Tumor Lysis Syndrome (see Appendix H). Subjects may be enrolled upon correction of electrolyte abnormalities.
5. Use of any other experimental drug or therapy within 28 days of baseline.
6. Known hypersensitivity to thalidomide.
7. The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide or similar drugs.
8. Any prior use of lenalidomide.
9. Concurrent use of other anti-cancer agents or treatments.
10. Known seropositive for or active viral infection with human immunodeficiency virus (HIV)
11. Positive serology for hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive and HBsAb negative, a HB DNA test will be performed and if positive the subject will be excluded. Note: If HBcAb positive and HBsAb positive, which is indicative of a past infection, the subject can be included. Patients who are seropositive because of hepatitis B virus vaccine are eligible. Consult with a physician experienced in care &

management of subjects with hepatitis B to manage/treat subjects who are anti-HBc positive

12. Positive serology for hepatitis C (HC) defined as a positive test for HCAb, in which case reflexively perform a HC RIBA immunoblot assay on the same sample to confirm the result
13. Subjects who have current active hepatic or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver metastases or stable chronic liver disease per investigator assessment) are ineligible.
14. Chronic or current infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment such as, but not limited to, chronic renal infection, chronic chest infection with bronchiectasis, tuberculosis and active Hepatitis C.
15. History of significant cerebrovascular disease in the past 6 months or ongoing event with active symptoms or sequelae
16. Clinically significant cardiac disease including unstable angina, acute myocardial infarction within six months prior to randomization, congestive heart failure (NYHA III-IV), and arrhythmia unless controlled by therapy, with the exception of extra systoles or minor conduction abnormalities.
17. Significant concurrent, uncontrolled medical condition including, but not limited to, renal, hepatic, gastrointestinal, endocrine, pulmonary, neurological, cerebral or psychiatric disease which in the opinion of the investigator may represent a risk for the patient.

5.4 Visit schedule and assessments

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

Research samples for storage will be drawn during screening, day 1 of cycle 4, day 1 of Maintenance Therapy (or at time of discontinuation therapy if earlier than cycle 12). At each timepoint the following tubes will be obtained: three 10 ml green tops and one 10 ml

plain red top tube. The samples will be stored in the Moffitt Cancer Center laboratory of Javier Pinilla, MD for examining sample phenotypics and analysis of functionality of T-cell sub-populations. At treatment discontinuation, subjects will undergo off study evaluations per the Schedule of Assessments, Section 2. Study subjects who have completed the 12 cycles of treatment protocol, have not progressed while on therapy, and do not continue on lenalidomide maintenance therapy (MT) will be followed every 6 months for survival until disease progression, study closure, withdrawal of consent, or death. Subjects who progress while on MT and discontinue treatment will do the end of treatment testing. If the bone marrow biopsy and CT scans have been performed in the past 28 days to determine progression of disease, it is not necessary to repeat these tests.

5.5 Drug Administration

Treatment will be administered at the outpatient H. Lee Moffitt Cancer Center Infusion Center. The patients will receive combination of high dose methylprednisolone IV and ofatumumab IV infusion for 3 cycles. This regimen will be followed by a combination of lenalidomide and ofatumumab starting on cycle 4-12 of a 28-day cycle in patients with CR, PR or stable disease. Subjects who do not achieve a CR by C12 may continue lenalidomide single agent at their current dose of lenalidomide until disease progression or unacceptable toxicities.

5.5.1 High dose methylprednisolone (HDMP)

HDMP will be administered at 1 gm/m2 IV over a minimum of 90 minutes daily with ofatumumab infusions 1-8. The patients will be premedicated with cimetidine (or equivalent) 300mg IV, acetaminophen 1000mg orally, and/or diphenhydramine (or equivalent) 50mg po or IV before receiving HDMP. See Section 5.6.1.5 for concomitant antimicrobial prophylactic therapy

5.5.2 Ofatumumab

Ofatumumab infusion will be administered immediately after HDMP. Please refer to dosing schema in Section 1 for ofatumumab dosing. Patients will be pre-medicated prior to infusion of HDMP as above on day 1 and before each ofatumumab infusions 2-8 within 30 minutes to 2 hours prior to the treatment. The last four doses of ofatumumab will follow the standard premedication regimen. Pre-medication before each ofatumumab infusion 9-12 must be given within 30 minutes to 2 hours (+ 15 minutes) prior to the treatment:

Pre-medication Requirements prior to Ofatumumab Infusions

Infusion #	**Acetaminophen (po)** or equivalent	**Antihistamine (iv or po)** diphenhydramine or equivalent	**Glucocorticoid (iv)** prednisolone or equivalent
9th	1000 mg	50 mg	50 mg
10th	1000 mg	50 mg	50 mg
11th-12th	1000 mg	50 mg	0 – 50 mg

First Infusion of 300 mg Ofatumumab

The first dose administered of ofatumumab in CLL should be 300 mg to minimize infusion reactions. The initial rate of the first infusion of 300 mg ofatumumab (0.3 mg/mL) should be 12 mL/h. If no infusion reactions occur the infusion rate should be increased every 30 minutes, to a maximum of 400 mL/h, according to the following table. If this schedule is followed, the infusion duration will be approximately 4.67 hours.

Infusion rate at 1st Ofatumumab infusion (300mg)

Time	mL/hour
0 – 30 minutes	12
31 – 60 minutes	25
61 – 90 minutes	50

91 – 120 minutes	100
121 - 150 minutes	200
151 - 180 minutes	300
181+ minutes	400

If an infusion reaction develops, the infusion should be temporarily slowed or interrupted. Upon restart, the infusion rate should be half of the infusion rate at the time the infusion was paused. If, however, the infusion rate was 12 mL/hour before the pause, the infusion should be restarted at 12 mL/hour. Thereafter, the infusion rate may be increased according to the judgment of the investigator, in the manner described in this section.

Subsequent Infusions of Ofatumumab 2000 mg

If the previous infusion has been completed without grade ≥ 3 infusion-associated adverse effects (AEs), the subsequent infusion of the 2000 mg ofatumumab (2 mg/mL) can start at a rate of 25 mL/hour and should be doubled every 30 minutes up to a maximum of 400 mL/h, according to the following table. Duration of the infusion will be approximately 4 hours if this schedule is followed. If the previous infusion has been completed with grade ≥ 3 infusion associated AEs, the subsequent infusion should start at a rate of 12 mL/hour according to table "Infusion rate at 1st Ofatumumab infusion (300mg)"

Infusion rate at subsequent ofatumumab infusion

Time	mL/hour
0 – 30 minutes	25
31 – 60 minutes	50
61 – 90 minutes	100
91 – 120 minutes	200
121+ minutes	400

During infusion the patient should be monitored closely and appropriate measurements should be performed whenever judged necessary. See Section 5.6.1.5 for concomitant antimicrobial prophylactic therapy

5.5.2.1 Ofatumumab Dose Interruptions or Discontinuation

Liver chemistry stopping and follow-up criteria have been designed to assure subject safety and evaluate liver event etiology.

5.5.2.1.1 Liver Chemistry Stopping Criteria:

1. ALT > 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin; bilirubin fractionation required)*

2. ALT > 8xULN

3. ALT ≥ 5xULN for more than 2 weeks

*NOTE: serum bilirubin fractionation should be performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin >2.0 x ULN, then the following actions must still be performed.

When any of the liver chemistry stopping criteria is met, do the following:

- Immediately withdraw investigational product
- Report the event to NOVARTIS and Celgene Corporation within 24 hours of learning its occurrence
- All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin), termed 'Hy's Law', must be reported as an SAE.

  NOTE: serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.

- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.
- Withdraw the subject from the study (unless further safety follow up is required) after completion of the liver chemistry monitoring as described below.
- Do not re-challenge with investigational product.

In addition, for criterion 1:

- Make every reasonable attempt to have subjects return to clinic within 24 hours for repeat liver chemistries, liver event follow up assessments (see below), and close monitoring
- A specialist or hepatology consultation is recommended
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values

For criteria 2 and 3:

- Make every reasonable attempt to have subjects return to clinic within 24-72 hrs for repeat liver chemistries and liver event follow up assessments (see below)
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values; criterion 5 subjects should be monitored as frequently as possible.

Subjects with ALT ≥5xULN which exhibit a decrease to ALT x≥3xULN, but <5xULN and bilirubin <2xULN without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks:

- Can continue ofatumumab

- Must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline
- If at any time these subjects meet the liver chemistry stopping criteria, proceed as described above
- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

5.2.2.1.2 Liver Chemistry Follow-up Assessments:

Make every attempt to carry out the liver event follow up assessments described below:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody;
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
  - Hepatitis C RNA;
  - Cytomegalovirus IgM antibody;
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
  - Hepatitis E IgM antibody (if subject resides outside the US or Canada, or has traveled outside US or Canada in past 3 months);
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2xULN
- Obtain complete blood count with differential to assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form

- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use on the liver event alcohol intake case report form

The following are required for subjects with ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

5.5.3 Lenalidomide

If it is determined the subject will continue to stage 2 of the protocol, on day 1 of Cycle 4, the subject will commence taking lenalidomide daily on a continuous basis. Subjects are to continue taking the lenalidomide after day 28 of each cycle until the day 1 visit of the subsequent cycle occurs. The lenalidomide starting dose will be based on baseline calculated creatinine clearance as follows:

Lenalidomide Starting Dose (Cycle 4) Based on Renal Function Prior to Cycle 4 of Treatment

Baseline Calculated Creatinine Clearance (by Cockcroft-Gault)	Starting Lenalidomide Dose
≥ 60 ml/min	10mg daily on Days 1-28 of each 28-day cycle
≥ 30 and < 60 ml/min	5mg daily on Days 1-28 of each 28-day cycle

At investigator discretion, subjects who have a CrCl between 30-60ml/min may have their lenalidomide dose increased from 5mg to 10mg at the start of cycle 5 or at the start

of subsequent treatment cycles, if they tolerated the prior treatment cycle without requiring dose modifications, interruptions or delays due to toxicity. The maximum allowable target dose for all study subjects is 10 mg daily on Days 1-28 of each 28-day cycle.

Dosing should be at approximately the same time each day but the time of day may be determined per patient to manage any side effects. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle. Prescriptions must be filled within 7 days. 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 section 5.5).

See Section 5.6.1.1 for allopurinol and oral hydration requirements as prophylaxis against tumor lysis syndrome (TLS).

See Section 5.6.1.2 for prophylactic anti-coagulation.

See Section 5.6.1.5 for concomitant antimicrobial prophylactic therapy

5.5.3.1 Special Handling Instructions

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

5.5.3.2 Record of administration

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

5.5.3.3 Lenalidomide Dose Continuation, Modification and Interruption

Sections below describe dose reduction steps, instructions for initiation of a new cycle of therapy and dose modifications during a cycle of therapy.

Additionally, at the discretion of the investigator, lenalidomide may be continued beyond cycle 12 on all patients who have achieved a complete response, partial response or stable disease.

5.5.3.4 Dose Modification Steps

Lenalidomide dose reductions should be taken one dose level at a time per the table below. Similarly, if lenalidomide dose escalation (or re-escalation) is permitted, it should be done one dose level at a time according to the table below (reverse of the dose reduction steps). See Section 5.5.3.6 for instructions related to lenalidomide dose re-escalation.

Table 1: Lenalidomide Dose Modification Steps

Current Lenalidomide Dose	**One Level Dose Reduction**
10 mg daily on Days 1-28 every 28 days	5 mg daily on Days 1-28 every 28 days
5 mg daily on Days 1-28 every 28 days	5 mg every other day during Days 1-28 every 28 days*
5 mg every other day during Days 1-28 every 28 days*	See * below

* Lenalidomide 5 mg every other day is the minimum lenalidomide dose. Lenalidomide will be discontinued in patients who cannot tolerate this dose. However, patients who experience toxicity requiring dose reduction while receiving lenalidomide 5 mg every other day may, at the discretion of their physician, have their dose held until toxicity resolves as described in Sections 5.5.3.6, and then restart lenalidomide 5 mg every other day. If the same toxicity recurs at lenalidomide 5 mg every other day, consideration should be given to discontinuing lenalidomide.

5.5.3.5 Instructions for Initiation of a New Lenalidomide Cycle

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

- The ANC is ≥ 500/mm³;
- The platelet count is ≥ 25,000/mm³;
- Any drug-related rash or neuropathy that may have occurred has resolved to ≤ grade 1 severity;
- Tumor lysis syndrome (TLS) has not exceeded grade 1 severity during previous cycle (see Appendix: Cairo-Bishop Definition of Tumor Lysis Syndrome);
- If TLS ≥ grade 2 during previous cycle (see Appendix: Cairo-Bishop Definition of Tumor Lysis Syndrome), electrolyte abnormalities have resolved to ≤ grade 0 severity;
- Any other drug-related adverse events that may have occurred have resolved to ≤ grade 2 severity.

If these conditions are not met on Day 1 of a new lenalidomide cycle, the subject will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above.

5.5.3.6 Instructions for lenalidomide dose modifications or interruption

Dose delay and dose reduction rules are as follows and in the table below.

- Lenalidomide dose reduction steps are outlined in Section 5.5.3.4
- For treatment interruptions during a cycle, the 28-day schedule of each cycle will continue to be followed. Missed doses of lenalidomide are not made up.
- For treatment interruptions that delay the scheduled start of a new cycle, when toxicity has resolved as required to allow the start of a new cycle (Section 5.5.3.5), the restart day of therapy becomes Day 1 of the next cycle.

Dose re-escalation following dose reductions due to neutropenia, thrombocytopenia, tumor lysis syndrome, or tumor flare:

- If the dose of lenalidomide has been reduced for neutropenia or thrombocytopenia, lenalidomide dose re-escalation is permitted if the subject completes one full cycle without experiencing any toxicity that requires dose interruption or reduction.
- If the dose of lenalidomide has been dose reduced for tumor lysis syndrome, lenalidomide dose re-escalation is permitted if the subject completes one full cycle without experiencing a laboratory TLS or ≥ Grade 1 TLS (see Appendix H: Cairo-Bishop Definition of Tumor Lysis Syndrome), unless the subject requires a dose interruption/reduction for other toxicity.
- If the dose of lenalidomide has been dose reduced for tumor flare, lenalidomide dose re-escalation is permitted if the subject completes one full cycle without experiencing ≥ Grade 1 tumor flare, unless the subject requires a dose interruption/reduction for other toxicity.
- If any of the above conditions are met, the lenalidomide dose may be increased by one dose level at the initiation of a new cycle of therapy up to the maximum allowable target dose (see Section 5.5.3 for the maximum allowable target dose and Section 5.5.3.4, Table 1, for appropriate dose escalation steps [reverse of the dose reduction steps in Table 1
- Serum chemistry and uric acid should be closely monitored for signs of laboratory or clinical TLS (see Appendix H: Cairo-Bishop Definition of Tumor Lysis Syndrome) following lenalidomide dose re-escalation (see Section 2, Schedule of Study Assessments, for details regarding serum chemistry and uric acid monitoring).
- TLS prophylaxis with allopurinol and hydration as described in Section 5.6.1.1 should be considered with each dose re-escalation.

Table 2: Dose Modifications	
NCI CTC Toxicity Grade	**Dose Modification Instructions (also see Instructions for Initiation of a New Cycle above)**
Grade 3 neutropenia associated with fever (temperature ≥ 38.5° C) or Grade 4 neutropenia	• Hold (interrupt) lenalidomide dose. Omitted doses are NOT made up. • Follow CBC weekly. • First episode: If neutropenia resolves to ≤ grade 3 without fever prior to the scheduled end of the current cycle, restart lenalidomide at the current dose level and continue through the scheduled end of the current cycle. Otherwise, omit for remainder of cycle and restart lenalidomide at the current dose level at the start of the next cycle. • Second and subsequent episodes: If patient is receiving supportive care with colony-stimulating factors, the dosage will be held until the grade 4 neutropenia resolves. At that time, the current dose level may be maintained at the investigator's discretion. • If colony stimulating factors are not being utilized, when neutropenia resolves to ≤ grade 3 without fever prior to the scheduled end of the current cycle, restart lenalidomide at the next lower dose level and continue through the scheduled end of the current cycle. Otherwise, omit for remainder of cycle and restart lenalidomide at the next lower dose level at the start of the next cycle.
Thrombocytopenia ≥Grade 4 (platelet count < 25,000/mm³)	• Hold (interrupt) lenalidomide dose. Omitted doses are NOT made up. • Follow CBC weekly. • If thrombocytopenia resolves to ≤ grade 3 prior to the scheduled end of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled end of the current cycle. Otherwise, omit for remainder of cycle and restart lenalidomide at the next lower dose level at the start of the next cycle.
Platelet count < 50,000/mm³	• Hold prophylactic anti-coagulation, if applicable. • Restart prophylactic anti-coagulation when platelet count is ≥ 50,000/mm³.

Table 2: Dose Modifications	
NCI CTC Toxicity Grade	**Dose Modification Instructions (also see Instructions for Initiation of a New Cycle above)**
Laboratory Tumor Lysis Syndrome (TLS) and Grade 1 TLS (see Section 5.6.1.3 and Appendix H: Cairo-Bishop Definition of TLS)	• Continue treatment as planned. Maintain current dose. • Institute vigorous intravenous hydration and consider rasburicase therapy as needed to reduce hyperuricemia, until correction of electrolyte abnormalities. • Other TLS prophylaxis measures outlined in Section 5.6.1.1 should be continued or re-instituted.
Tumor Lysis Syndrome (TLS) ≥Grade 2 (see Section 5.6.1.3 and Appendix H: Cairo-Bishop Definition of TLS)	• Hold (interrupt) lenalidomide dose. Maintain schedule of cycle. Omitted doses are NOT made up. • First episode: If electrolyte abnormalities resolve to Grade 0 prior to the scheduled end of the current cycle, restart lenalidomide at the current dose with appropriate TLS prophylaxis (Section 5.6.1.1) and continue through the scheduled end of the current cycle. Otherwise, omit for remainder of cycle and restart lenalidomide at the current dose at the start of the next cycle with appropriate TLS prophylaxis (Section 5.6.1.1). • Subsequent episodes: If electrolyte abnormalities resolve to Grade 0 prior to the scheduled end of the current cycle, restart lenalidomide with appropriate TLS prophylaxis (Section 5.6.1.1) and continue through the scheduled end of the current cycle. Otherwise, omit for remainder of cycle and restart lenalidomide at the start of the next cycle with appropriate TLS prophylaxis (Section 5.6.1.1). At physician discretion, the lenalidomide dose may be restarted at the current dose or lenalidomide may be reduced by 1 dose level. • First or subsequent episodes: subjects should be closely monitored for signs of TLS after resuming treatment. To monitor for TLS, serum chemistry and uric acid tests should be performed at least every week following re-initiation of lenalidomide for 4 consecutive weeks and on Day 3 or Day 4 following re-initiation of lenalidomide. See Section 2, Schedule of Study Assessments, for additional specifics regarding serum chemistry and uric acid testing.

Table 2: Dose Modifications	
NCI CTC Toxicity Grade	**Dose Modification Instructions (also see Instructions for Initiation of a New Cycle above)**
Non-blistering rash **Grade 3** **Grade 4**	• If Grade 3, hold (interrupt) lenalidomide dose. Follow weekly. • If the toxicity resolves to ≤ grade 1 prior to the scheduled end of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled end of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. • If Grade 4, discontinue lenalidomide. Remove patient from study.
Desquamating (blistering) rash- any Grade	• Discontinue lenalidomide. Remove patient from study.
Neuropathy **Grade 3** **Grade 4**	• If Grade 3, hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to the scheduled end of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled end of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. • If Grade 4, discontinue lenalidomide. Remove patient from study.
Venous thrombosis/embolism ≥ Grade 3	• Hold (interrupt) lenalidomide and start therapeutic anticoagulation, if appropriate. • Restart lenalidomide at investigator's discretion (maintain dose level). • See Anticoagulation Consideration (Section 5.6.1.2).

Table 2: Dose Modifications	
NCI CTC Toxicity Grade	**Dose Modification Instructions (also see Instructions for Initiation of a New Cycle above)**
Hyperthyroidism or hypothyroidism	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level*.
other non-hematologic toxicity ≥ Grade 3	• Hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 2 prior to the scheduled end of the current cycle, restart lenalidomide and continue through the scheduled end of the current cycle. Otherwise, omit for remainder of cycle. Omitted doses are not made up. For toxicity attributed to lenalidomide, reduce the lenalidomide dose by 1 dose level when restarting lenalidomide.

5.5.3.7 Treatment adherence

Research center personnel will review the dosing instructions with subjects. Subjects will be asked to maintain a diary to record lenalidomide administration. Subjects will be asked to bring any unused lenalidomide and empty drug containers to the research center at their next visit. Research personnel will count and record the number of used and unused drug at each visit and reconcile with the patient diary.

Any unused Revlimid® (lenalidomide) should be returned to the patient for disposition in accordance with the REMS® program.

5.6 Concomitant therapy

5.6.1 Recommended concomitant therapy

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, hematopoietic growth factors, analgesics, and antiemetics when appropriate.

5.6.1.1 Tumor Lysis Syndrome (TLS) Prophylaxis (allopurinol and hydration)

Tumor lysis syndrome (TLS), characterized by hyperkalemia, hyperuricemia, and hyperphosphatemia resulting from the rapid release of potassium, uric acid, and phosphate, has been reported in CLL patients treated with lenalidomide necessitating TLS prophylaxis including allopurinol and oral hydration. The risk of TLS is highest during the first cycle of therapy and decreases after resolution of lymphocytosis. Allopurinol 300mg po daily will be given at the beginning at least 3 days before cycle 1 and continuing through the end of cycle 1. TLS prophylaxis is required for all subjects in cycle 1. It can be considered prior to initiation of lenalidomide in subsequent cycles at the discretion of the investigator. Subjects should be instructed to maintain adequate hydration and maintain urinary output as an additional measure to prevent TLS. To maintain fluid intake, subjects should be instructed to drink 8 to 10 eight ounce glasses of water each day for the first 14 days of Cycle 1. Hydration levels should be adjusted according to age and clinical status, and lowered if the subject's cardiovascular status indicates the possibility of volume overload. Based on clinical and laboratory parameters, TLS prophylaxis may be continued or restarted as needed at the Investigator's discretion.

5.6.1.2 Anticoagulation Consideration

Lenalidomide increases the risk of thrombotic events in patients who are at high risk or with a history a thrombosis, in particular when combined with other drugs known to cause thrombosis. When lenalidomide is combined with other agents such as steroids (e.g. dexamethasone, prednisone), anthracyclines (Doxil, Adriamycin) and erythropoietin the risk of thrombosis is increased. For information on the risk of venous thromboembolism with combined oral contraception see Appendix: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

All patients should receive prophylactic anti-coagulation. Aspirin (81 or 325 mg) is the recommended agent for anti-coagulation prophylaxis. Low molecular weight heparin

may be utilized in patients that are intolerant to ASA. Coumadin should be used with caution and close monitoring of INR.

Patients with a history of venous thromboembolism should be closely monitored throughout the study, especially during periods of fluctuating platelet counts.

Prophylactic anti-coagulation should be held for platelet counts < 50,000/mm³ and then restarted when platelet counts are above this level.

Full therapeutic anti-coagulation should be considered for patients who have a history of venous thromboembolism.

5.6.1.3 Treatment and Dose Modification for Tumor Lysis Syndrome

All subjects meeting criteria of laboratory TLS or ≥ Grade 1 TLS according to the Cairo-Bishop Definition of Tumor Lysis Syndrome (see Appendix) should receive vigorous intravenous hydration and should be considered for rasburicase therapy as needed to reduce hyperuricemia, until correction of electrolyte abnormalities.

5.6.1.4 Tumor Flare Reaction (TFR):

Prophylaxis for (TFR) is not recommended. Grade 1 TFR may be treated with NSAIDs (i.e. ibuprofen 400-600 mg orally every 4-6 hours as needed). TFR ≥ Grade 2 may be treated with corticosteroids. Narcotic analgesics may be added as needed for pain control in subjects experiencing ≥ Grade 2 tumor flare. If corticosteroids are used, the following dosage schedule is recommended; prednisone 20mg PO QD x 7 days followed by 10mg PO QD x 7 days.

Tumor flare occurring during the first 2 weeks of Cycle 4 of treatment protocol should be recorded as an adverse event and not as progressive disease (PD). For tumor flare occurring after the first 2 weeks of Cycle 4 of treatment protocol, differentiate tumor flare from progression.

5.6.1.5 Prophylaxis of infections

Patients will receive prophylaxis for Pneumocystis carini pneumonia with trimethoprim-sulfamethoxazole or equivalent, prophylaxis for herpes virus with acyclovir 400mg twice per day or equivalent and antifungal prophylaxis with fluconazole 100mg daily or equivalent. Prophylaxis will be administered throughout the treatment period until end of cycle 5.

5.6.1.6 Growth Factor Support

Patients may receive growth factor support in the form of granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), or erythropoietin at the discretion of the treating physician.

5.6.2 Prohibited concomitant therapy

Concomitant use of other anti-cancer therapies, including radiation, thalidomide, or other investigational agents is not permitted while subjects are receiving protocol therapy during the treatment phase of the study.

5.7 Discontinuation of Study Treatment (See Also Section 5.5.3.5 and 5.5.3.6)

Treatment will continue as per dosing schema. Treatment will be discontinued at the occurrence of any of the following events.

- Disease progression
- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of the treatment regimen.
- Discontinuation of treatment protocol for any reason.
- Major violation of the study protocol.
- Withdrawal of consent
- Lost to follow up

- Death
- Pregnancy or a positive pregnancy test

5.8 Lenalidomide Maintenance Therapy (MT)

Per protocol Section 5.5, subjects who do not achieve a CR by Cycle 12 may continue lenalidomide single agent until disease progression or unacceptable toxicities. Any subject completing 12 cycles of protocol therapy may begin Lenalidomide Maintenance Therapy (MT).

During MT the following study procedures will be initiated:

1. The subject will have a safety CBC with differential and CMP every four weeks which will not be recorded in the database.
2. Physical examinations will be at the discretion of the investigator or per standard of care. The physical exam results will not be recorded in the database.
3. For the purpose of the study, vital signs, weight, and concomitant medications are not required to be recorded in the database.
4. No subject pill diary or source documentation of dosing will be maintained. The patient report of daily dosing will be sufficient to document adherence.
5. The only adverse events collected and entered into the database will be grade 3 or grade 4 cytopenias.
6. All standard of care guidelines as outlined by the Celgene Corporation for lenalidomide administration, including prophylactic anticoagulation, pregnancy prevention, and counseling through the Revlimid REMS program will continue to be followed.
7. Serious adverse events will be collected and reported as outlined in section 6.
8. A bone marrow biopsy and CT scan will be performed every six months for two years. After this time point, these tests need only be performed at the discretion of the treating physician.

At the discretion of the investigator:

1. Lenalidomide dose may be maintained at the subject's current dose or if previously dose reduced, may be escalated to the maximum of 10 mg daily.
2. Lenalidomide dose reductions may be initiated to 5 mg daily or 5 mg every other day.

5.9 Follow-Up

If a subject discontinues study treatment at any time during cycles 1-12, "Discontinuation from Protocol Therapy" on the Schedule of Assessments, Section 2 will be performed. If the bone marrow biopsy and CT scans have been performed in the past 28 days to determine progression of disease, it is not necessary to repeat them.

The subject will then enter the follow-up period unless consent is withdrawn. If a subject enters Maintenance Therapy (MT) after cycle 12, the follow-up period will begin after discontinuation of lenalidomide in MT. If a subject completes 12 cycles and does not enter MT, follow-up will begin at the completion of cycle 12.

6 Adverse Events

Adverse events will be recorded in the medical record at each visit from the time the patient receives the first dose of study drug. The first dose of study drug includes all three drugs (methylprednisolone, ofatumumab, and lenalidomide). Adverse event data entry will be captured in the Oncore database on day 1 of each cycle. The NCI CTCAE v4.0 (see Appendix G) will be used as a guide for the grading of adverse event severity.

All adverse events will be followed for 30 days after the last dose in cycle 12 of study treatment, unless the subject withdraws consent, or begins other CLL treatment.

If a subject completes all 12 cycles of the protocol therapy and enters lenalidomide Maintenance Therapy (MT), any unresolved adverse events will be considered ongoing. In MT, only grade 3 or 4 cytopenias will be captured as adverse events and recorded in Oncore.

6.1 Serious adverse event reporting to Celgene Corporation

Celgene Corporation must be notified according to Celgene 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]
- 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.

6.1.1 Adverse Event Reporting

Toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (HTTP://CTEP.INFO.NIH.GOV). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to

the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

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

6.1.2 Pregnancies

Pregnancy of a female subject or the female partner of a male subject occurring while the subject is on lenalidomide or within 4 weeks after the subject's last dose of lenalidomide are considered expedited reportable events. If the subject is on lenalidomide, it is to be discontinued immediately and the subject is to be instructed to return any unused portion of lenalidomide to the Investigator. The pregnancy must be reported to Celgene and Novartis Drug Safety within 24 hours of the Investigator's knowledge of the pregnancy by phone and facsimile using the SAE Form.

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

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

Any suspected fetal exposure to lenalidomide must be reported to Celgene and Novartis within 24 hours of being made aware of the event. The pregnant female should be

referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the *in utero* exposure to lenalidomide should also be reported.

In the case of a live "normal" birth, Celgene and Novartis Drug Safety should be advised as soon as the information is available.

6.1.3 Celgene Drug Safety Contact Information:

Celgene Corporation
Drug Safety
86 Morris Avenue
Summit, N.J. 07901
Toll Free: (800)-640-7854
Phone: (908) 673-9667
Fax: (908) 673-9115
e-mail: drugsafety@celgene.com

6.1.4 Investigator Reporting Responsibilities

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

IND Annual Reports

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The

Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Celgene Corporation as a supporter of this study as follows.

Celgene Corporation
Attn: Medical 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 (e.g. mild, moderate, severe), relationship to drug (e.g. 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.

6.1.5 Expedited reporting by investigator to Celgene

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (RV-CLL-PI-0560) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

6.2 Serious Adverse Event Reporting to Novartis

NOVARTIS must be informed according to NOVARTIS Serious Adverse Event Definitions.

Adverse Events:

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events meeting the definition of an AE include:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose per se will not be reported as an AE/SAE)

“Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Any clinically significant abnormal laboratory finding or other abnormal safety assessments that is associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- B cell depletion and hypogammaglobulinemia due to ofatumumab treatment

6.2.1 Definition of a Serious Adverse Event (SAE)

An SAE is an Adverse Event that, at any dose:

a. Results in death

b. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria,

the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

An overnight hospital stay due to slow infusion rates will not be considered a Serious Adverse Event.

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

6.2.2 Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs

measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator **are** to be recorded as AEs or SAEs.

- All events meeting liver stopping criteria must be recorded as an SAE.
- However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.
- B cell depletion, IgG below LLN, low CD19+ count, and hypogammaglobulinemia due to treatment with ofatumumab are **not** to be reported as AEs or SAEs.
- Infusion related AEs may lead to a prolonged infusion time. Overnight stay at the hospital due to slow infusion rate is **not** to be reported as a SAE.

6.2.3 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression) does not need to be reported as an SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with investigational product or protocol design/procedures and the disease progression, then this must be reported as an SAE.

6.2.4 Time Period and Frequency of Detecting and SAEs

Once an investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to Novartis within 24 hours of being notified of the event. All SAEs regardless of relationship to investigational product will be collected from the first dose of investigational product to after the last dose of investigational product (minimum of 6 months or until the end of the follow-up period which ever is longer). All SAEs regardless of causality will be collected until the end of the follow-up period.

From the time a subject consents to participate in and completes the study all SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to NOVARTIS concomitant medication, will be reported promptly to NOVARTIS.

Any SAE brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to investigational product must be reported to NOVARTIS.

This includes serious, related, not related, labeled (expected) and, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within24 hours.

Any SAEs experienced after the follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. The end date of the first event must be provided.

The original copy of the SAE Report and the fax confirmation sheet must be kept within the Trial Master File at the study site.

Follow-up information is sent to the same fax number as the original SAE Report Form was sent, using a new fax cover sheet, stating that this is a follow-up to the previously reported SAE, and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Ofatumumab Investigator Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a DS&E associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has

been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements.

For medical emergencies, the contact is:

Gaetano Bonifacio MD
Medical Director
US CD MA Hematology
Novartis Pharmaceuticals Corporation
One Health Plaza, 345/4th
East Hanover, NJ 07936-1080
Mobile +1 610 427 3613
gaetano.bonifacio@novartis.com

6.2.5 Pregnancy

Any pregnancy that occurs during study participation must be reported to NOVARTIS. To ensure subject safety, each pregnancy must be reported to NOVARTIS within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to NOVARTIS. In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to NOVARTIS as described above.

6.2.6 Novartis Drug Safety Contact Information:

SAEs should be reported to Novartis by fax, using the FAX coversheets provided by Novartis.
Fax to: **U.S. Drug Safety & Epidemiology at Fax #: 877-778-9739**
Email: Should the designated SAE Fax# be non-functional please send SAEs to the designated SAE mailbox: clinicalsafetyop.phuseh@novartis.com)
SAE Submissions must reference your Novartis Study Code: COMB157BUS21T

For medical emergencies, the contact is:

Gaetano Bonifacio MD
Medical Director
US CD MA Hematology
Novartis Pharmaceuticals Corporation
One Health Plaza, 345/4th
East Hanover, NJ 07936-1080
Mobile +1 610 427 3613
gaetano.bonifacio@novartis.com

6.3 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.

6.4 Investigator Reporting to the FDA

Serious adverse events (SAEs) that are **unlisted/unexpected, and at least possibly associated to the drug,** and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) by telephone or by fax. Fatal or life threatening SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 7 calendar days after awareness of the event. All other SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 15 calendar days after awareness of the event. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

6.5 Adverse event updates/IND safety reports

The supporters (NOVARTIS and Celgene Corporation) shall notify the Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of 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 the supporters and the IRB/EC, on file (see Section 11.4 for records retention information).

7 Response Criteria

Baseline lesion assessments must occur within ≤ 28 days of protocol therapy initiation or as indicated in Section 2, Schedule of Study Assessments.

Efficacy assessments will be performed as delineated in Section 2, Schedule of Study Assessments Table.

Assessment for response will be made following the NCIWG 2008 CLL criteria for response (See Appendix F: NCIWG 2008 CLL Criteria for Response).

8 Protocol Amendments/Deviations

8.1 Protocol amendments

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

8.2 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.

Non-emergency minor deviations from the protocol will be permitted with approval of the Principal Investigator.

9 Data Management

9.1 Analyses and Reporting

Data will be analyzed and reported after completion of treatment protocol. All subsequent data collected will be analyzed and reported in a follow-up clinical report.

9.2 Study auditing

9.2.1 Investigator responsibilities

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

Investigators must enter study data onto CRFs or other data collection system. The Investigator will permit study-related audits by Celgene or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

9.2.2 Internal Monitoring

Data will be captured in Oncore, Moffitt's Clinical Trials Database. The Case Report Forms will be reviewed by Moffitt's Internal Monitors, periodically, approximately every 3 months, throughout the conduct of the trial. The monitoring will include source data verification utilizing research subjects' medical records.

10 Statistical Considerations

10.1 Study Design/Endpoints

This is a phase II, single institution, and non-randomized study of patients with untreated CLL/SLL, utilizing a two-stage trial design. The primary endpoint for this trial is the combined complete and partial response rate (at 3 months-the end of cycle 3) to the protocol therapy. We anticipate this trial will have a CR+PR response rate of at least 80%.

A two-stage design is employed for this trial. The null/unacceptable CR+PR response rate is ≤60% while the anticipated true response rate to the protocol treatment is at least 80% for each disease cohort. At the first stage, 26 patients will be accrued to the trial. If 15 or fewer of these patients respond, then the trial will be terminated early and the response rate to the protocol treatment will be deemed unacceptable (≤60%). Otherwise, if more than 15 patients respond during the first stage, an additional 19 patients will be enrolled to this trial during stage 2 for a total of 45 patients. If 32 or fewer of these 45 patients respond to the protocol treatment at the end of stage 2, no further investigation of the protocol treatment is considered warranted. On the other hand, if more than 32 patients out of the 45 enrolled patients respond, the protocol treatment will be considered promising. If the true response rate is ≤60%, the probability of ending the trial at stage 1 is 0.48. If, however, the true response rate is at least 80%, then the probability of ending the trial at stage 1 is only 0.01. This two-stage design has an overall alpha level of 0.045 and a power of 0.90.

10.2 Sample Size/Accrual Rate

Up to 45 patients will be enrolled into this study. During the interim analysis at the end of stage 1, the patient accrual to the trial will not be suspended while pending the interim analysis results unless the observed objective response rate among those patients whose objective response data are available is below 55%. The accrual rate will be approximately 2-3 patients per month. The entire accrual for this trial should be completed in about 1.5 years.

10.3 Stratification Factors

There are no stratification factors planned for this study.

10.4 Data Analysis, Reporting and Exclusions Regarding Efficacy Endpoints

The objective response (CR+PR) rate will be summarized using both a point estimate and its exact confidence interval based on the binomial distribution.

Progression-free survival (PFS), defined as the time from study entry to disease progression, relapse or death due to any cause, whichever is earlier, will be summarized with the Kaplan-Meier curve. Confidence intervals for the median and survival rates at different time points will be constructed if needed. The other secondary endpoint, overall survival (OS), will be analyzed similarly. Both of these two secondary endpoints will be reported descriptively.

The intent-to-treat approach will be used for data analysis of this trial. That means all patients who receive at least one dose of the protocol treatment will be included in the interim and final data analyses. Patients who are lost to follow-up or drop out of study prior to their scheduled response evaluation time due to any reason will be treated as non-responders for response determination and censored for time-to-event type of endpoints at the time of their last assessment/follow-up if no relevant event has occurred by then. A secondary analysis that includes only all eligible patients may be conducted in addition to the primary analysis described above at the discretion of the trial PI and study biostatistician. Other subanalyses may also be considered on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early discontinuation of treatment, major protocol violations, etc.). However, these

subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.

10.5 Toxicity Monitoring and Stopping Rules

All patients will be evaluable for toxicity and adverse events from the time of their first protocol treatment. Toxicity will be reported by type and severity according to the CTCAE version 4.0.

During the entire study period, toxicity will be closely monitored by the PI and clinical trial coordinator of this study, even though no formal stopping rules are stipulated in this protocol. In the event that toxicity is thought to be excessive for the study patient population at any point of the trial, the patient accrual to the trial will be suspended immediately, pending a review of all toxicity data. A final decision will be made by the PI and sponsor as to whether the trial should be amended, terminated or continue accrual. Such decision should be filed with and pre-approved by the institutional Protocol Monitoring Committee.

10.6 Evaluation of Response

All patients treated on the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

11 Regulatory Considerations

11.1 Institutional Review Board/Ethics Committee approval

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

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

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

Any 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.

11.2 Informed consent

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

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files.

11.3 Subject confidentiality

Celgene affirms the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, Celgene requires the Investigator to permit representatives of Celgene Corporation and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

11.4 Study records requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the protocol therapy, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; SAE reports, 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 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.

11.5 Premature discontinuation of study

The Principal Investigator, institution, Celgene, and Novartis have the right to discontinue this study at any time for reasonable medical or administrative reasons. Possible reasons for termination of the study could be but are not limited to:

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

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

12 Appendices

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

Risks Associated with Pregnancy

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

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

Criteria for females of childbearing potential (FCBP)

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

The investigator must ensure that:

- Females of childbearing potential comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Females NOT of childbearing potential acknowledge that she understands the hazards and necessary precautions associated with the use of lenalidomide

- Male patients taking lenalidomide acknowledge that he understands that traces of lenalidomide have been found in semen, that he understands the potential teratogenic risk if engaged in sexual activity with a female of childbearing potential, and that he understands the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a female of childbearing potential.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) throughout the entire duration of lenalidomide treatment; 3) during dose interruptions; and 4) for at least 28 days after lenalidomide discontinuation.

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

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

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

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

Pregnancy testing

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

Before starting lenalidomide

Female Patients:

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

Male Patients:

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

During study participation and for 28 days following lenalidomide discontinuation

Female Patients:

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

Male Patients:

- Must practice complete abstinence or use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28

days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.

- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions

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

Appendix B: ECOG Performance Status Scale

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

Appendix C: Cockcroft-Gault estimation of CrCl

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

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

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

Appendix D: Staging of Chronic Lymphocytic Leukemia

Modified Rai clinical staging system

Risk	Stage	Description
Low	0	Lymphocytosis in blood or bone marrow
Intermediate	I	Lymphocytosis + enlarged lymph nodes
	II	Lymphocytosis + enlarged liver or spleen with or without lymphadenopathy
High	III	Lymphocytosis + anemia (Hgb <11 g/dL) with or without enlarged liver, spleen, or lymph nodes
	IV	Lymphocytosis + thrombocytopenia (platelet count <100,000/μL) with or without anemia or enlarged liver, spleen, or lymph nodes

Binet Staging System

Stage	Description
A	Two or less lymphoid bearing areas enlarged*
B	Three or more lymphoid bearing areas enlarged*
C	Presence of anemia (Hgb <10.0 g/dL) or thrombocytopenia (platelet count <100,000/microL)

* Five lymphoid bearing areas are possible: cervical, axillary, inguino-femoral, spleen, and liver.

Appendix E: Criteria for Treatment of CLL

1. Weakness, night sweats, weight loss of ≥ 10% over a six month period, painful lymphadenopathy, or fever.
2. Symptomatic anemia and/or thrombocytopenia (Rai stages III or IV; Binet stage C)
3. Autoimmune hemolytic anemia and/or thrombocytopenia poorly responsive to corticosteroid therapy.
4. Progressive disease, as demonstrated by increasing lymphocytosis with a lymphocyte doubling time less than six months, and/or rapidly enlarging lymph nodes, spleen, and liver.
5. Repeated episodes of infection. Hypogammaglobulinemia without repeated episodes of infection is not a clear indication for therapy.

Appendix F: NCIWG 2008 Response Criteria

PARAMETER	**CR***	**PR***	**PD***
Group A			
Lymphadenopathy†	None> 1.5 cm	Decrease ≥ 50%	Increase ≥ 50%
Hepatomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Splenomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Blood Lymphocytes	<4000/*u*L	Decrease ≥ 50% over baseline	Increase ≥ 50% over baseline
Marrow	Normocellular, <30% lymphocytes, no B-lymphoid nodules, Hypocellular marrow defines Cri (5.1.6).	50% reduction in marrow infiltrate or B-lymphoid nodules	
Group B			
Platelet count	>100 000/*u*L	> 100 000/*u*L or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL
Hemoglobin	> 11.0 g/dL	> 11 g/dL or increase ≥ 50% over baseline	Decrease ≥ 2 g/dL from baseline secondary to CLL
Neutrophils‡	> 1500/*u*L	> 1500/*u*L or > 50% improvement over baseline	

Group A criteria define the tumor load, Group B criteria define the functions of the hematopoietic system (or marrow).
*CR (complete remission): all of the criteria have to be met, and patients have the lack disease-related constitutional symptoms: PR (partial remission): at least two of the criteria of Group A plus one of the criteria of group B have to be met; SD is the absence of progressive disease (PD) and failure to achieve at lease a PR; PD: at least one of the above criteria of Group A or Group B has to be met.
† Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical examination in general practice).
‡ These parameters are irrelevant for some response categories.

Appendix G: NCI CTC Version 4.0

Toxicity will be scored using NCI CTC Version 4.0 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4.0 can be downloaded from the CTEP homepage: (http://ctep.info.nih.gov). All appropriate treatment areas have access to a copy of the CTC Version.

APPENDIX H: Cairo-Bishop Definition of Tumor Lysis Syndrome
(Cairo MS et al. Br J Haematol 2004)

Table: Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome (LTLS)

Uric Acid	≥ 476 µmol/l (≥ 8.0 mg/dl) or 25% increase from baseline
Potassium	≥ 6.0 mmol/l (≥ 6.0 mEq/l) or 25% increase from baseline
Phosphorous	≥1.45 mmol/l (≥ 4.5 mg/dl) or 25 % increase from baseline
Calcium	≤ 1.75 mmol/l (≤ 7.0 mg/dl) or 25% decrease from baseline
Laboratory tumor lysis syndrome (LTLS) is defined as either a 25% change or level above or below normal, as defined above, for any two or more serum values of uric acid, potassium, phosphate, and calcium within 3 days before or 7 days after the initiation of chemotherapy. This assessment assumes that a patient has or will receive adequate hydration (± alkalinization) and a hypouricemic agent(s).	

Table: Cairo-Bishop Definition of Clinical TLS

The presence of laboratory TLS and one or more of the following criteria:
1. Creatinine: ≥ 1.5 ULN (age > 12 years or age adjusted) 2. Cardiac arrhythmia / sudden death 3. Seizure*

ULN, Upper limit of normal

*Not directly attributable to a therapeutic agent

Table: Cairo-Bishop Grading System for TLS

Grade	LTLS	Creatinine	Cardiac Arrhythmia	Seizure
0	-	≤ 1.5 x ULN	None	None
1	+	1.5 x ULN	Intervention not indicated	None
2	+	> 1.5 – 3.0 x ULN	Non-urgent medical intervention indicated	One brief generalized seizure; seizure(s) well controlled or infrequent; focal motor seizures not interfering with ADL
3	+	> 3.0 – 6.0 x ULN	Symptomatic and incompletely controlled medically or controlled with device	Seizure in which consciousness is altered; poorly controlled seizure disorder; breakthrough generalized seizures despite medical intervention
4	+	> 6.0 x ULN	Life-Threatening	Seizures of any kind that are prolonged, repetitive, or difficult to control
5	+	Death*	Death*	Death*

LTLS, laboratory tumor lysis syndrome; ULN, upper limit of normal; ADL, activities of daily living

*Probably or definitely attributable to clinical TLS

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