THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Combination of Lenalidomide and Ofatumumab in Patients with Previously Treated Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma (CLL/SLL) 2009-0283

Core Protocol Information

Short Title	Lenalidomide and Ofatumumab in Previously Treated CLL/SLL
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Which Committee will review this protocol?

(●) The Clinical Research Committee - (CRC)

Protocol Body

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1.0 Objectives

The objective of this study is to evaluate efficacy and tolerability of the combination of ofatumumab and lenalidomide in patients with recurrent CLL.

The primary end-point will be efficacy and an overall response rate of 40% or higher will be the target for this combination. The secondary endpoint is tolerance of the combination. Excessive toxicity will consist in a rate of grade 3-4 non-hematological toxicity in more than 50% of the patients.

2.0 Background

CLL is the most common form of adult leukemia in the United States. It has been estimated that there are approximately 150,000 individuals living with CLL in the United States. The use of combination of chemoimmunotherapy as initial therapy is associated with a high response rates. Unfortunately, once disease relapse has been observed second line treatment is less effective and responses obtained tend to be shorter(1). A treatment for second line consists in the use of the monoclonal antibody (mAb) alemtuzumab. Alemtuzumab is able to induce a response in up to 30% of the patients, but is associated with significant immunosuppression. Also, it lacks activity in patients that have developed bulk lymphadenopathies (larger than 5 centimeters)(2). Combination of purine-analogue based regimens have limited activity: the combination of fludarabine, cyclophosphamide, rituximab, alemtuzumab (CFAR) is associated with an overall response rate of 65% in patients that have received prior therapy and once patients are fludarabine refractory their median survival is less than twelve months based on our published experience (3,4).

Lenalidomide is a thalidomide derivative with immunomodulatory and anti-angiogenic properties. Lenalidomide has been studied in patients with previously treated CLL as a single-agent and has shown encouraging activity with an overall response rate of 30-50% (5,6). The mechanism of action of lenalidomide in CLL is not completely known at this point: there is indication that its activity could be mediated through the stimulation of the immune system. An increased number of circulating T-cells has been observed in patients with CLL treated with this agent. Lenalidomide has also the ability to affect the interaction between the leukemic cells and the bone marrow stromal cells and T-cells (supported by pre-clinical data) and is able to suppress TNF-alpha and alter the cytokines milieu that is potentially important for CLL proliferation (7,8).

Ofatumumab is a novel anti-CD20 mAb, and has potential advantages over rituximab in the specific setting of CLL. Ofatumumab is a fully human monoclonal antibody (IgG1) produced via a transgenic mouse technology and binds specifically to a unique epitope on the human CD20 molecule expressed on B-

cells. Ofatumumab has shown clinical activity in a phase II study of patients with refractory CLL, the overall response rate was 58% in patients refractory to fludarabine and alemtuzumab and 47% in patients with bulky lympho-nodes and refractory to fludarabine (9, 10). The toxicity profile was favorable with mainly infusion-related reactions.

On human tissue sections ofatumumab demonstrated tissue reactivity that is consistent with its target antigen specificity. Following the binding of ofatumumab to tumor B-cells clustering of CD20 into lipid rafts, as seen with rituximab, was observed. Strong differences in antibody cell-surface off-rates were detected between ofatumumab and rituximab. Ofatumumab dissociated much more slowly from surface CD20 than rituximab, corresponding to a half life of 180 minutes for ofatumumab and 90 minutes for rituximab. In this respect, both efficient clustering into rafts and a lower off-rate value for ofatumumab are important characteristics for an effective activation of the complement and may explain the superiority of ofatumumab over rituximab in CDC of B-cells. Ofatumumab-CD20 was able to induce complement-mediated lysis of freshly isolated human B-CLL tumor cells, and rituximab-resistant cells lines expressing low levels of CD20 and high levels of CD55/CD59, which is known to diminish the lytic effect of complement. Ofatumumab -CD20- and rituximab-mediated Antibody Dependent Cell-mediated Cytotoxicity (ADCC) were equivalent. In an in vivo study employing a SCID mouse tumor model, HuMax-CD20-treated animals showed a dose-dependent prolongation of survival that was superior to rituximab. A pilot pharmacokinetic study in cynomolgus monkeys demonstrated that depletion of CD20 expressing B lymphocytes occurred rapidly after antibody administration. Depletion of B cells with ofatumumab lasted four times longer than depletion observed after administration of a similar dose of rituximab (11,12)

The rationale for combining lenalidomide and ofatumumab is to potentiate the clinical efficacy of these agents without increasing their toxicity. This is based on different mechanisms of action and non-overlapping toxicity profile. The toxicity of ofatumumab consists mainly in infusion reactions and lenalidomide toxicity consisting mainly of early myelosuppression, fatigue, skin rash, diarrhea, and tumor flare. There is also the possibility that the combination will ameliorate the tumor flare reaction seen with lenalidomide because of the rapid reduction in tumor burden seen with anti-CD20 mAb therapy. Because of the debulking properties of ofatumumab, lenalidomide will be started on day 9, after two doses of ofatumumab have been administered.

Current experience with the combination of lenalidomide and the anti-CD20 mAb rituximab (MDACC study 2007-0208) shows favorable activity with 7 of the first 12 patients responding and 8 non-hematological grade >3 adverse events during the 39 treatment cycles administered (data on file).

3.0 Study Design

This is a single center open label phase II study to evaluate the efficacy and safety of the combination of lenalidomide and ofatumumab in patients with CLL who have received prior treatment. Celgene Corporation will supply lenalidomide as capsules via the RevAssist® program and GlaxoSmithKline (GSK) will supply ofatumumab for this study.

4.0 Treatment Plan

The administration of ofatumumab will be four weekly IV infusions at the dose of 300mg week 1, 1,000 mg week 2, 3 and 4, then monthly during months 2-6 and once every two months during months 7-24 (even months: 8,10,12 etc.). Lenalidomide will be given at the dose of 10mg daily. Lenalidomide will be started on day 9 – the day after the second infusion of ofatumumab and will be continued daily. Treatment duration will be 24 cycles and it will be possible to continue lenalidomide beyond 24 cycles if there is a significant benefit such as an ongoing PR or CR. Response will be evaluated after three, six, twelve, eighteen and twenty-four cycles. Only enough lenalidomide for 28 days of therapy will be supplied to the patient each cycle. Each cycle consists of 28 days. Patients with baseline creatinine clearance or calculated GFR ≥ 30ml/min but < 50ml/min will begin treatment at Dose Level – 1 (lenalidomide 5mg daily). These patients may be escalated to lenalidomide 10mg daily on Day 29 or later at physician discretion based on tolerability. Dose reduction steps will follow in accordance with Table 4 taken from their current dose.

Drug Dispensing Requirements

Lenalidomide:

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

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

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

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

Labeling and Lenalidomide Distribution

Lenalidomide will be shipped directly to patients via a specialty, Registered Pharmacy. Bottles will contain a sufficient number of capsules for one cycle of dosing.

Unused Lenalidomide supplies

All unused lenalidomide shall be returned via procedures outlined in the RevAssist® program.

Special Handling Instructions

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

Ofatumumab

The investigational medicinal product (IMP) is a clear colorless liquid concentrate intended for intravenous infusion after dilution in sterile, pyrogen free 0.9% sodium chloride. During infusion the IMP will be filtered using a 0.2 mm in-line filter.

Ofatumumab is supplied as a 100 mg (5 mL) vial or as a 1000 mg (50 mL) vial.

Packaging and Labeling of Ofatumumab IMP

The Ofatumomab IMP will be supplied to the site/pharmacy in cartons, each containing 10 vials. Labeling will be according to local legal requirements.

Storage of Ofatumomab IMP

The IMP will be stored refrigerated (2-8°C) in a safe and secure place. The IMP will not be frozen. A temperature log with daily readings will be kept.
After dilution in 0.9% sodium chloride the IMP can be kept at room temperature and will be administered to the patient within 24 hours. Exact time of dilution will be written on the infusion bag label.

The IMP will not be utilized after the expiry date printed on the label, unless extended in writing by the sponsor (MDACC) based on ongoing stability studies.

Drug supplies will be kept in an appropriate restricted area, accessible only to the investigator,pharmacist or duly designated person. Returned, unused or expired ofatumumab will be destroyed according to MDACC guidelines.

Ofatumumab Drug Accountability and Compliance Check.
The investigator will ensure that a designated person receives IMP deliveries from GlaxoSmithKline (GSK).

Ofatumumab administration:

Pre-medication before each ofatumumab infusion must be given within 30 minutes to 2 hours prior to the treatment:

Table 1 Pre-medication Requirements prior to Ofatumumab Infusions

Infusion #	Acetaminophen (po) or equivalent	Antihistamine (iv or po) diphenhydramine or equivalent	Glucocorticoid (iv) prednisolone or equivalent
1st	1000 mg	50 mg	50 mg
2nd	1000 mg	50 mg	50 mg
3rd -Nth	1000 mg	50 mg	0 – 50 mg[1]

1.If the 2nd infusion has been completed without the subject experiencing any grade = 3 adverse events (AEs), pre-medication with glucocorticoid may be reduced or omitted before the 3rd to Nth infusion at the discretion of the investigator.

Ofatumumab dosing recommendation for combination therapy in CLL: the first cycle of ofatumumab in combination with chemotherapy should consist of an infusion of 300 mg on Day 1 and an infusion of 1000 of Day 8 of Cycle 1. For subsequent cycles, a dose of 1000 mg should be infused on Day 1 of each cycle.

First Infusion of 300mg Ofatumumab
The first dose administered of ofatumumab should be 300 mg to minimize infusion reactions. The initial rate of the first infusion of 300mg ofatumumab (0.3mg/ml) should be 12ml/h. If no infusion reactions occur the infusion rate should be increased every 30 minutes, to a maximum of 400 ml/h, according to Table 2. If this schedule is followed, the infusion duration will be approximately 4.5 hours.

Table 2 Infusion rate at 1st Ofatumumab infusion

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. Hereafter, the infusion rate may be increased according to the judgment of the investigator, in the manner described in this section.

Subsequent infusion of full dose Ofatumumab

If the previous infusion has been completed without grade ≥ 3 infusion-associated AEs, the subsequent infusion of the first full dose of ofatumumab 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 Table 3. 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 2.

Table 3 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.

Dose Reduction: DOSE REDUCTION GUIDELINES FOR OFATUMUMAB.
No dose reduction is planned for ofatumumab, its administration will be held for grade 3 or higher hepatic toxicity and can be omitted if clinically indicated.

Dose Reduction: DOSE REDUCTION GUIDELINES FOR LENALIDOMIDE.

Table 4: LENALIDOMIDE Dose Reduction Steps

Starting Dose	10 mg daily
Dose Level – 1	5 mg daily
Dose Level – 2	5 mg daily, day 1-21 of a 28 days cycle - or 5 mg every other day for 28 days.
Dose Level – 3	5 mg every third day

Table 4: Dose Modification Guidelines for Lenalidomide

NCI CTC Toxicity Grade	Action
Sustained (>7 days) Grade 3 neutropenia, or Grade 3 neutropenia associated with fever (temperature >38.5o C) or Grade 4 neutropenia (ANC <500/mm3, or <25% of baseline ANC)*.	1) Hold (interrupt dose). 2) Follow CBC weekly until resolution or stabilization 3) If neutropenia has resolved to ≤grade 2, or 50% of baseline ANC, implement one dose reduction step and continue therapy***.
Thrombocytopenia Grade 4 (platelet count <25,000/mm3) or <25% of baseline platelet count.*	1) Hold (interrupt dose). 2) Follow CBC weekly until resolution or stabilization 3) If thrombocytopenia resolves to ≤ grade 2, or 50% of baseline thrombocytopenia implement one dose reduction step and continue therapy***.
Non-blistering rash Grade 3	1) If grade 3, hold (interrupt) dose. Follow weekly until resolution or stabilization. 2) If the toxicity resolves to ≤grade 1, implement one dose reduction step and continue therapy***.
Grade 4	1) Discontinue lenalidomide.
Desquamating (blistering) rash-any Grade	Discontinue lenalidomide.
Erythema multiforme Grade 3	Discontinue lenalidomide.
Neuropathy Grade 3	1) If grade 3, hold (interrupt) dose. Follow weekly until resolution or stabilization. 2) If the toxicity resolves to <grade 2, implement one dose reduction step and continue therapy***.
Grade 4	Discontinue lenalidomide.
Sinus bradycardia/other cardiac arrhythmia Grade 2	1) Hold (interrupt dose). Follow at least weekly until resolution or stabilization. 2) If the toxicity resolves to <grade 1, implement one dose reduction step and continue therapy***.
> Grade 3	Discontinue lenalidomide.

Allergic reaction or hypersensitivity Grade 3	1) Hold (interrupt dose). Follow at least weekly until resolution or stabilization 2) If the toxicity resolves to ≤grade 1, implement one dose reduction step and continue therapy***.
Grade 4	Discontinue lenalidomide.
Constipation Grade 1-2	1) Initiate bowel regimen and maintain dose level
> Grade 3	If the toxicity resolves to <grade 2, implement one dose reduction step and continue therapy***.
Venous thrombosis/embolism >Grade 3	Hold (interrupt) dose and start anticoagulation; restart at investigator's discretion (maintain dose level).
Hepatic or other** non-hematologic toxicity assessed as lenalidomide-related > Grade 3	1) Hold (interrupt) dose. Follow at least weekly until resolution or stabilization. 2) If the toxicity resolves to <grade 2, implement one dose reduction step and continue therapy***.
Tumor flare refractory to oral pain meds	Hold dose and differentiate tumor flare from progression. Restart therapy at the investigator's discretion.

*The use of cytokine support and/or transfusions to maintain adequate blood neutrophil and platelet counts may be considered at the investigator's discretion and as clinically indicated.
**Further dose reduction will be allowed at the discretion of the investigator in case of persistent non hematological toxicity of Grade 3 or less and in case of a change in laboratory evaluation such as platelet count, absolute neutrophil count, or hemoglobin count that indicates upcoming myelosuppression or as clinically indicated.
***Once toxicity has resolved, lenalidomide dose can be increased to 10 mg/daily at the discretion of the investigator or to the dose that is clinically indicated.

Concomitant Medication:

Tumor Lysis:

Tumor lysis syndrome (TLS) has been reported in CLL patients treated with lenalidomide and ofatumumab. 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.
Allopurinol at the dose of 300mg daily will be given during the first two weeks of treatment as standard tumor lysis prophylaxis, it can then be continued at the discretion of the treating physician as clinically indicated.

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. Within the first 3 cycles of therapy, additional oral hydration should be considered concurrent with any dose escalation (or re-escalation, if permitted) of lenalidomide, when lenalidomide is restarted after having been held for any reason or in concomitance with ofatumumab administration.

Based on a patient's reaction and laboratory parameters, TLS prophylaxis may be continued or restarted as needed as clinically indicated.

Prophylactic hepatitis treatment will be initiated if clinically indicated.

Anticoagulation Consideration:

Lenalidomide increases the risk of thrombotic events in patients who are at high risk or who have a history of 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, erythropoietin, Adriamycin and daunorubicin), anthracyclines (Doxil, Adriamycin), the risk of thrombosis is increased. Treating physicians may consider the use of aspirin (81mg or 325mg) or low molecular weight heparin in patients at high risk for thrombotic events.

5.0 Patient Eligibility

Inclusion Criteria:

Patients will be eligible for inclusion in the study if they meet all of the following criteria:

1. Patients age > 18 years at the time of signing informed consent. Understand and voluntarily sign an informed consent.

2. Patients with CLL or SLL with active disease.

3. Prior treatment with purine analog based chemotherapy or chemoimmunotherapy.

4. Platelet count $\geq$ 30,000 mm^3

5. ECOG/WHO performance status of 0-2

6. Adequate renal function indicated by creatinine clearance > 30ml/min (calculated by 24 hours urine collection) or a GFR > 30 ml/min estimated using the Cockcroft-Gault equation. Adequate hepatic function indicated as total bilirubin less or equal to 2 mg/dl and ALT less or equal to two times the upper limit of normal.

7. Disease free of prior malignancies for 3 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix or breast. Patients with malignancies with indolent behavior such as prostate cancer treated with radiation or surgery can be enrolled in the study as long as they have a reasonable expectation to have been cured with the treatment modality received.

8. Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to starting lenalidomide and again within 24 hours prior to prescribing lenalidomide (prescriptions must be filled within 7 days) and prior to first administration of ofatumumab 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 and continue it for 6 months after therapy has been completed. 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. All study participants must be registered into the mandatory RevAssist® program, and be willing and able to comply with the requirements of RevAssist®. See Appendix: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

Exclusion Criteria:

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

1. Known sensitivity to lenalidomide, other thalidomide derivatives or ofatumumab.

2. Documented prolymphocytic leukemia (prolymphocytes more than 55% in the blood).

3. Known positivity for HIV or active hepatitis B or C.

Known positivity for HIV or active hepatitis B or C. Positive serology for hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive regardless of HbsAb status, a HB DNA test will be performed and if positive the subject will be excluded.

4. Pregnant or breast feeding females. Women of childbearing potential must have a negative pregnancy test at screening. Male subjects unable or unwilling to use adequate contraception methods from study start to one year after the last dose of protocol therapy.

5. 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 and tuberculosis. History of tuberculosis treated within the last five years or recent exposure to tuberculosis.

6. Any serious medical condition, laboratory abnormality, or psychiatric illness that places the subject at unacceptable risk if he/she were to participate in the study.

7. Patients with a recent history of deep vein thrombosis (DVT) or pulmonary embolus (PE), in the six months prior to enrollment are not eligible for this study..

8.Treatment with any known non-marketed drug substance or experimental therapy within 5 terminal half lives or 4 weeks prior to enrollment, whichever is longer, or currently participating in any other interventional clinical study

9. Prior treatment with other monoclonal antibodies within 4 weeks prior to enrollment.

10. Subjects meeting any of the following criteria must not be enrolled on study: Positive serology for Hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive (regardless of HBsAb status), a HB DNA test will be performed and if positive, the subject will be excluded.

6.0 Pretreatment Evaluation

Pretreatment evaluation will include a physical examination including vital signs ECOG/WHO performance status and query for concomitant medications, height and weight and recording of concurrent medications (within 7 days of Day 1).

Clinical laboratory evaluation will include serum chemistry. This will include sodium, potassium, calcium, magnesium, phosphorus, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, and TSH and Beta-2-microglobulin (within 7 days of Day 1).

Hematology: Complete CBC (white blood cell, hemoglobin, platelets and differential) and differential and peripheral blood lymphocyte subset and immunoglobulin levels (within 7 days of registration).

Bone marrow aspiration and biopsy within one month from registration. Bone marrow will be evaluated by flow cytometry for clonality and for IgVH mutation studies (unless known) ZAP-70 expression (unless known), cytogenetic and genomic abnormalities by FISH (unless known).

Electrocardiogram monitoring will be conducted at baseline (within 7 days of Day 1).

Pregnancy Testing and Counseling per the RevAssist® program, assess patient child bearing potential according to the RevAssist® program guidelines outlined below.

Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Pregnancy tests must occur within 10 – 14 days prior to starting lenalidomide, and again within 24 hours prior to prescribing lenalidomide (prescriptions must be filled within 7 days) and prior to first administration of ofatumumab. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

Lenalidomide must be prescribed through and in compliance with the RevAssist® 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 lenalidomide administration 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 RevAssist® program.

7.0 Evaluation during Study

Clinic visits (this will include vital signs and physical exam) at The University of Texas, M.D. Anderson Cancer Center are required at the end of cycles 3, 7,13,19, 23, and every 6 cycles (± 14 days) after that. Hematology complete blood counts (white blood cell, hemoglobin, platelets and differential) will be monitored once weekly (± 3 days) for the first five weeks and once every two weeks (± 5 days) in case of dose increase until a stable dose of lenalidomide has been established for the specific patient (the once every two weeks laboratory monitoring will not apply if the dose is decreased for non-hematological or laboratory measurable toxicity), and then every four weeks (once per cycle) thereafter. Pregnancy testing and counseling per the RevAssist® program. Serum chemistry basic metabolic profile, (sodium, potassium, chloride, CO2, BUN, creatinine, uric acid, calcium and phosphorus, ALT, AST, alkaline phosphatase, (bilirubin and glucose) will be monitored once weekly (± 3 days) for the first five weeks and then once every two weeks (±5 days) until a stable dose of lenalidomide has been established for the specific patient and then every four weeks (once per cycle) thereafter. Additional laboratory evaluations may be obtained after the first dose of lenalidomide, in week 2 of cycle 1 and at any time during the study if clinically indicated. TSH, beta-2-microglobulin, lymphocyte subset, immunoglobulin levels, bone marrow biopsy and aspiration will be performed at the end of cycles 3,7,13,19,23, and every 6 cycles after that (± 14 days). If patients continue on the study past 24 cycles a bone marrow biopsy and aspirate (with flow cytometry and molecular studies if indicated) to check the status of the disease will be obtained once every 6-12 cycles (± 28 days) as clinically indicated and blood will also be drawn for routine tests. Electrocardiogram will be conducted as clinically indicated during and after treatment.

In subjects that are HBsAg negative, HBcAb positive and have a negative HBV DNA testing at study entry monitoring for hepatitis B reactivation by HBV DNA PCR testing is required during the on treatment periods at least every 2 months and during follow up at a minimum of every 2-3 months up to 6 months after the last dose of ofatumumab.

Once treatment has been completed or discontinued, liver function test (ALT, AST, alkaline phosphatase and bilirubin) will be performed 6 months (± 28 days) after the last dose of ofatumumab has been administered unless patients have received subsequent treatment for their CLL. Correlative laboratory studies and Quality of Life questionnaire (Appendix E) are optional and if the patient agrees they will be collected at baseline, at the end of cycles 3, 7, 13,19, 23 and every 6 cycles after that (± 14 days).

You will be required to use TWO reliable forms of birth control, one highly effective method and one additional effective method at the same time or

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) while participating in this study; and 3) for at least 28 days after discontinuation from the study. The following are the acceptable birth control methods:

Highly Effective Methods	Additional Effective Methods
Intrauterine device (IUD)	Latex condom
Hormonal (birth control pills, injections, implants)	Diaphragm
Tubal ligation	Cervical Cap
Partner's vasectomy	

Females must not breastfeed a baby while participating in this study and for at least 28 days after you have been discontinued from the study.

Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following discontinuation from the study. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following discontinuation from the study.

8.0 Criteria for Response

The 1996 NCI Working Group criteria will be used. (See Appendix F). Responses will be assessed after 3, 7, 13, 19 and 23 cycles and every 6-12 months as clinically indicated.

9.0 Evaluation of Toxicity

Adverse events are reported as per UTMDACC and Leukemia Phase 2-3 studies (Appendix H and Appendix I).

Adverse Events with Lenalidomide

Most frequently reported adverse events reported during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching, infections, sepsis, pneumonia, UTI, upper respiratory infection, cellulitis, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA,

convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures.

Please refer to lenalidomide package insert or Investigator Brochure for a complete list.

Adverse Events with Ofatumumab

The following reactions should be regarded as expected infusion-related adverse reactions in connection with the use of ofatumumab as a consequence of B-lymphocyte depletion: 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 artralgia. Profound and long-lasting depletion of CD20+ B lymphocytes has been seen during treatment with ofatumumab as expected with an anti-CD20 antibody, but so far without any signs of an increased risk of infectious complications. In all clinical studies adverse events were reported with substantially higher frequency on the first infusion day, compared to the subsequent infusions.

Further information can be found in the Ofatumumab Investigator's Brochure.

Myelosuppression and associated complications are expected events during leukemia therapy and are part of the treatment success (marrow emptying of leukemic cells). Therefore, myelosuppression and associated complications such as fever, infections, bleeding and related hospitalizations will not be reported as individual adverse drug reactions (ADRs), but will be summarized in the updated and final reports. Only prolonged myelosuppression, as defined by the new NCI criteria specific for leukemia, i.e., marrow cellularity < 5% on day 42 or later (6 weeks) from start of therapy without evidence of leukemia, will be reported.

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

Serious Adverse Event (SAE) Definition

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

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

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.
[2]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.
[3]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

Adverse Drug Reaction Reporting

AS PER UTMDACC AND LEUKEMIA PHASE II-III STUDIES (APPENDIX H AND APPENDIX I), Toxicity will be scored using CTCAE Version 3.0 for toxicity and adverse event reporting and myelosuppression will be reported according to the recommended guidelines for CLL (Appendix J). A copy of the CTCAE Version 3.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0. All adverse clinical experiences (according to Appendix H), 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. Abnormal lab values are only significant if they require intervention or treatment.

Serious Adverse Events Reporting: The principal investigator has the obligation to report all serious adverse events to The University of Texas M. D. Anderson Cancer Center (MDACC) IRB via the Office of Protocol Research in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events and to Celgene and GSK within 24 hours.

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to ORERM, regardless of attribution (within 5 working days of knowledge of the event).

All life-threatening or fatal events, expected or unexpected, and regardless of attribution to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in ORERM.

The MDACC “Internal SAE Report Form for Prompt Reporting” will be used for reporting to ORERM.

Serious adverse events will be captured from the time the patient signs consent until 30 days after the last dose of lenalidomide and for a minimum of 5 half lives (6 months) after the last dose of ofatumumab If a subject does start other therapy, then SAEs will no longer be required to be reported.

Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to ORERM. This may include the development of a secondary malignancy.

Reporting to FDA:

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

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor’s guidelines, and Institutional Review Board policy.

NOTE: Instructions concerning procedures and reporting for pregnancies below.

Pregnancies

Pregnancy of a female subject or the female partner of a male subject occurring while the subject is on lenalidomide and ofatumumab or within 4 weeks after the

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

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

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

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

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

Drug Safety Contact Information:

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

Toll Free: (800)-640-7854

Phone: (908) 673-9667
Fax: (908) 673-9115
e-mail: drugsafety@celgene.com

GlaxoSmithKline
1250 South Collegeville Road
Collegeville, PA 19426, USA
Fax: 610-917-6715
E-mail: Robert.a.friedman@gsk.com

Investigator Reporting Responsibilities

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

IND Annual Reports
If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed with MD Anderson's ORERM, who will then forward to FDA. An additional copy should be placed in the study's Regulatory Binder and a copy must be sent by the PI/research team to Celgene and GSK as supporters of this study as follows.

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

GlaxoSmithKline
1250 South Collegeville Road
Collegeville, PA 19426, USA
Phone: 610-917-7000

All adverse experience reports must include the patient number, age, sex, severity of reaction (mild, moderate, severe), relationship to study drug (probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical

treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for “serious” and as defined above are present. The investigator is responsible for reporting adverse events to Celgene and GSK as described below.

Expedited reporting by Principal Investigator to Celgene and GSK

Serious adverse events (SAE) are defined above. The investigator should inform Celgene and GSK of any SAE within 24 hours of being aware of the event. The date of awareness should be noted on the report. This must be documented on an MD Anderson SAE form. This form must be completed and supplied to Celgene and GSK within 24 hours/1 business day at the latest on the following working day. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up MD Anderson SAE form. A final report to document resolution of the SAE is required. The Celgene protocol number (RV-CLL-PI-0468) should be included on SAE reports to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene and GSK should be attached to the SAE and retained with the patient records.

Report of Adverse Events to the Institutional Review Board

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

Sponsor Reporting to the FDA

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

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

Adverse event updates/IND safety reports

Celgene and GSK shall notify the Investigator via an IND Safety Report of the following information:

1. Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.

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

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

The Investigator must keep copies of all AE information, including correspondence with Celgene and the IRB/EC, on file.

10.0 Statistical Design

This is a single-arm, phase II study of combination of lenalidomide and ofatumumab. The study population consists of patients with previously treated CLL/SLL and patients will have to have received at least one purine analog-based regimen. The primary outcome is overall response. A Simon's two-stage minmax design will be used for this study. A sample size of 36 is chosen to differentiate between a good response rate of 40% and a poor response rate of 20% with 90% power at a significance level of 0.1. In particular, 19 patients will be enrolled at the first stage. If there are 3 or fewer responses in the first 19 patients, accrual will be suspended until we have 4 responders among the first 19 patients. The trial will be terminated if all 19 patients have been evaluated for 6 cycles and there are 3 or fewer responses**;** otherwise another 17 patients will be treated for a total of 36 patients. If there are 10 or fewer responses among 36 patients, the treatment will be concluded ineffective. The probability of early termination due to futility is 0.46. Overall response includes complete remission (CR) and partial remission (PR). Patients are considered non-responders if there is progression of disease. CR, PR and SD allow continuation of treatment.

The probability of toxicity (grade 3 and 4 non-hematological) will be monitored based on the Bayesian model (beta-binomial) by assuming a priori probability of toxicity following Beta (1,1). The trial will be terminated if Prob(toxicity > 0.33 | data) > .85. Following this rule, the trial will be terminated if [# toxicities]/[# patients evaluated] >/= 3/5, 5/10, 7/15, 9/20, 11/25, 13/30, and 15/35. A simulation study was performed to show the operating characteristics for the stopping rule based on 10,000 repetitions. The results are summarized in the

following table. For example, the trial will be terminated early 90.8% of times if the true toxicity rate is 50%.

True Prob(tox)	Pr(stop)	Median #Pts (25%, 75%)
0.10	0.011	36 (36, 36)
0.20	0.084	36 (36, 36)
0.30	0.305	36 (15, 36)
0.40	0.646	15 (5, 36)
0.50	0.908	10 (5, 15)
0.60	0.991	5 (5, 10)

The first time point to evaluate efficacy and toxicity will be at completion of cycle 6 of treatment. Toxicity will be monitored closely during the entire treatment, but toxicities occurring after cycle 6 will not be applied to the stopping boundaries. The descriptive statistical analysis can be used to explore the data, including histograms or box-plots, proportions, mean, standard deviations. The Fisher's exact test will be used for the univariate analysis on categorical variables (response variable with Yes versus No, for example). The t-test or Wilcoxon test will be used for continuous variables (Age and WBC, for example). Descriptive statistical analysis will also be used to report correlative studies and the quality of life questionnaire.

11.0 Amendments, Deviations, Regulatory

Protocol Amendments

Any amendment to this protocol must be agreed to by the Principal Investigator and by M. D. Anderson Cancer Center and by Celgene and GSK. Amendments should only be submitted to IRB after consideration of M. D. Anderson Cancer Center, Celgene and GSK review. Written verification of IRB approval will be obtained before any amendment is implemented.

Protocol Deviations

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

Investigator Responsibilities

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

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

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

Institutional Review Board/Ethics Committee Approval

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

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

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number. Any amendments to the protocol after receipt of IRB/EC approval must be submitted by the Investigator to the IRB/EC for approval. The Investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

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

Informed consent

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

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the

subject's source documents. A copy of 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.

Study records requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

Premature Discontinuation of Study

Single Center

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

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

12.0 Optional Correlative Studies

Quality of life questionnaire. The M.D. Anderson symptom inventory (MDASI) will be collected at baseline, at the end of cycles 3, 6,12, and every 6 cycles after that. (Appendix E).
At baseline, at the end of cycles 3, 6, 12,18, and every 6 cycles after that, PBMNC will be collected to measure the number of CLL B-cells that express constitutively active, pSTAT3, the percentage of Annexin-V+ leukemic cell, the

number of Treg cells and the function of T cells measured by the ability of anti-CD3 activated T cells to synthesis of IL-2, IFN-gamma, and IL-10; and NK cell cytotoxicity of K562 targets. At baseline, at the end of cycles 3, 6, 12,18, and every 6 cycles after that, plasma will be collected to measure VEGF, bFGF, TSP-1, and IFN-gamma using Luminex Multiplex assay system. At baseline, at the end of cycles 3, 6, 12,18, and every 6 cycles after that, the ability of neoplastic unstimulated and CD40L-activated B cells to act as APC for T-cell activation will be assessed by the production of IL-2 and IL-10, and T-cell proliferation in mixed lymphocyte cultures.

13.0 References

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