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PROTOCOL

TITLE:	COMBINATION OF LENALIDOMIDE AND OBINUTUZUMAB (GA101) IN PATIENTS WITH RECURRENT CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA (CLL/SLL)
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1. INTRODUCTION CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic leukemia/Small lymphocytic lymphoma (CLLISLL) is a lymphoproliferative disorder that accounts for approximately 30% of adult leukemias and 25% of non-Hodgkin's lymphomas (NHLs). In 2010, there were approximately 14,900 new cases in the United States (U.S.: American Cancer Society 2010). The median age at diagnosis is 72 years.

CLL/SLL is a disease of B-cell origin, with a characteristic immunophenotype (CDS positive, CD23 positive, weak surface expression of CD19, CD20, CD79b, and IgM or IgD) and blood smear morphology (mature lymphocytes, Gumprecht shadows) [1].

Natural History

CLL/SLL often is an indolent disease that does not need treatment for many years. Many CLL/SLL patients initially present with lymphocytosis in the absence of other symptoms. However, when the disease advances, there is the appearance of lymphadenopathy, hepatomegaly or splenomegaly, and bone marrow failure. B-symptoms (i.e., fever, night sweats, and weight loss), general fatigue, and recurrent infections are common in patients with late-stage CLLISLL but can occasionally be found earlier in the course of the disease.

The individual survival time of CLLISLL patients is highly variable, with a range of less than 2 years to 20 years or more. There are two clinical staging systems (Rai and Binet) currently in use for CLLISLL that allow a rough division of patients into three prognostic groups: good, intermediate, and poor prognosis. In the Rai staging system, the low-risk (Rai Stage 0) group accounts for 31% of all patients with CLL/SLL, and these patients have a median survival of more than 10 years [2]. Intermediate-risk (Rai Stages I and II) patients (61% of all CLLISLL patients) have a median survival of 7 to 9 years. High-risk (Rai Stages III and IV) patients (8% of all CLL/SLL patients) have a median survival of 5 years [3]. In the Binet staging system, CLL/SLL is divided into three stages of A, B, and C [4]

Current Management

Because there is no survival benefit associated with early intervention [5], asymptomatic patients with early-stage CLL/SLL (Binet Stages A and B) are usually not treated but are followed with a "watch and wait" approach. Treatment is usually initiated when patients become symptomatic or progress to late stage; 50% of CLL/SLL patients ultimately require therapy.

In the recent past, first-line treatment of CLLISLL has evolved from single-agent therapy with alkylating drugs (e.g., chlorambucil [Cib]) to combination therapy incorporating

purine analogues (i.e., fludarabine, pentostatin, and cladribine) and monoclonal antibodies (i.e., rituximab and alemtuzumab) [6 9]. Currently, fludarabine, cyclophosphamide, and rituximab (FCR) is the standard of care in fit previously untreated patients with CLLISLL requiring treatment [9].

In patients with recurrent disease the choice of the treatment depends on the duration of the first or previous lines of treatment, age, comorbidities, cytogenetic abnormalities (absence of del11q and 17p) and donor availability. The options include retreatment as in first line therapy in patients with long response to first line therapy (>3 years) or treatment with other agents with activity in this disease. The National Comprehensive Cancer Care Network, CLL/SLL Guidelines, 2013 include: bendamustine ± rituximab, high dose methylprednisolone (HDMP) + rituximab; ofatumumab; alemtuzumab ± rituximab and lenalidomide ± rituximab).

OBINUTUZUMAB

Obinutuzumab (GA101, R05072759), is a glycoengineered, humanized, type II anti- CD20 monoclonal antibody (mAb). Obinutuzumab was derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering leading to the following characteristics: high antibody-dependent cellular cytotoxicity (ADCC); high affinity binding to the CD20 antigen; low complement-dependent cytotoxicity (CDC) activity; and antibody dependent cellular phagocytosis (ADCP) through recruitment of FcyRIII positive immune effector cells such as natural killer (NK) cells, macrophages and monocytes; and high direct cell death induction. Given the direct cell death inducing properties of obinutuzumab and the significantly enhanced ADCC in preclinical assays, it is possible that obinutuzumab may have greater efficacy than the widely used anti-CD20-mAb rituximab.

Obinutuzumab has been approved by the FDA in combination with chlorambucil for the initial treatment of patients with CLL/SLL. Please refer to Appendix D (Obinutuzumab package insert) for additional information. Phase I-III studies have been conducted and demonstrated safety and efficacy of obinutuzumab as single agent. 8021004 (CLL11; NCT01010061) is a large randomized phase 3 trial investigating first-line chemoimmunotherapy in 663 CLUSLL patients with comorbidities, i.e. patients typically treated in daily practice. Treatment-na"ive CLL/SLL patients with a Cumulative Illness Rating Scale (CIRS) total score >6 and/or an estimated creatinine clearance (CrCl) <70 mllmin were eligible. Patients received Clb alone (0.5 mg/kg po d1, d15 q28 days, 6 cycles), GCib (100 mg iv d1, 900 mg d2, 1000 mg d8, d15 of cycle 1, 1000 mg d1 cycles 2-6), or RCib (375 mg/m^2 iv d1 cycle 1, 500 mg/m^2 d1 cycles 2-6). Primary endpoint was investigator-assessed progression-free survival (PFS). Response rates, minimal residual disease (MRD), and overall survival (OS) were key secondary efficacy endpoints. Final results of the stage 2 analysis: Median observation time was 19 months. The GCib and RCib treatment arms were well balanced for baseline characteristics. Median age, CIRS

THerronscore, and CrCI at baseline were 73 years, 8, and 63 mllmin respectively. Key efficacy and safety results are shown in the table 1.

Table 1 CLL11 study results.

Stage	GCib	RCib
	Stage	
Total N = 663	N = 333	N = 330
Overall response rate,%*	78	65
Complete response rate, %*	21	7
MedianPFS,months HR, CI, p	26,7#	15.2
	0.39, 0.31-0.49, <.0001	
Median OS, months HR, CI, p	NR	NR
	0.66, 0.41-1.06, 0.09	
Grade 3-5 adverse events, %**	66	47
Infusion-related reaction***	20	4
Neutropenia***	33	27
Infections	7	7

• At the end of treatment
•• During treatment
••• No deaths (grade 5 AE) in these categories
Still immature, 10% at risk at time of median

The PFS benefit of GCib over RCib was supported by all pre-planned subgroup analyses (including the cytogenetic subgroups 17p-, 11q-, 12+, 13q-). The number of patients with MRD negative blood samples at end-of-treatment was more than 10-fold higher with GCib compared with RCib (63/214 [29.4%] vs. 6/243 [2.5%]). Grade 3-4 infusion-related reactions with GCib occurred at first infusion only. Updated results of the stage 1 analysis: Median observation time was 23 months. Confirming the primary stage 1 results, GCib or RCib compared with Clb alone was associated with statistically significant and clinically meaningful improvement in PFS (GCib vs. Clb: HR 0.18, CI 0.13-0.24, p<.0001, RCib vs. Clb: HR 0.44, CI 0.34-0.57, p<.0001). The updated median PFS in GCib, RCib and Clb were 26.7, 16.3 and 11.1 months, respectively. Updated OS analysis demonstrated a benefit of GCib over Clb (HR 0.41, CI 0.23-0.74, p=0.002). OS analysis for RCib over Clb showed HR 0.66, CI 0.39-1.11, p=0.113. At the data cut-off, 9%, 15%, and 20% of the patients in the GCib, RCib, and Clb arms, respectively, had died. OS medians were not reached. In this study, obinutuzumab, in combination with Clb (GCib regimen) demonstrated statistically significant and clinically meaningful prolongation of PFS, and higher complete response rate and MRD negativity rate compared with RCib in previously untreated CLL patients with comorbidities. Infusion- related reactions and neutropenia were more common with GCib without an increase in infections. Furthermore, GCib vs. Clb alone demonstrated a prolongation of OS[10].

Lenalidomide

Lenalidomide is an immunomodulatory agent with activity in the treatment of activity in multiple myeloma and various lymphoproliferative disorders [11]. In CLLISLL, lenalidomide alters the tumor microenvironment by modulating cytokine production by dendritic cells as well as modifying expression of co-stimulatory molecules by T-cells, potentially repairing defective humoral immunity and defective T -cell to B-cell synapse formation characteristic of CLL[12].

Please refer to Appendix E (lenalidomide package insert) for additional information

In 2006 Chanan-Khan et al published the results of a phase II trial with lenalidomide in relapsed or refractory 8-cell CLL/SLL patients. Lenalidomide was administered orally at 25 mg on days 1through 21 of a 28-day cycle. Patients were to continue treatment until disease progression, unacceptable toxicity, or complete remission. Rituximab was added to lenalidomide on disease progression. The overall response rate was 47%, with 9% of the patients attaining a complete remission. Fatigue, thrombocytopenia , and neutropenia were the most common adverse effects noted in 83%, 78%, and 78% of the patients, respectively .

NCT00267059 study investigated the activity of lenalidomide in patients CLLISLL. Lenalidomide was given at 10 mg daily with dose escalation up to 25 mg daily. Three patients (7%) achieved a complete response (CR), one a nodular partial remission, and 10 patients a PR, for OR rate of 32%. The most common toxicity was myelosuppression , and the median daily dose of lenalidomide tolerated was 10 mg [14]

Chen and collaborators conducted a trial with lenalidomide in untreated patients as single-agent. Using a starting dose of lenalidomide 10 mg/d for 21 days of a 28-day cycle and weekly 5-mg dose escalations to a target of 25 mg, they encountered severe toxicities (tumor lysis, fatal sepsis) in the first two patients enrolled. The study was halted and the protocol amended to a more conservative regimen: starting dose of lenalidomide 2.5 mg with monthly escalations to a target dose of 10 mg, and extended tumor lysis prophylaxis and monitoring. Twenty-five patients were enrolled on the amended protocol. No further tumor lysis events were reported. Tumor flare was common (88%) but mild. Grade 3 to 4 neutropenia occurred in 72% of patients, with only five episodes of febrile neutropenia. The overall response rate was 56% (no complete responses) [15] .

Lenalidomide in combination with Rituximab (NCT00759603) (Phase II)

In a multicenter phase II study of the CLL Research Consortium, previously untreated patients with CLLISLL (69 patients) were treated with lenalidomide (initial dose of 2.5 mg/d, with dose escalation up to 10 mg/d; given 21 days of a 28-day cycle) combined with rituximab (dose escalated to 375 mg/m^2 cycle 1; 375 mg/m^2 weekly for 4 weeks in

cycle 2, then on day 1 for cycles 3-7) (James et al. abst Blood 2011; 118:3489-3498). Patients in this trial were stratified by age group (age< or 65 years). Only 59% of the older patient group completed the planned 7 cycles of therapy compared with 90% of patients younger than 65 years. Tumor flare reactions occurred in 71% of patients, but were grade 1 or 2 in nearly all cases. The most common grade 3 or 4 toxicity was neutropenia, which was reported in 49% of patients. Neutropenic fever occurred in 4 patients (6%). Among evaluable patients, the ORR in those younger than 65 years was 94% (CR in 20%) and the ORR in older patients was 77% (CR in 9%).

NCT00759603 is a single center, phase II trial for previously treated patients. Rituximab was administered intravenously on days 1, 8, 15, and 22 during cycle one and once every 4 weeks on day 1 for cycle two to 12. Lenalidomide was started on day 9 of cycle one at 10 mg per day and administered continuously. Treatment duration was planned 12 cycles but could continue lenalidomide indefinitively beyond 12 cycles if there was a significant clinical benefit, such as ongoing partial or complete response.

The OR was 66%, including 12% complete responses and 12% nodular partial remissions. Time to treatment failure was 17.4 months. Median OS has not been reached; estimated survival at 36 months is 71%. The most common grad 3 or 4 toxicity was neutropenia (73% of patients). Fourteen patients (24%) experienced a grade 3 to 4 infection and febrile episode . There was one episode of grade 3 tumor lysis; one patient experienced renal failure during the first cycle of therapy, and one venous thromboembolic event occurred during the study [16].

STUDY RATIONALE

Monoclonal antibody therapy has been found to potentiate the activity of chemotherapeutic agents. There is sinergystic activity between rituximab and lenalidomide against CLLISLL and non-Hodgkin lymphoma in vitro [11]. Furthermore, the results our phase II trial of lenalidomide in combination with rituximab in relapsed or refractory CLL/SLL support the clinical activity of this combination [16].

Based on the promising results from the lenalidomide plus rituximab combination in terms of both efficacy and safety in relapsed/refractory patients and on the increasing data suggesting the higher efficacy of the second generation of anti CD20 monoclonal antibodies in B cell malignancies, we aim to test the effect of combining lenalidomide to obinutuzumab in patients with recurrent CLLISLL of all ages.

2. PRIMARY OBJECTIVES

The primary end point will be overall response defined as CR or PR.

SECONDARY

The secondary end points will be safety of the combination, response according to prognostic markers at diagnosis, time to next treatment and overall survival.

3. STUDY DESIGN DESCRIPTION OF THE STUDY

This is a single arm phase II study of Combination of Lenalidomide and Obinutuzumab in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL-SLL) with recurrent disease. Up to 30patients will be enrolled from M. D. Anderson Cancer Center, at a rate of 1-3patients per month. The primary efficacy endpoint is overall response and safety is one of the secondary endpoints. We will monitor futility and safety of the treatment combination using a Bayesian design by Thall, Simon and Estey, in cohort size of 10.

Response to treatment will be assessed according to NCI-WG 2008 working group criteria at 3, 6 months from the beginning of therapy and every 6 months thereafter. The investigator assessment of response and progression will be considered primary for all endpoints described in the study.

The estimated patient accrual is 1-3 per month. And the trial accrual time is estimated to be about 10-20 months. The end of study is defined as 5 years after the last patient was enrolled (unless all patients have died).

OUTCOME MEASURES

Efficacy Outcome Measures

Response will be assessed by means of clinic visits, complete blood counts, imaging if clinically indicated radiographic images as clinically indicated).

Clinic visits (this will include vital signs and physical exam) at the University of Texas, M D Anderson Cancer Center (UTMDACC) are required after 3, 6 cycles (obinutuzumab and lenalidomide) and 12 cycles (lenalidomide) and once every 6 cycles thereafter. Hematology complete blood counts (white blood cells, hemoglobin, platelets and differential) will be monitored once weekly for the first five weeks and once every two weeks in case of dose increase until a stable, dose of lenalidomide has been established for the specific patient. Blood will be drawn for routine tests.

Bone marrow biopsy and aspiration will be performed and evaluated by flow cytometry after 3, 6 cycles (obinutuzumab and lenalidomide) and after 12 cycles (lenalidomide). If patients stay on the study past 12 cycles, once every 6 cycles, they will have if clinically indicated a bone

marrow biopsy and aspirate evaluated by flow cytometry to check the status of the disease .

Safety Outcome Measures

Hematology complete blood counts (white blood cells, hemoglobin, platelets and differential) will be monitored once weekly for the first five weeks and once every two weeks 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 decreasing for non-hematological or laboratory measurable toxicity), and then every four weeks thereafter. Serum chemistry basic metabolic profile (sodium, potassium, BUN, creatinine and glucose) will be monitored once a week for the first five
weeks and then once every two weeks until a stable dose of lenalidomide has been established for the specific patient and then every four weeks thereafter.

Additionally, beta-2-microglobulin, lymphocyte subsets, immunoglobulin levels will be performed and evaluated by flow cytometry after 3, 6 cycles (obinutuzumab and lenalidomide) and after 12 cycles (lenalidomide).

4. PATIENT ELEGIBILITY INCLUSION CRITERIA

Patients must meet the following criteria for study entry:

- Age 18 years or older at the time of signing informed consent. Able to understand and to provide voluntarily informed consent;
- Have documented CLL/SLL according to NCI criteria;
- Recurrent or refractory disease according to NCI criteria;
- Patient are eligible if they have received one or more prior treatment;
- ECOG performance status of 0-2 (Appendix 1);
- Life expectancy > 6 months;
- Adequate renal function indicated by serum creatinine less or equal to 2 mg/dl;
- Adequate hepatic function indicated as total bilirubin less or equal to 2 mg/dl and ALT/GPT less or equal to two times the upper normal limit;
- 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;
- No prior history of myelodysplastic syndrome or other myeloid malignancy;

- All participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the Revlimid REMS®;
- Females of childbearing potential (FCBP) must have a negative serum and/or urine pregnancy test with a sensitive of at least 50 miU/mL within 10-14 days and again within 24 hours prior to prescribe lenalidomide for cycle 1 (prescriptions must be filled within 7 days as required by Revlimid REMS®) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy.

Revlimid(REMS) is available to patients through a restricted distribution program called the REVLIMID Risk Evaluation and Mitigation Strategy (REMS)™ (formerly known as the RevAssist® program).

Upon consent and confirmation of protocol eligibility, patients will be required to complete a Revlimid REMS enrollment form in order to receive their clinical trial supply of Revlimid directly from Celgene.

For more information visit www.CelgeneRiskManagement.com or call the Celgene Customer Care Center at 1-888-423-5436

EXCLUSION CRITERIA

Patients who meet any of the following criteria will be excluded from study entry:

- Known sensitivity to lenalidomide or other thalidomide derivatives or anti CD20;
- Documented prolymphocytic leukemia (prolymphocytes more than 55% in the blood);
- Known history of infection with Human immunodeficiency virus (HIV) or Human T Cell Leukemia Virus 1 (HTLV-1);
- Serologic status reflecting active hepatitis B or C. Patients with hepatitis B (HBV) antibody positive but who have positivity for Hepatitis B surface antigen (HBsAg) or anti Hepatitis B core antibody (anti-HBc) and patients who are positive for anti-HCV will need to have a negative PCR (viral HBV DNA or HCV RNA) result prior to enrollment. Those who are HBsAg positive or HBV DNA positive and those who are positive for HCV (RNA) will be excluded;
- Pregnant or breastfeeding females;
- History of tuberculosis treated within the last five years or recent exposure to tuberculosis;

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

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

5. TREATMENT PLAN

This is a single arm phase II study of Combination of Lenalidomide and Obinutuzumab in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL-SLL) with recurrent disease.

Obinutuzumab will be given 100 mg iv d1, 900 mg iv d2 and 1000 mg d8(+/-3 days) and d15 (+/-3 days) for the first cycle, and 1000 mg d1(+/-10 days) along cycles 2-6 in a 28 days cycle. Lenalidomide will be given at 5mg per day from day 9 until day 56 and at 10 mg per/day from day 57 until progression or excessive toxicity. See Study Calendar (Appendix 2).

Patients will self-administer lenalidomide daily.

This research study protocol allows the patient to receive up to 9 infusions of Obinutuzumab .

Response will be evaluated after three, six and twelve cycles and every 6 months thereafter .

The estimated patient accrual is 3-6 per month. And the trial accrual time is estimated to be about 10-20 months. The end of study is defined as 5 years after the last patient was enrolled (unless all patients have died).

6. STUDY MEDICATION FORMULATION, STORAGE, AND PREPARATION

Obinutuzumab
Formulation

Obinutuzumab is provided as a single-use vial. Each vial contains a sterile liquid formulation in a 50-mL pharmaceutical-grade glass vial containing a nominal dose of 1000 mg of obinutuzumab.

Storage

The recommended storage conditions for the obinutuzumab drug product are between 2°C and 8°C, protected from light. Chemical and physical in-use stability for obinutuzumab dilutions in 0.9% sodium chloride (NaCl) at concentrations of 0.2-20 mg/mL have been demonstrated for 24 hours at 2°C-8°C and an additional 24 hours at ambient temperature and ambient room lighting.

Split dosing

Split dosing: Splitting the first dose of obinutuzumab in Cycle 1 is mandatory. The first dose (1000 mg) must be administered over Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2).

Obinutuzumab drug product intended for IV infusion is prepared by dilution of the drug product into an infusion bag containing 0.9% NaCl.

Lenalidomide

Formulation and Storage

Lenalidomide is provided as pills. Lenalidomide will be obtained by the Revlimid REMS program

DOSAGE AND ADMINISTRATION

Obinutuzumab

Obinutuzumab administered by IV infusion for up to 6 cycles (28-day cycles):

- On Cycle 1, Day 1, 100 mg obinutuzumab will be administered
- On Cycle 1, Day 2, 900 mg of obinutuzumab will be administered
- On Cycle 1, Days 8 (+/-3 days) and 15 (+/-3 days), 1000 mg of obinutuzumab will be administered.
- On Cycles 2-6, Day 1 (+/-10 days), 1000 mg of obinutuzumab will be administered

Obinutuzumab should be given as a slow IV infusion through a dedicated line. IV infusion pumps should be used to control the infusion rate of obinutuzumab. Do not administer as an IV push or bolus.

Premedication Requirements

Infusion-Related Reactions (IRR)

Since some patients may develop hypersensitivity or other IRRs to obinutuzumab, pre-medication is recommended to reduce the risk of infusion reactions as outlined below:

- Cycle 1, Days 1 and 2, all patients require pre-medication with:

  IV glucocorticoid: dexamethasone (20 mg) or methylprednisolone (80 mg) administered at least one hour prior to obinutuzumab infusion.

  An oral acetaminophen (1000 mg) and an antihistamine such as diphenhydramine (50 mg) administered at least 30 minutes before starting each obinutuzumab infusion.

If a patient experiences any grade infusion reaction during infusion, adjust the infusion as outlined below:

- Grade 4 (life threatening):Stop infusion and discontinue therapy.
- Grade 3 (severe): Temporarily interrupt infusion and treat symptoms. Upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the infusion reaction occurred) and, if patient does not experience any infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose.
- Grade 1-2 (mild to moderate): Reduce infusion rate and treat symptoms. Upon resolution of symptoms, continue infusion and, if patient does not experience any infusion reaction symptoms,infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose.

Dosage Modification and Toxicity Management
Assessment of Hematologic Toxicities

Dose modification decisions for patients with cytopenia (below the lower limit of the normal range) at baseline will be based on the NCI sponsored Working Group (NCI-WG) grading scale for hematologic toxicity in CLL/SLL studies[9] (Table 2). For patients with a normal neutrophil count, platelet count, and/or hemoglobin value at baseline, the NCI CTCAE, v4.0, will be used.

Table 2 NCI grading scale for hematological toxicity in CLLISLL studies.

Decrease in platelets or Hb from pretreatment	Grades	ANC/IJL
No change to 10%	0	2000
11%-24%	1	1500 and <2000
25%-49%	2	1000 and <1500
50%-74%	3	500 and <1000
75%	4	<500

Dosage Modifications

No reduction in the dose of obinutuzumab is allowed. Splitting the first dose of obinutuzumab in Cycle 1 is mandatory. The first dose (1000 mg) must be administered over Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2). Infusions should be interrupted or slowed if patients experience infusion reactions (see "Management of infusion related reactions and anaphylaxis" paragraph). If a planned dose of obinutuzumab is missed, it should be administered as soon as possible.

The guidelines for obinutuzumab dose delay due to Grade 3 or 4 cytopenia are outlined in Table 3.

Table 3 Dose Modification for Cytopenia

Grade	Obinutuzumab
Grade 3 or 4 cytopenia	No reduction in the dose of obinutuzumab is allowed. A dose delay is allowed if clinically indicated. If improvement to Grade 2, administer full dose
Grade 1 or 2 cytopenia	No dose reduction or delay

a In patients with cytopenia at baseline, dose modifications will be based on the NCI grading scale for hematological toxicity in CLL/SLL studies (see Appendix 3)

b Or baseline

Administration of Granulocyte Colony-Stimulating Factor

G-CSF may be administered as primary prophylaxis in each cycle of therapy,as per the American Society of Clinical Oncology (ASCO) guidelines or each site's institutional standards.

Hepatitis 8 Virus Reactivation

Positive serology for Hepatitis B is defined as positivity for Hepatitis B surface antigen (HBsAg) or Hepatitis B core antibody (anti-HBc).Patients who are positive for anti-HBc may be considered for inclusion in the study on a case-by-case basis if they are Hepatitis B viral DNA negative and are willing to undergo ongoing HBV DNA testing by real-time PCR. Patients with positive serology may be referred to a specialist for appropriate monitoring and management.

For the subset of patients who are Hepatitis B viral DNA negative and anti-HBc positive and have undetectable Hepatitis B viral DNA levels at screening, Hepatitis B viral DNA levels must be followed regularly.

Management of Infusion-Related Reactions and Anaphylaxis

Please refer to Section "Premedication requirements" for information relating to concomitant medications. Medications (including subcutaneous epinephrine, corticosteroids, and intravenous diphenhydramine) and resuscitation equipment should be available for immediate use.

Life-Threatening Infusion-Related Reactions and Anaphylaxis

In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or IgE-mediated anaphylactic reaction, obinutuzumab should be discontinued and no additional obinutuzumab should be administered (see Table 4). Patients who experience any of these reactions should receive aggressive treatment of symptoms and will be discontinued from study treatment.

Table 4 Management of Infusion-Related Symptoms

Infusion-Related Symptoms	Guidance
Grades 1-2	• Slow or hold infusion • Give supportive treatment • Upon symptom resolution, may resume infusion rate escalation at the investigator's discretion c
Grade 3	• Discontinue infusion • Give supportive treatment b • Upon symptom resolution, may resume infusion rate escalation, at investigator discretion • Note: If the same adverse event recurs with the same severity, treatment must be permanently discontinued.
Grade 4	

Tumor Lysis Syndrome

For patients with evidence of TLS, obinutuzumab should be discontinued and the patient treated as clinically indicated. Following the complete resolution of TLS complications, obinutuzumab may be re administered at the full dose during the next infusion in conjunction with prophylactic therapy.

Lenalidomide

Lenalidomide will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers and in accordance with the Revlimid REMS® program of Celgene Corporation. Per standard Revlimid REMS ® requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must be filled within 14 days, unless the patient is a female of childbearing potential, in which case the prescription must be filled within 7 days. Only enough lenalidomide for one cycle will be supplied to the patient each cycle.

Lenalidomide will be given at 5 mg per day, day 9-56, followed by 10 mg per day, day 57 until end of treatment. Lenalidomide will start on day 9 and continued for one year with the possibility to prolong the end of treatment until progression or excessive toxicity. Patients will self administer lenalidomide daily, per mouth.

Dosage modification and Toxicity management of lenalidomide

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.

The dose of lenalidomide will be adapted depending on the assessment of toxicity. The evaluation of potential treatment-induced toxicity, in particular of hematological toxicity, in patients with advanced CLL/SLL required careful consideration. At diagnosis, in fact, cytopenia could be the expression of progressive bone marrow failure. As a consequence, dose modification decisions for patients with cytopenia (below the lower limit of the normal range) at baseline will be based on the NCI grading scale for haematological toxicity in CLL!SLL studies (see Table 2). For patients with a normal neutrophils count, platelet count and or hemoglobin value at baseline, the NCI common terminology criteria for adverse events (CTCAE) version 4.0 will be used (Appendix 3).

For lenalidomide the dose reduction is describe below.

Table 5 Dosage modifications for lenalidomide study drug.

	Lenalidomide
Sustained (>7 days) Grade 3 neutropenia or Grade 3 associated to fever > 38.5 C or Grade 4 neutropeniaa	• administer G-CSF as clinical indicated • Follow CBC weekly until resolution or stabilization • If improvement to </= Grade 2*, implement one
Thrombocytopeniaa Grade 4	• Hold (interrupt dose) for a maximum of 4 weeks and eventually transfuse platelets • Follow CBC weekly until resolution or stabilization • If improvement to </= 5 Grade 2*, implement one dose reduction step and continue therapy
Not desquamating (blistering) rash Grade 3 Grade 4	• Hold (Interrupt) the dose and follow weekly until resolution or stabilization • If the toxicity resolved to grade 1, implement one dose reduction step and continue therapy
Desquamating (blistering) rash Any grade	• Discontinue lenalidomide study drug
Erythema multiforme Grade 3-4	• Discontinue lenalidomide study drug
Neuropathy Grade 3 Grade 4	• Hold(interrupt) the dose and follow weekly until resolution or stabilization • If toxicity resolves to grade 2, implement one dose reduction and continue therapy • Discontinue lenalidomide study drug

Sinus bradycardia/other cardiac arytmia Grade 2	• Hold (interrupt) the dose and follow at least weekly until resolution and stabilization If the toxicity resolves to >grade 1, implement one dose reduction step and continue therapy
Sinus bradycardia/other cardiac arytmia Grade 3	• Discontinue lenalidomide study drug
Allergic reaction or hypersensitivity Grade >/= 3 Grade 4	• Hold (interrupt) the dose and follow at least weekly until resolution and stabilization • If the toxicity resolves to !>grade 1, implement one dose reduction step and continue therapy
Constipation Grade 1-2	• Initiate bowel regimen and maintain dose level • If the toxicity resolves to </= grade2, implement one dose reduction step and continue therapy
Grade 3	• Discontinue lenalidomide study drug
Venous thrombosis/embolism grade 3	• Hold (interrupt) dose and start anticoagulant; restart at investigator's discretion (maintain dose level)
Hepatic or other non-hematologicic toxicity assessed as lenalidomide-related c >/= grade 3	• Hold (interrupt) the dose and follow at least weekly until resolution and stabilization • If the toxicity resolves to </= grade 2, implement the dose reduction step
Tumor flair refractory to oral pain medications	Hold (interrupt) dose and differentiate tumor flare from progression. • Restart therapy at the investigator's discretion

a In patients with cytopenia at baseline, dose modifications will be based on the NCI grading scale for

haematological toxicity in CLL/SLL studies (see Table 2).

b Once toxicity has resolved, lenalidomide dose can be increased to 10 mg/daily at the discretion of the investigator or the dose that is clinically indicated.

c Further dose reduction will be allowed at the discretion of the investigator in case of persistent non haematological toxicity of grade 3 or less and in case of a change in laboratory evaluation such as platelet count, ANC, or hemoglobin count that indicates upcoming myelosuppression or as clinically indicated.

d For patients who experienced TFRs while treated with lenalidomide-containing

regimens, steroids will be allowed to manage lymph node enlargement and inflammation, and anthistamines to manage rash/pruritus. For patients with bulky(> 5 em) lymph-nodes before the start of therapy ,tumor flair prophylaxis with steroids may be considered for the first 10-14 days of therapy.

Table 6 Dose level for lenalidomide.

Level	10 mg Dose	5 mg Dose
-1	5 mg daily	5 mg daily, day 1-21 of a 28 days cycle or 5 mg every other day for 28
-2	5 mg daily, day 1-21 of a 28 days cycle or 5 mg every other day for 28 days	5 mg twice a week
-3	5 mg twice a week	5 mg once a week
-4	5 mg once a week	N/A

CONCOMITANT MEDICATIONS

Concomitant therapy

All concomitant medications should be recorded in the patient electronic records.

Prophylaxis for Tumor Lysis Syndrome

All patients should then be carefully monitored during the initial weeks of treatment. Patients still considered at risk for TLS because of persistently high tumor burden before the second and subsequent infusions of obinutuzumab should continue TLS prophylaxis until the risk is abated, as determined by the investigator.

Other Concomitant Medications

Necessary supportive measures for optimal medical care will be given throughout the study as clinical indicated, including the use of growth factors if clinically indicated.

Anticoagulant Prophylaxis

Lenalidomide has been associated with increased risk for venous thromboembolism (deep vein thrombosis or pulmonary embolism) in patients with myelodisplastic or multiple myeloma, particularly when combined with dexamethasone or chemotherapeutic agents.

Routine prophylaxis for venous thromboembolic events is not recommended in patients with CLL/SLL undergoing lenalidomide-containing regimens. However, NCCN NHL Panel recommend prohylaxis with daily low-dose aspirin in patients with extremely high platelet counts at baseline (National Comprehensive Cancer Care Network, CLLISLL Guidelines, 2013). Thus, the investigator may consider the use of aspirin (81 mg or 325 mg/daily per mouth) or LMWH subcutaneously at prophylactic dose in patients at high risk for thrombotic events.

7. CRITERIA FOR STUDY DISCONTINUATION GENERAL CRITERIA

- Inability of patient to comply with study requirements
- Determination by the investigator that it is no longer safe for the patient to continue therapy
- Disease progression
- Patient's preference

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

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

8. CLINICAL AND LABORATORY EVALUATIONS PRETREATMENT E V A L U A T I O N S

Pretreatment evaluation will include:

- Medical history and a physical examination including vital signs ECOG performance status, height and weight and recording of concurrent medications (within 7 days of day 1).
- Hematology: complete CBC and differential, peripheral blood lymphocyte subsets (CD4, CD8, NK) and immunoglobulin levels (within 7 days of registration).
- Serum chemistry. This will include sodium,potassium, calcium, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, LDH, total bilirubin, ALT(SGPT), uric acid, and TSH. Beta-2-microglobulin (within 7 days of day 1).
- Serology for HBV, HIV and HCV (within 3 months of registration).

Bone marrow aspiration and biopsy within one month from registration.Bone marrow will be evaluated for flow cytometry, for clonality and for IgVH mutational status (unless known), ZAP-70 (unless known) and CD38 expression, cytogenetic and genomic abnormalities by FISH (unless known).

- CT SCAN or/and PET and/or US and/or MRI within 30 days of registration if clinically indicated.

- For FCBP (female of childbearing potential) serum and/or urine pregnancy test must be done within 10-14 days prior to start therapy and 24 hours prior to prescribe lenalidomide for cycle 1. Females of childbearing potential (FCBP) is a sexually mature female who:1) has not undergone a hysterectomy or bilateral oophorectomy; 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has not had menses at any time in the preceding 24 consecutive months).

EVALUATIONS DURING TREATMENT

- Clinic visits (this will include vital signs and physical exam) at the University of Texas, MD Anderson Cancer Center (UTMDACC) are required for treatment initiation and at the start of cycles 2-6 (+/10 days from Day 1). Clinic visits (this will include vital signs and physical exam) at UTMDACC are required after 3, 6 cycles (obinutuzumab and lenalidomide) and 12 cycles (lenalidomide) and once every 6 cycles thereafter (+/-14 days from Day 1 of subsequent cycle). Hematology complete blood counts (white blood cells, hemoglobin, platelets and differential) will be monitored once weekly for the first five weeks and once every two weeks 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 decreasing for non-hematological or laboratory measurable toxicity), and every two or four weeks thereafter.

- Serum chemistry basic metabolic profile (sodium, potassium, BUN, creatinine and glucose) will be monitored once a week for the first five weeks and then once every two weeks until a stable dose of lenalidomide has been established for the specific patient and then every two or four weeks thereafter.

- TSH, beta-2-microglobulin, lymphocyte subsets, immunoglobulin levels, bone marrow biopsy and aspiration, flow cytometry will be performed and evaluated after 3, 6 cycles (obinutuzumab and lenalidomide) and after 12 cycles (lenalidomide).

- If patient stay on the study past 12 cycles, once every 6 cycles, he will have a bone marrow biopsy and aspirate evaluated by flow cytometry to check the status of the disease if clinically indicated.

- Blood lymphocyte subsets (CD4, CD8, NK) and immunoglobulin levels every 3 months for the first year, and once every 6 months thereafter.

- CT scan and/or PET, and/or US and/or MRI as clinical indicated

- Response to treatment will be assessed according to IW-CLL 2008 criteria.

- 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 4 Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

- In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed until they have returned to the normal range, baseline value and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the eCRF.

9. EVALUATION OF RESPONSE

The primary efficacy endpoint is overall response, defined as CR or PR. The secondary endpoints will be safety of the combination,response according to prognostic markers at diagnosis,time to next treatment and overall survival. Response to treatment will be assessed according to NCI-WG 2008 working group criteria at 3 months from the beginning of therapy and every 6 months thereafter.

10. STATISTICAL CONSIDERATIONS

DETERMINATION OF SAMPLE SIZE

The patient sample size will be 30 patients and the Bayesian method of Thall, Simon and Estey [21] will be employed to perform interim futility and safety monitoring.

PLANNED EFFICACY EVALUATIONS

The primary efficacy endpoint is overall response, defined as CR or PR. The secondary endpoints will be safety of the combination, response according to prognostic markers at diagnosis,time to next treatment and overall survival. Response to treatment will be assessed according to NCI-WG 2008 working group criteria at 3, 6 months from the beginning of therapy and every 6 months thereafter.

PRIMARY EFFICACY VARIABLES

Overall response, defined as CR or PR.

SECONDARY EFFICACY VARIABLES

The secondary endpoints will be safety of the combination,response according to prognostic markers at diagnosis,time to next treatment and overall survival.

METHOD OF ANALYSIS

We will monitor futility and safety of the treatment combination using a Bayesian design by Thall, Simon and Estey, in cohort size of 10. Specifically, assuming a beta (0.8, 1.2) prior for the overall response (OR) rate, we will stop trial if Prob {p(OR) > 0.40 data} < 0.05, where p(OR) is the probability of overall response. That is, if at any time during the trial we determine that there is less than 5% chance that the overall response rate is at least 40%, we will stop the trial. For futility monitoring purpose, we will assess patients' OR rate at 3 months post treatment, and at each planned cohort (i.e., 10, 20, 30, etc.) for interim look, if there is not enough number of responders (such as 1 or fewer out of the first 10, 4 or fewer out of the first 20, etc.) we will temporarily suspend accrual until all patients in the current cohort has been fully evaluated. Similarly, we will stop the trial if Prob{p(TOX) > 0.50 data} > 0.95, where p(TOX) is the probability of grade 3 or higher non-hematological toxicity and a beta(1, 1) prior was used for toxicity rate. That is, if at any time during the trial we determine that there is more than 95% chance that the toxicity rate is at least 50%, we will stop the trial due to safety concern. The corresponding stopping boundaries for futility and safety are shown in Tables 7 and 8 respectively. The operating characteristics of the design are illustrated in Table 9. MuItc Lean Desktop (v2.1.0) was used for generating the stopping boundaries and the OC table.

If the trial did not stop due to either futility or toxicity, then with a total sample size of 30, the 95% credible interval for the overall response rate will be (0.24, 0.57), assuming an OR rate of 0.40and a beta(0.8 , 1.2) prior.

The proportion of patients achieving OR and its 95% credible interval will be presented. In addition, we will compute the posterior probability of OR rate being greater than 40%. Similar methods will be used to analyze the toxicity data. Univariate and multivariable logistic regression models will be fit to assess the association between OR and prognostic biomarkers. The time-to-event outcomes (such as time to next treatment or overall survival) will be estimated using the Kaplan-Meier method.

Table 7. Interim futility stopping boundaries in cohort size of 10.

Number of Patients Evaluated	Stop the trial if <=OR Observed
10	1
20	4
30	7

Table 8. Interim toxicity stopping boundaries in cohort size of 10.

Among These Number of Patients	Stop the trial if >/= Toxicity Observed
10	8
20	14
30	20

Table 9 The operating characteristics of futility and toxicity monitoring.

True OR rate	True Toxicity Rate	Prob (stop early)	Average number of patients
0.3	0.3	0.28	25.6
0.3	0.5	0.35	24.5
0.3	0.7	0.75	17.8
0.4	0.3	0.08	28.7
0.4	0.5	0.16	27.4
0.4	0.7	0.68	19.1
0.5	0.3	0.02	29.7
0.5	0.5	0.10	28.3
0.5	0.7	0.65	19.6

In addition, we will monitor the grade 4 and grade 5 non-hematological toxicities separately, throughout the study and in cohort size of 10. Specifically, the trial will be stopped if Prob{p(TOX4) > 0.25 | data} > 0.95 or Prob{p(TOX5) > 0.10 | data} > 0.95 , where p(TOX4) and p(TOX5) are the probabilities of grade 4 and grade 5 non-hematological toxicities, respectively. A beta(0.5, 1.5) prior is assumed for p(TOX4) and a beta(0.2, 1.8) prior is assumed p(TOX5). Based on these stopping criteria, the trial will be stopped early if [#patients with grade 4 toxicities]/[#patients evaluated] >= 6/10, 9/20, 12/30OR [#patients with grade 5 toxicities]/[#patients evaluated] >= 4/10, 5/20, 7/30.

This protocol will use PDMS and CORE as database repositories

REPORTING OF ADVERSE EVENTS ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and reporting AEs and SAEs that are considered related to obinutuzumab or/and lenalidomide, all events of death, and any study specific issue of concern.

Adverse Events

An AE is any unfavorable and unintended sign, temporarily associated with the use of an

investigational medicinal product (IMP) or other protocol- imposed intervention, regardless of attribution.

Serious Adverse Event Reporting for MD Anderson- Sponsored IND Protocols
An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

Death
A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
Inpatient hospitalization or prolongation of existing hospitalization
A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical 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 (21 CFR 312.32).

Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the INDIND Sponsor, IND Office.

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 for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB for participants enrolled at MDACC.

Reporting for all sites:

- **All life-threatening or fatal events,** that are unexpected, and related 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 the IND Office. -
- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. 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 the IND Office. This may include the development of a secondary malignancy.**
- **All events reported to the supporting company must also be report to the IND Office.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) 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.

Genetech requested reporting:

Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with CLL/SLL that were not present prior to the AE reporting period.

Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).

If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.

Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

It results in death (i.e., the AE actually causes or leads to death).

It is life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
It requires or prolongs inpatient hospitalization.

It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions).

It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all AEs and SAEs, that are observed or reported during the study, are collected and reported to the U.S. Food and Drug Administration (FDA), appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the obinutuzumab (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of the obinutuzumab and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the obinutuzumab and/or the AE abates or resolves upon discontinuation of the obinutuzumab or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than the obinutuzumab (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to obinutuzumab administration (e.g., cancer diagnosed 2 days after first dose of obinutuzumab).

Expected AEs are those AEs that are listed or characterized in the Package Insert or current Investigator Brochure.

Unexpected AEs are those not listed in the Package Insert (P.I.) or current Investigator's Brochure or not identified. This includes AEs for which the specificity or severity is not consistent with the description in the P.I. or Investigator's Brochure. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or Investigator's Brochure only referred to elevated hepatic enzymes or hepatitis.

PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all patient evaluation timepoints should be adopted. Examples of non-directive questions include:

"How have you felt since your last clinical visit?"

"Have you had any new or changed health problems since you were last here?

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

Diagnosis versus Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

Deaths

All deaths that occur during the protocol-specified AE reporting period regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

- Hospitalizations for the following reasons do not require reporting:
- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

Pregnancy

If a female patient becomes pregnant while receiving obinutuzumab or within one year after the last dose of obinutuzumab, or the partner of a male patient becomes pregnant while receiving therapy or within three months of completing therapy, a report should be completed and expeditiously submitted to the Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female patient exposed to obinutuzumab should be reported as an SAE.

Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a patient has completed or discontinued study participation if attributed to prior obinutuzumab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female patient who participated in the study, this should be reported as an SAE.

Safety Reconciliation

The Sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange monthly line listings of cases received by the other party. If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

Adverse Events of Special Interest (AESIs)

AEs of special interest (AESIs) are defined as a potential safety problem, identified as a result of safety monitoring of the Product.

The following AEs are considered of special interest and must be reported to the Sponsor expeditiously irrespective of regulatory seriousness criteria:

- TLS (Tumor Lysis Syndrome; all grades)
- Abnormal Liver Functions Tests

Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law.

The finding of an elevated ALT or AST ($> 3 \times$ ULN) in combination with either an elevated total bilirubin ($> 2 \times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN

- Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study drug, as defined below:
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when contamination of the study drug is suspected.

Investigator Communications with Genentech:

Investigators must report all SAEs to Genentech within the timelines described below. The completed MDACC SAE reporting form/case report should be faxed immediately upon completion to Genentech Drug Safety at:

(650) 225 4682

OR

(650) 225 5288

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.

Serious AE reports that are related to obinutuzumab and AEs of Special Interest (regardless of causality) will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.

Serious AE reports that are unrelated to obinutuzumab will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.

Additional reporting requirements to Genentech include the following:

Any reports of pregnancy following the start of administration with the obinutuzumab and within the follow-up period (for female patients within one year after the last dose of obinutuzumab or the partner of a male patient within three months of completing therapy) will be transmitted to Genentech within 30 days of the Awareness Date.

All non-serious *obinutuzumab* AEs originating from the study will be forwarded Genentech *quarterly*

Note: Investigators should also report events to their IRB as required.

Follow-Up Information

Additional information may be added to a previously submitted report by any of the following methods:

Adding to the original **MDACC** SAE report and submitting it as follow-up

Adding supplemental summary information and submitting it as follow-up with the original MDACC SAE reporting form. Summarizing new information and faxing it with a cover letter including patient identifiers (i.e., D.O.B. initial, patient number), protocol description and number, if assigned, brief AE description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report). Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and AE was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

Investigator Communications with Celgene:

Pregnancies

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

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

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

Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking lenalidomide should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.
Celgene Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

Expedited Reporting by Investigator to Celgene
For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events of being related to lenalidomide based on the Investigator Brochure. In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using the MDACC SAE reporting form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (RV-CL-CLL- PI-004319) 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.

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Appendix 1ECOG Performance Status

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on 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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

*As published in Am. J. Clin. Oncol:

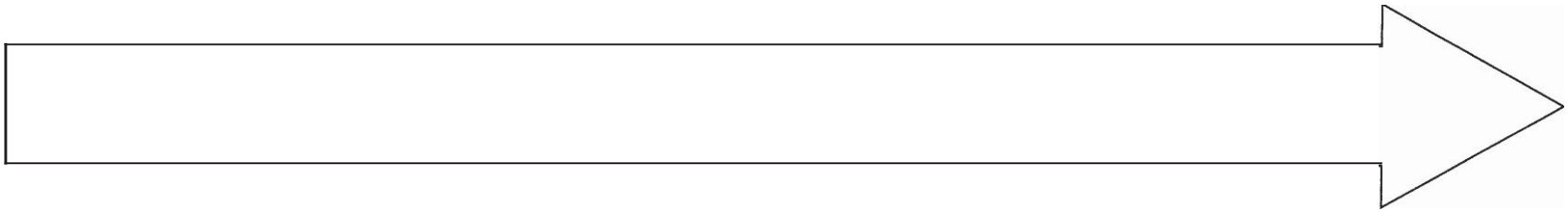
Oken, M.M., Creech, R.H., Tanney, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Appendix 2 Treatment Schedule

Cycle 1 (28-day cycles) Cycles 2–6 Obinutuzumab (mg)

	100	900	1000		1000		1000
Day	1		2	8	15		1

Day 9 - 56 Lenalidomide 10 mg daily Day 57 until progression



Appendix 3 Current NCI Common Terminology Criteria for Adverse Events (CTCAE)

In the present study, toxicities will be graded according NCI CTCAE, version 4.0.

Please use the following link to the NCI CTCAE website:

http://ctep.cancer.gov/protocolDevelopment/electronic applications/etc.htm

Appendix 4 Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

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

Criteria for females of childbearing potential (FCBP)

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

Counseling

For a female of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- She understands the potential teratogenic risk to the unborn child

- She understands the need for effective contraception, without interruption, 4 weeks before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment

  She should be capable of complying with effective contraceptive measures

- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy

- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test

- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol

- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

The investigator must ensure that for females of childbearing potential:

- Complies with the condition for pregnancy risk minimization including confirmation that she has an adequate level of understanding

- Acknowledge the aforementioned requirements

- For a female NOT of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females NOT of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

Traces of lenalidomide have been found in semen. Male patients taking lenalidomide must meet the following conditions (i.e., all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential

- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or 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 contact during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) dose interruptions; and 4) for at least 28 days after study treatment 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

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

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

Before starting study drug

Female Patients:

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

Male Patients:

Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation Female Patients:

FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following study drug discontinuation. 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 discontinuation.
study14and 28 following study drug discontinuation, and at days

At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.

- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.

- If pregnancy or a positive pregnancy test does occur in a study patient, study drug 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. Study drug treatment must be discontinued during this evaluation.

Females must agree to abstain from breast feeding during study participation and for at least 28 days after study drug discontinuation.

Male Patients:

- Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to lenalidomide must be conducted at a minimum of every 28 days.

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 this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.

- Female patients should not donate blood during therapy and for at least 28 days following discontinuation of study drug.

- Male patients should not donate blood, semen or sperm during therapy or for at least 28 days following discontinuation of study drug.

- Only enough study drug for one cycle of therapy may be dispensed with each cycle of therapy.

Pregnancies:

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP (Investigational Product), or within (insert time-frame which must be at least 28 days of the subject's last dose of IP), are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy

test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form. If the outcome of the pregnancy was abnormal (e.g., spontaneousor therapeutic abortion), the Investigator shouldreport the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

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

Male Subjects

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

Appendix 5 FDA MDACC SAE reporting

http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm