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MD Anderson Cancer Center

Houston, Texas

Study Title

A Phase I/II study of Lenalidomide and Obinutuzumab (GA101) in Relapsed Indolent Non-Hodgkin's Lymphoma

Study Drug

Obinutuzumab

Lenalidomide

Support Provided By

Genentech, Inc.

Sponsor Investigator

Loretta Nastoupil MD

Study Number: **2013-0261**

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ABC	activated B cell
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
anti-HBc	antibody to hepatitis B core antigen
aPTT	activated partial thromboplastin time
BM	bone marrow
ASCO	American Society of Clinical Oncology
AUC	area under the concentration–time curve
BSA	body surface area
CDC	complement-dependent cytotoxicity
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration observed
CNS	central nervous system
CR	complete response or complete remission
Cru	unconfirmed complete response
CSR	Clinical Study Report
D	Day
DFS	disease-free survival
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
EC	Ethics Committee
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
F	phenylalanine
FACS	fluorescent-activated cell sorter
FcγR	leukocyte receptors for the Fc portion of IgG
^{18}F-FDG	^{18}F-fleurodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FISH	fluorescence in situ hybridization
GCB	germinal center B cell

Abbreviation	Definition
GCP	Good Clinical Practice
GCSF	granulocyte-colony stimulating factor
GEP	gene expression profiling
G	GA101(obinutuzumab)
G-FC	GA101(obinutuzumab) in combination with fludarabine and cyclophosphamide
HAHA	human anti-human antibodies
HBcAb	hepatitis B core antibodyd
HBsAg	hepatitis B surface antigen
HBV	hepatits B virus
HCV	hepatitis C virus
HD	high dose
HTLV	human T-cell leukemia virus
ICH	International Conference on Harmonisation
Ig	immunoglobulin
IHC	immunohistochemistry
IND	Investigational New Drug
IMC	Internal Monitoring Committee
IRR	infusion-related reaction
IV	intravenous
IL	interleukin
IPI	International Prognostic Index
IVRS	interactive voice response system
LD	low dose
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
MCL	mantle-cell lymphoma
MUGA	multigated acquisition scan
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
NONMEM	Non-Linear Mixed Effect Model
ORR	overall response rate
OS	overall survival
PD	progressive disease
PICC	peripherally inserted central catheter
PK	pharmacokinetic

Abbreviation	Definition
PET	positron emission tomography
PFS	progression-free survival
PML	progressive multifocal leukoencephalopathy
PR	partial response or partial remission
R-CHOP	rituximab in combination with cyclophosphamide, doxorubicin, vincristine, prednisone
SAE	serious adverse event
SD	stable disease
SDI	shorter duration of infusion
SLL	small lymphocytic lymphoma
SOC	Scientific Oversight Committee
TLS	tumor lysis syndrome
ULN	upper limit of normal
V	valine
WHO	World Health Organization

1. INTRODUCTION

1.1 DISEASE BACKGROUND

1.1.1 NON-HODGKIN'S LYMPHOMA

Non-Hodgkin's lymphoma (NHL) is the most common hematologic malignancy in adults. It is estimated that in 2010 there were 93,172 new cases of NHL in Europe and 65,540 new cases of NHL in the United States (American Cancer Society 2010; GLOBOCAN 2010). The majority of NHLs are of B-cell origin and are characterized by the expression of membrane antigen CD20 which is important in cell cycle initiation and differentiation (Anderson et al. 1984).

Indolent NHLs are a heterogeneous group of malignant lymphomas and account for about one-third of all NHLs. Follicular lymphoma is the most common subtype of indolent NHL in the Western hemisphere and is associated with follicle center B cells that typically contain the *BCL2* chromosome translocation t(14:18), which leads to overexpression of the intracellular anti-apoptotic protein Bcl-2. Although follicular lymphoma is the most common subtype of indolent NHL, there are also many histological non-follicular subtypes, including marginal zone lymphoma (MZL), and small lymphocytic lymphoma (SLL). Early-stage indolent NHL may be effectively treated with radiation therapy, but advanced stages remain incurable.

1.1.2 NATURAL HISTORY AND CURRENT MANAGEMENT OF INDOLENT NON-HODGKIN'S LYMPHOMA

The clinical course of indolent NHL is characterized by remission and relapse (Gallagher et al. 1986). The disease often initially responds to immunochemotherapy, but most patients eventually suffer multiple relapses distinguished by increasing resistance and decreasing duration of response in subsequent lines of therapy. Patients with advance-stage disease are not usually cured with conventional treatment and ultimately die from recurrent disease or treatment-related toxicity.

a. Immunochemotherapy in Follicular Lymphoma

There is no standard treatment for the management of advanced follicular lymphoma, and data from the National LymphoCare registry demonstrate that practice varies widely among physicians (Friedberg et al. 2009). For follicular lymphoma patients requiring treatment, immunochemotherapy with rituximab, a monoclonal antibody directed against CD20, plus chemotherapy has demonstrated improvements in response rates, progression-free survival (PFS), and overall survival compared with chemotherapy alone in four studies (Hiddemann et al. 2005; Herold et al. 2007; Marcus et al. 2008; Salles et al. 2008). Rituximab in combination with chemotherapy (e.g., CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone], CVP

[cyclophosphamide, vincristine, and prednisone], or purine analogue–based schemes such as those with fludarabine or bendamustine) for newly diagnosed patients with advanced Stage III and IV disease requiring treatment is strongly supported by both the 2009 European Society for Medical Oncology (ESMO) Guidelines Working Group recommendations (level of evidence: I; grade of recommendation: B) and the 2010 National Comprehensive Cancer Network (NCCN) guidelines (Category 1 recommendation based on high-level evidence, with a uniform NCCN consensus) (Dreyling 2009; Zelenetz et al. 2010).

b. Immunochemotherapy in Non-Follicular Indolent Lymphoma

Rituximab has also demonstrated efficacy in patients with non-follicular indolent lymphoma, including MZL, WM, and SLL (Foran et al. 2000; Treon et al. 2001; Hainsworth et al. 2003). A Phase II trial conducted in 39 patients with MZL (Brown et al. 2009) showed high response rates (overall response rate [ORR] of 85%; complete response [CR] rate of 54%) with durable responses (79.5% PFS after 3.1 years) following treatment with rituximab and chemotherapy.

Rituximab is listed as an option for the treatment of advanced MZL in the most recent ESMO and NCCN Clinical Practice Guidelines (Zelenetz et al. 2010; Zucca et al. 2010).

c. Maintenance Therapy after Induction Treatment

In addition to immunochemotherapy induction, two randomized clinical trials have demonstrated the benefit of maintenance rituximab in responding patients with both previously untreated and relapsed follicular lymphoma. In a clinical trial of patients with relapsed follicular lymphoma, responders to rituximab plus CHOP (R-CHOP) or CHOP underwent a second randomization to maintenance rituximab or observation. Patients who received maintenance rituximab demonstrated a superior median PFS (52 vs. 15 months) and 3-year overall survival (85% vs. 77%) compared with patients who underwent observation (van Oers et al. 2006). Updated results from this study, with a median follow-up of 6 years, continued to demonstrate a significant improvement in PFS with rituximab maintenance versus observation (median PFS: 3.7 years vs. 1.3 years; $p<0.001$; hazard ratio, 0.55) and in 5-year overall survival (74% vs. 64%) after either R-CHOP or CHOP induction (van Oers et al. 2010). More recently, a study of patients with previously untreated follicular lymphoma that responded to rituximab in combination with CVP, CHOP, or FCM (fludarabine, cyclophosphamide, and mitoxantrone) who were later randomized to observation or 2 years of maintenance rituximab (the Primary Rituximab and Maintenance [PRIMA] trial) demonstrated an improvement in PFS with the addition of maintenance rituximab (2-year PFS of 82% for rituximab maintenance compared with 66% for the observation group [$p<0.001$; hazard ratio, 0.50]) (Salles et al. 2011).

1.2 OBINUTUZUMAB BACKGROUND

1.2.1 STRUCTURE AND MECHANISM OF ACTION OF OBINUTUZUMAB

Obinutuzumab (RO5072759) is a novel, Type II, glycoengineered monoclonal antibody derived by humanization of the parental B-Ly1 mouse antibody. (Beers et al. 2010; Mössner et al. 2010, Aldujai et al. 2011).

Obinutuzumab has an elbow hinge amino acid exchange in the Fc region of the antibody that results in a different angle of binding to the CD20 epitope compared to Type I anti-CD20 antibodies. This Type II binding induces more potent direct cell death compared to Type I antibodies, including rituximab. In addition, the Fc portion of obinutuzumab has been glycoengineered to reduce fucosylation resulting in higher affinity for the FcγRIIIa receptors on natural killer cells and monocytes leading to enhanced ADCC.

Given the significantly greater ADCC and direct cell-death induction, it is possible that obinutuzumab may have greater efficacy than rituximab, particularly in the 80% to 85% of patients who are carriers of the FcγRIIIa low-affinity receptor polymorphism.

1.2.2 NONCLINICAL EFFICACY WITH OBINUTUZUMAB

Obinutuzumab has demonstrated in vivo efficacy superior to that of rituximab in various human lymphoma xenograft models. Both antibodies have been compared in human SUDHL-4 cells (a diffuse large B-cell lymphoma [DLBCL] model) that were subcutaneously injected into severe combined immunodeficient beige mice. Therapy began when tumors were established and rapidly growing.

It was shown that rituximab at 10 mg/kg inhibited tumor growth more than rituximab at 1 mg/kg; however, increasing the dose to 30 mg/kg did not result in increased efficacy of rituximab. In contrast, obinutuzumab showed a dose-dependent increase in efficacy in the range of 1–30 mg/kg and resulted in complete tumor regression in all animals and in lasting tumor eradication in 9 of 10 animals at the highest dose of 30 mg/kg and in 1 of 10 animals at a dose of 10 mg/kg.

Additional studies have shown that obinutuzumab treatment was able to control tumor growth when vehicle- and rituximab-treated tumors were not controlled (Mössner et al. 2010).

For more detailed nonclinical information on obinutuzumab, please refer to the current version of the obinutuzumab Investigator's Brochure.

1.2.3 CLINICAL EXPERIENCE WITH OBINUTUZUMAB IN NON-HODGKIN'S LYMPHOMA

As of December 2011, clinical data on obinutuzumab are available from four Phase I or II studies (Studies BO20999, BO21003, BO21000, and JO21900) and two

Phase III studies (Studies GAO4753g and BO21004/CLL-11). More than 550 patients with CD20-positive malignant disease have been treated with obinutuzumab.

Results from the aggressive and indolent NHL cohorts in ongoing studies are described below.

1. **Study BO20999 (Phase I/II): OBINUTUZUMAB Monotherapy**

Patients with Indolent Non-Hodgkin's Lymphoma

Forty patients with relapsed or refractory indolent NHL were randomized to receive obinutuzumab in a low-dose cohort (n = 18) or a high-dose cohort (n = 22). The low-dose cohort received obinutuzumab 400 mg on Days 1 and 8 of Cycle 1 and 400 mg on Day 1 of Cycles 2–8 (21-day cycles), and the high-dose cohort received obinutuzumab 1600 mg on Days 1 and 8 of Cycle 1 followed by 800 mg on Day 1 of Cycles 2–8 (21-day cycles). Patients had been pretreated with a median of three prior regimens (range, 1–11), and the majority (38 of 40) had received prior rituximab treatment. More than half of these patients (22 of 40) were considered to be rituximab refractory, and 35% (14 of 40) of all patients had previously received an autologous stem-cell transplant. The best overall response rate in the follicular lymphoma patients was 36% in the low-dose cohort (1/14 CR/CRu, 4/14 PR) and 60% in the high-dose cohort (4/20 CR/CRu, 8/20 PR). (Salles et al. 2011)

The most common adverse event of any grade was infusion-related reaction (IRR; 72% low-dose cohort, 73% high-dose cohort). Fifty-five percent of patients had Grade 3 or 4 adverse events; the most common Grade 3/4 adverse events across cohorts were infections (14%), neutropenia (14%), and IRRs (9%), all in the high-dose cohort.

Patients with Aggressive Non-Hodgkin's Lymphoma

Forty patients with aggressive NHL were enrolled into the Phase II part of the study. Of these patients with aggressive NHL (25 with DLBCL and 15 with mantle-cell lymphoma [MCL]), 19 were treated in the high-dose cohort (15 with DLBCL and 4 with MCL) and 21 were treated in the low-dose cohort (10 with DLBCL and 11 with MCL). Patients were heavily pretreated (median of three prior therapies), with 63% of patients having not responded to or relapsed within 6 months after a previous rituximab-containing regimen (rituximab refractory). The best overall response rate was 24% in the low-dose cohort (DLBCL: 2 PR, 1 CRu); MCL: 2 CR) and 37% in the high-dose cohort (DLBCL: 3 CR, 2 PR; MCL: 2 PR). (Morschhauser et al. 2011)

The most common adverse event of any grade was IRR (81% low dose cohort, 68% high dose cohort). Grade 3 or 4 adverse events occurring with ≥ 5% frequency were anemia (10%), thrombocytopenia (8%), IRR (8%), tumor lysis syndrome (5%) and cardiac failure (5%). Adverse events did not increase in the high-dose cohort compared to the low-dose cohort. There was one Grade 5

adverse event, cardiorespiratory arrest that was thought to be secondary to ventricular arrhythmia.

b. Study BO21003 (Phase II): Obinutuzumab Monotherapy plus Maintenance

Study BO21003 is an ongoing, open-label, multicenter, randomized, Phase I/II study to investigate the efficacy and safety of obinutuzumab monotherapy compared with that of rituximab monotherapy in patients with relapsed indolent NHL. In the Phase II portion of the study 175 patients (149 follicular, 26 non-follicular) were randomized to receive 4 weekly infusions of obinutuzumab (1000 mg) or rituximab (375mg/m^2). Patients without progression continued therapy with obinutuzumab or rituximab every 2 months for 2 years. The ORR at the end of treatment in the follicular lymphoma cohort was 45% for obinutuzumab and 33% for rituximab, as assessed by the investigators. A blinded central review was also performed and the ORR was 45% for obinutuzumab and 27% for rituximab. (Sehn et al. 2011)

More IRRs were reported in the obinutuzumab arm (any grade: 72% vs. 49%, Grade 3/4: 11% vs. 5%, for obinutuzumab and rituximab, respectively). Other AEs of any grade that occurred with ≥ 5% frequency with obinutuzumab compared to rituximab were fatigue, cough, back pain, and decreased appetite.

c. Study BO21000 (Phase Ib): Obinutuzumab in Combination with Chemotherapy

Study BO21000 is an ongoing, open-label, randomized Phase I/II trial investigating two doses of obinutuzumab (400 mg in all cycles and 1600 cycle 1/800 mg subsequent cycles) in combination with chemotherapy given every 4 weeks for a maximum of six cycles (obinutuzumab plus fludarabine and cyclophosphamide [G-FC]) or a maximum of eight cycles (obinutuzumab plus CHOP [G-CHOP]) in patients with relapsed or refractory follicular lymphoma. Patients with a PR or CR who complete a minimum of four cycles of G-FC or six cycles of G-CHOP have the option of receiving maintenance therapy with obinutuzumab alone every 3 months for up to 2 years. All patients (28/28) who received G-CHOP and 22/28 who received G-FC completed treatment. Reasons for withdrawal from the G-FC arm were PD (1 patient), neutropenia (3 patients) and rash and infection (1 patient each) (Radford et al. 2011)

Overall, the rate of adverse events was similar between the high-dose and low-dose arms. The most common AE in both groups was IRRs, mostly during cycle 1. The rate of IRRs was 64% of patients in the G-CHOP arm and 79% of patients in the G-FC arm; 7% of IRR events were Grade 3 or 4 events in both chemotherapy arms. There were fewer dose delays, dose reductions, and neutropenia in the G-CHOP versus the G-FC cohorts. Grade 3/4 neutropenia was seen in 39% of the G-CHOP patients and 50% of the G-FC patients. In the G-CHOP arm 6% of cycles were delayed due to neutropenia or infection and the dose of any CHOP component was reduced in 29% of patients. In the G-FC arm, 10% of cycles were delayed due to neutropenia or infection with dose reductions

in 36% of patients. Three deaths were reported following G-FC induction treatment (progressive disease, n=1; underlying Parkinson's disease, n=1; and chronic obstructive pulmonary disease during maintenance, n=1) with none considered to be treatment-related.

The overall response rate (ORR) at the end of induction was 96% in the G-CHOP group (39% CR) and 93% in the G-FC group (50% CR). Data from the G-CHOP cohort were compared in a matched-pair analysis to the rituximab plus CHOP (R-CHOP) arm from study M39022 (EORTC 20981) in a similar patient population. Response rates to G-CHOP compared favorably to response rates to R-CHOP.

The protocol was amended to include obinutuzumab at a flat dose of 1000 mg plus bendamustine (G-bendamustine) or CHOP in previously untreated patients with follicular lymphoma. Again, patients with a PR or CR who complete a minimum of six cycles of G-CHOP or four cycles of G-bendamustine have the option of receiving maintenance therapy with GA101 alone every 3 months for up to 2 years. The Data and Safety Monitoring Board evaluated safety of the first 20 patients without requesting modifications to the protocol.

d. Study GAO4753g (Phase III): Obinutuzumab in Combination with Chemotherapy

Study GAO4753g is an ongoing, open-label, multicenter, randomized, Phase III study to investigate the efficacy and safety of bendamustine compared with bendamustine plus obinutuzumab in patients with rituximab-refractory indolent NHL. Approximately 360 patients will be enrolled. The Data and Safety Monitoring Board evaluated safety of the first 20 patients without requesting modifications to the protocol. Since the initial review of the first 20 patients in April 2011, two additional Data and Safety Monitoring Board meetings have convened, and they recommended that the trial continue.

e. Summary of Safety and Efficacy Results

With consideration of the available obinutuzumab Phase I and II data, obinutuzumab has an acceptable safety profile and there is rationale to investigate whether obinutuzumab is an effective treatment for patients with B-cell malignancies.

For more information relating to safety and efficacy in the NHL indication, please refer to the obinutuzumab Investigator's Brochure.

1.2.4 PHARMACOKINETIC AND PHARMACODYNAMIC OBINUTUZUMAB DATA

A population pharmacokinetic model has been developed for Studies BO20999 and BO21003 to characterize the pharmacokinetics of obinutuzumab and its variability. A two-compartment model, comprising both a linear clearance pathway and a non-linear time-varying clearance pathway, was fitted to the data. Data are available for a total of 134 patients following intravenous (IV)

administration of obinutuzumab in Studies BO20999 (n = 114) and BO21003 (n = 20).

Following infusion of obinutuzumab, the elimination appears to be characterized by a clearance that is dependent on time; that is, starting at a typical value of 594 mL/day and then gradually decreasing to an asymptote of 112 mL/day at steady state. Tumor burden potentially contributes significantly to the clearance of obinutuzumab, especially at the beginning of treatment when there is an excess of CD20 cells. As tumor burden decreases, the clearance reaches an asymptote, which is thought to be primarily a function of the proteolytic metabolic clearance. Consequently, some patients with a high tumor burden appear to clear the drug from the plasma faster than patients with a low tumor burden because obinutuzumab binds to the CD20-positive tumor cells and is effectively removed from the plasma. Therefore, the clearance of the drug will vary with time since repeated treatments with GA101 will reduce the quantity of CD20-positive tumor cells.

Treatment with obinutuzumab resulted in extensive B-cell depletion, with all patients showing a reduction in cell count to absolute zero at some stage of their treatment cycle. Overall, there has been no notable increase in complement levels before or after infusion, but changes have been observed in the levels of interleukin-6 and interleukin-8 b

1.3 LENALIDOMIDE

Lenalidomide, an oral agent, is a thalidomide derivative that belongs to a new class of agents known as immunomodulatory drugs (IMiDs). Lenalidomide has clinical activity in non-Hodgkin's lymphoma (NHL) and has been shown to possess several immunomodulatory properties. Despite the clinical activity of the IMiDs in various malignant diseases, the exact mechanism of their antitumor activity remains elusive. In addition to its known effect on various cytokines, lenalidomide may affect the immune cellular component of the tumor microenvironment. Potential effects include inducing lymphocyte proliferation, increasing the production of IL-2/INF-g by effector cells and angiogenesis inhibition.

Lenalidomide Description

The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2*H*-isoindol-2-yl) piperidine-2,6-dione .

The empirical formula for lenalidomide is C13H13N3O3, and the gram molecular weight is 259.3.

Lenalidomide is off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is

more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

Lenalidomide is available in 5 mg and 10 mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The 5 mg capsule shell contains gelatin, titanium dioxide and black ink. The 10 mg capsule shell contains gelatin, FD&C blue #2, yellow iron oxide, titanium dioxide and black ink.

Pharmacokinetics and Drug Metabolism:

Absorption:

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

Multiple dosing at the recommended dose-regimen does not result in drug accumulation. Pharmacokinetic sampling in myelodysplastic syndrome (MDS) patients was not performed. In multiple myeloma patients maximum plasma concentrations occurred between 0.5 and 4.0 hours post-dose both on Days 1 and 28. AUC and Cmax values increase proportionally with dose following single and multiple doses. Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

Pharmacokinetic Parameters:

Distribution:

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

Metabolism and Excretion:

The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and

therefore is partially or entirely active. Half-life of elimination is approximately 3 hours.

1.3.1 Lenalidomide in NHL

Lenalidomide induced growth arrest and apoptosis of lymphoma cell lines as well as enhancing NK-cell–mediated antibody-dependent cellular cytotoxicity (ADCC) of rituximab. (Wu et al 2006) In addition, using a lymphoma xenograft mouse model (Hernandez-Ilizaliturri et al 2005) demonstrated that IMiD molecules enhanced the antitumor activity of rituximab, resulting in improved survival of tumor-bearing animals.

Aggressive NHL

Wiernik et al reported preliminary results of lenalidomide monotherapy in patients with relapsed or refractory non-Hodgkin's lymphoma. Lenalidomide (25 mg/d) was administered on days 1 to 21 of a 28-day cycle and continued for 52 weeks as tolerated or until disease progression. Patients with various aggressive histologic subtypes (including diffuse large B-cell, follicular center cell, mantle cell, and transformed NHL) were enrolled. Forty-one of the 50 patients were assessable for response. Clinical responses were observed in all lymphoma subtypes. The ORR was 34% (n = 14) including five patients with CR unconfirmed (CRu), with a median progression-free survival in patients achieving a CRu of more than 239 (> 191 to > 373 days) days. (Witzig et al 2007) An ongoing multicenter clinical trial is further investigating clinical efficacy of single agent lenalidomide in patients with aggressive NHL.

Kaufman et al first reported the clinical efficacy of thalidomide combined with rituximab in patients with relapsed/refractory mantle-cell lymphoma (MCL). The ORR and CR rate in this study was 81% and 31%, respectively with a median progression-free survival of 20.4 months. (Kaufman et al 2004) On the basis of these findings, a phase I clinical trial of lenalidomide (5 to 25 mg) in combination with rituximab was initiated for MCL. The MTD was 20 mg/d, 21 of 28 days. The DLT was prolonged neutropenia. Thirteen of 15 patients were assessable and had a median of three1-4 prior therapies. Although there were no responses in the 10- and 15-mg dose cohorts, five of six patients in the 20-mg cohort responded including a complete response. (Wang et al 2007) On the basis of the important single-agent activity of lenalidomide and bortezomib in MCL, CALGB is currently conducting a phase II trial of the combination of the two agents in patients with relapsed or refractory MCL.

Indolent NHL

Witzig et al reported a phase II study of lenalidomide (25 mg/d for 21 of 28 days) in patients with relapsed or refractory indolent NHL.70 Among 27 assessable patients with a median of three (range, one to 17) prior therapies, the ORR was

26% (n = 7) including two CRs, whereas the overall clinical benefit (stable disease or better response) was observed in 59% of the patients. (Witzig 2007) A large, randomized, multicenter clinical trial conducted by the Cancer and Leukemia Group B (CALGB) is investigating the clinical benefit of lenalidomide versus lenalidomide/rituximab in patients with relapsed follicular NHL.

Lenalidomide plus Rituximab in Indolent Lymphoma

At MD Anderson, we are currently conducting an investigator initiated phase II, single arm study with a combination of lenalidomide and rituximab in patients with untreated indolent NHL. Patients receive lenalidomide 20 mg/day on days 1-21 of each 28 day cycle. Rituximab is given at 375 mg/m2 on day 1 of each cycle. We have reported high overall response rates, with a complete response rate of over 90% in patients with follicular lymphoma. Toxicity has been mild to moderate, with the most common non-hematologic adverse event reported as grade 1-2 fatigue and rash. (Fowler N, et al 2011)

1.4 STUDY RATIONALE

We hypothesize that the high clinical responses noted in indolent lymphoma patients following lenalidomide and rituximab is related to the combination's ability to augment the immune response, and subsequent ADCC through alteration of immune cell subsets in the tumor and peripheral blood. Lenalidomide has been shown to activate NK cells, T cells, or both and leads to expansion of immune effector cells in-vivo in NHL and CLL models. In preclinical models, we have also shown the synergistic anti-tumor effect of combining lenalidomide with anti-CD20 molecules.

As noted above, obinutuzumab is a new, humanized anti-CD20 monoclonal antibody which binds to a unique type II epitope on the cell surface. Obinutuzumab has demonstrated increased affinity to the FCgRIIIa receptor, and may have increased ADCC when compared to rituximab. Preliminary studies also suggest the obinutuzumab is effective in patients with relapsed/refractory indolent lymphoma. (Salles et al 2011)

Combining an anti-CD20 antibody with increased affinity for the FCgRIIIa receptor with a immunomodulatory agent that increases ADCC is rational and has the potential to build upon the anti-lymphoma characteristics of both agents. Both agents are well tolerated, and the expected toxicity profile is mild.

The starting dose of lenalidomide is based upon the initial dose finding study by Wang et al which determined the maximum tolerated dose of lenalidomide with rituximab was 20mg daily in relapsed NHL. Although we do not expect

significant additional toxicity with obinutuzumab the first cohort of patients will be started at dose level 1 (10mg daily) of lenalidomide. (Wang et al 2012)

A unit dose of 1000 mg of GA101 was chosen for studies of NHL after a review of data from completed Phase I studies was undertaken. This unit dose of GA101 to be used in future studies was based on the following findings:

• No dose-limiting toxicities were observed and no maximum tolerated dose was reached in Phase I (doses from 50 mg to 2000 mg were tested).

• Clinical activity (responses) was observed at all dose levels tested.

• PK analyses suggested that a decreased variability of drug exposure related to tumor burden was achieved at doses above 800 mg given on Days 1, 8, 22 and every 3 weeks for nine doses.

• GA101 was well tolerated with a preliminary safety profile similar to that of rituximab in NHL patients (i.e., mainly Grade 1−2 toxicities, with more frequent IRRs around the time of the first infusion, decreasing with subsequent infusions).

After a comprehensive review of all safety, efficacy, and PK data obtained in Phase I studies, a total GA101 dose of 1000 mg for all infusions was chosen as the dose to be used in future Phase II and Phase III studies by the sponsor since it was the dose most likely to be well tolerated and efficacious in a majority of NHL patients regardless of their initial tumor burden.

In order to coordinate the dosing of study drugs during the first 6 months of treatment, GA101 will be given on 28-day cycles for the first six cycles in this study. On cycle 1 of therapy, the dose of GA101 will be divided over 2 days; day 1, 100mg and Day 2, 900mg. PK modeling suggests that giving additional doses of GA101 on Days 8 and 15 of Cycle 1, and then every 2 months beyond 6 months, will be needed in order to saturate target-mediated clearance achieve and maintain a steady state of drug early and as long as possible during treatment.

After the maximum tolerated dose is found, patients will be enrolled in two cohorts. Prior studies in various B cell malignancies have observed different response profiles in patients with SLL and marginal zone lymphoma compared to patients with follicular lymphoma (Fowler et al).

2. STUDY DESIGN

2.1 SCHEDULE OF STUDY ASSESSMENTS

	SCHEDULE OF STUDY ASSESSMENTS									
Procedure 8*	**Screening** ≤ 30days from Baseline (First day study drug administration)	**Cycle 1**				**All Cycles ***	**All Cycles ***	**Following Cycles 3, 6, 9[13], 12[13] then every 4 months during obinutuzumab maintenance*[15]**	**Discontinuation From Study Drug**	**Follow-Up Phase**
		Day **1**	Day **8**	Day **15**	Day **22**	Day **1**	Day **14**			**Every 3[6] months**
Record prior medications, treatments	X									
Record prior anti-cancer therapies	X									
Medical History	X	X				X				
HTLV1, HIV and Hepatitis B/C screening[10]	X									
Physical examination, vital signs, weight	X	X				X			X	
ECOG performance status	X	X				X			X	
CT of the chest & abdomen / pelvis, neck, PET CT. [8*]	X							X	X	X [6]
Chest x-ray	X								X	
Electrocardiogram (EKG)	X									
Bilateral bone marrow Bx, BM cytogenetics. On Follicular lymphoma histology do BM and blood PCR for Bcl-2 rearrangement. On SLL do ZAP70, CD38 staining and somatic mutation analysis on BM and tumor tissue.	X [2]							X[2]	X[2]	

Register patient into Revlimid REMS® program[1]	X									
Prescribe lenalidomide via Revlimid REMS® program [1]	X					X				
obinutuzumab infusion [12,14]		X	X	X	X	X[12]				
Hematology Test: hematocrit, platelet count, WBC count with differential, Absolute neutrophil count (ANC) and absolute lymphocyte count (ALC). [9, 11]	X	X	x	X	X	X[11]	X		X	
Serum chemistry: Blood chemistries should include sodium, potassium, chloride, CO2, blood urea nitrogen (BUN), creatinine, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), calcium,	X	X	X	X	X	X	X		X	
Pregnancy test [3,4]	X[4]	X	X	X	X	X [4]			X [4]	
Tumor lesions assessment	X							X	X	X[6]
Response assessment using IWG criteria								X	X	
Record concomitant therapies/procedures	x					X			X	
Obtain Follow-Up anti-cancer treatments									X	X[6]
Obtain Follow-Up survival information										X[6]

* Variations of +/- 3 days of the schedule are permitted.
** Staging CTs and BM Bx will be done up to 7 days of end of cycle

1. Lenalidomide must be prescribed through and in compliance with Celgene's Revlimid REMS® program. Prescriptions must be filled within 7 days.
2. Repeat BM evaluation to confirm morphologic and genetic markers of disease. Zap 70 and CD38 staining will be done if tissue is available. Repeat BM biopsy is at investigators discretion to confirm complete remission (as determined by radiographic imaging). Screening bone marrow biopsy can be obtained up to 60 days prior to study entry.
3. Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
4. Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide (prescriptions must be filled within 7 days). FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).
5. Thyroid Stimulating Hormone (TSH) will be drawn at baseline and prior to cycles 4
6. Follow-up and tumor assessment – Patients will be evaluated every 3 months for one year, every 6 months for 1 year and then yearly with CT of neck, thorax, abdomen and pelvis and other studies as recommend by the treating physician for 1 year. Timing of imaging studies will be calculated from date of last scan. Tumor assessments, as well as timeline for tumor assessments are recommendations only. Exact timing of follow-up tumor assessments are at the discretion of the treating physician. Patients will have a minimum of imaging studies every 6 months for the first. Imaging can be done plus/-21 days of recommended time points.
7. Patient evaluation and predose labs can occur up to 3 days prior to starting each cycle. If possible, patients should be seen at least 24 hours prior to each cycle
8. If a patient is allergic to IV contrast, non-contrast PET/CT images can be used for tumor evaluation, response assessment. If patient has a history of PET negative disease, repeat PET is not required prior to study entry. If patient has full CT at specified timepoint, PET is recommended, but not required for study entry or on follow up visits.
9. If not reported on patients CBC, patient's ANC and ALC can be calculated from absolute neutrophil percent and absolute lymphocyte percent.
10. In the absence of a history of blood transfusion or intravenous drug use in the past 6 months, patients can have hepatitis B/C andHIV testing up to 8 weeks prior to study entry.
11. Hematology testing will occur on day 1 and day 14 (+/- 4 days) of cycles 2-12. If patient discontinues lenalidomide, day 14 labs are not required in cycle #2 and beyond.
12. Obinutuzumab is given on day 1, 2, 8, 15, and 22 of cycle one and on day 1 of each subsequent cycle up to 6 additional months during lenalidomide dosing. In months 12 and beyond, obinutuzumab is given every 56 days.
13. Patients can receive up to 12 cycles of lenalidomide and obinutuzumab. Restaging will occur every 3 cycles while the patient is on combination therapy, and every 112 days during obinutuzumab monotherapy (maintenance phase).
14. Obinutuzumab will be given 100mg IV on day 1, and 900mgIV on day 2 of cycle 1. Subsequent cycles will receive 1000 mg on each dose day as tolerated.
15. Cycles are 28 days long during the first 11 months of treatment (during combination and single agent dosing of obinutuzumab). The remaining cycles are 56 days. If the patient is on single agent obinutuzumab during cycle 7-12, physical exam, labs, follow up visit, ecog, vital signs, and medical history will only be done on cycles 8, 10, and 12.

2.2OBJECTIVES

2.2.1 Primary Objectives

Part 1 (phase 1).

1. To determine the maximum tolerated dose of lenalidomide plus obinutuzumab in relapsed/refractory indolent lymphoma.

Part 2 (phase 2).

1. To evaluate the safety of lenalidomide in combination with obinutuzumab in patients with relapsed/refractory indolent lymphoma.

2. To determine the overall response rate (ORR) of the combination in patients with relapsed/refractory indolent lymphoma.

2.2.2 Secondary Objectives

1. To determine the complete response rate, time to progression (TTP), and progression free survival in patients with indolent lymphoma following treatment with obinutuzumab + lenalidomide.

2. To evaluate changes in immune effector cells and the tumor microenvironment following treatment with obinutuzumab + lenalidomide.

2.3 STUDYDESIGN

2.3.1 DESCRIPTION OF THE STUDY

This is a single-center, open label, phase I/II study in patients with refractory or relapsed indolent lymphoma. The feasibility of administrating lenalidomide in combination with obinutuzumab and the MTD of the combination will be determined in the phase I part of the study. When the MTD has been established, the efficacy of the combination will be further evaluated in the phase II part of the study in two patient cohorts simultaneously. All patients will receive a combination of daily lenalidomide for 21 days with IV obinutuzumab on day 1,2, 8, 15, and 22 of cycle one (obinutuzumab will be given 100mg IV on day 1, and 900mgIV on day 2, subsequent doses will be given over 1 day)and on day 1 of each subsequent cycle up to 6 cycles. Patients who do not progress following 6 cycles and are deriving benefit from the combination in the opinion of the treating physician can receive up to 12 cycles of lenalidomide therapy. After completing combination lenalidomide therapy,patients will then enter a “maintenance phase” and receive obinutuzumab on day 1 of each 2 month cycle for up to 2 years or a total of 30 months on treatment (combination + maintenance), whichever occurs first. The two patient cohorts are patients with follicular lymphoma (grade 1-3a) and the patients with any indolent lymphoma including follicular, marginal zone or SLL. A maximum of 72 patients (18 in phase I and 60 in phase II; the 6 patients treated at the MTD in phase I will be included in analysis

of the first group of patients treated in phase II) will be enrolled in this study on an intent-to-treat basis.

2.3.2 Phase I

The primary objective of the phase I part of the study is to determine the maximum tolerated dose (MTD) of lenalidomide when given in combination with obinutuzumab for subsequent testing in the phase II part of the trial. There are three predefined dose levels for lenalidomide (10 mg, 15 mg, 20 mg) with a fixed dose of obinutuzumab (1000 mg) as outlined in Table 1.

Dose limiting toxicity (DLT) will be assessed during the first course of each cohort (28 days), and refers to a medically significant event which meets one of the following criteria using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4:

- Grade 3 or higher non-hematologic AE which is felt to be related to the study drug by the investigator with the exception of the following:
  - Transient grade 3 or less infusion reaction that completely resolves within 24 hours.
- Grade 4 hematologic toxicity (Platelet count is defined as <25,000 for the purposes of determining DLT.
- Grade 3 neutropenia with elevated temperature (defined as >/= 101 degrees F to be confirmed on two occasions).
- Grade 3 thrombocytopenia with bleeding.
- Treatment delay of greater than 2 weeks due to treatment related toxicity.

Prior to advancing/changing dose levels a cohort summary will be completed and submitted to the Clinical Research Monitor in the IND Office.

2.3.3 Phase II

The objective for the phase II part is to further evaluate the safety and efficacy of lenalidomide when given in combination with obinutuzumab at the MTD of lenalidomide determined in phase I. The maximum number of patients that will be recruited for the phase II part is 60 with 30 for each of the two patient cohorts: the patients with follicular lymphoma (grade 1-3a) and the patients with any indolent lymphoma. The patients who are treated at the MTD in the phase I part will be counted as the first group of patients treated in phase II.

2.3.4 Evaluation of response

Response criteria for patients enrolled onto the study will follow the guidelines recommended by the1999 International Workshop on Response Criteria for NHL. (Cheson et al.1999) All responses will be characterized as either complete remission (CR), unconfirmed complete remission (CRu), partial remission (PR), stable disease (SD), or progression of disease (POD). Response will be assessed after every three cycles of combination therapy. Response will be assessed every 4 months thereafter while the patient receives obinutuzumab maintenance treatment.

3. STUDY POPULATION

3.1 INCLUSION CRITERIA

Patients must meet the following criteria for study entry:

- A diagnosis of small lymphocytic lymphoma, follicular lymphoma (grades 1-3a), or marginal zone lymphoma.
- Evidence of progression or lack of response following at least 1 prior treatment for indolent lymphoma.
- Able and willing to provide written informed consent and to comply with the study protocol
- Age $\geq$ 18 years
- Must have at least 1 node greater than 1.5cm in short axis diameter
- Adequate hematologic function (unless abnormalities are related to NHL), defined as follows:
  - Hemoglobin $\geq$ 9.0 g/dL
  - Absolute neutrophil count $\geq 1.5 \times 10^9$/L
  - Platelet count $\geq 75 \times 10^9$/L
  - ANC < 1.5 x 10^9 /L or PLT count less than 100 x10^9/L if cytopenia is due to extensive bone marrow involvement of disease as determined by the treating physician.
- For men who are not surgically sterile, agreement to use a barrier method of contraception for $\geq$6 months after the last obinutuzumab dose. In addition, male patients must agree to request that their partners use an additional method of contraception, such as oral contraceptives, intrauterine device, barrier method of contraception or spermicidal jelly

- For women of reproductive potential who are not surgically sterile, agreement to use two adequate methods of contraception, such as oral contraceptives, intrauterine device, or barrier method of contraception in conjunction with spermicidal jelly for ≥18 months after the last obinutuzumab dose.
- Females of childbearing potential (FCBP)† must have a negative serum pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to and again within 24 hours of prescribing lenalidomide and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 4 weeks before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a female of child bearing potential even if they have had a successful vasectomy.
- 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® program.

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

- Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program. Able to take aspirin (81 or 325 mg) daily as prophylactic anticoagulation (patients intolerant to ASA may use warfarin or low molecular weight heparin).

† 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).

3.2 EXCLUSION CRITERIA

- Evidence ongoing transformation into aggressive NHL.
- History of severe allergic or anaphylactic reactions to monoclonal antibody therapy
- Known hypersensitivity to thalidomide or lenalidomide.
- Regular treatment with corticosteroids during the 4 weeks prior to the start of Cycle 1, unless administered for indications other than NHL at a dose equivalent to ≤30 mg/day prednisone

- History of prior malignancy within the last 5 years, with the exception of curatively treated basal or squamous cell carcinoma of the skin and low-grade in situ carcinoma of the cervix
- Evidence or history of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, severe arrhythmia, myocardial infarction within the previous 6 months, unstable arrhythmias, or unstable angina) or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics, except if for tumor fever) within 4 weeks prior to the start of Cycle 1

  Patients with suspected active or latent tuberculosis (latent tuberculosis needs to be confirmed by positive Interferon-gamma release assay)
- Vaccination with live vaccines within 28 days prior to start of treatment
- Any of the following abnormal laboratory values (unless any of these abnormalities are due to underlying lymphoma):

  Creatinine $>$ 1.5 times the upper limit of normal (ULN) (unless creatinine clearance normal), or calculated creatinine clearance $<$ 40 mL/min (using Cockcroft–Gault formula; see Appendix D)

  AST or ALT $>2.5\times$ ULN

  Total bilirubin $>1.5\times$ ULN (or $>3\times$ ULN for patients with documented Gilbert syndrome)

  Any history of hepatitis B infection.
- Positive test results for hepatitis C (hepatitis C virus [HCV] antibody serology testing)

  Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA
- Known history of HIV seropositive status
- Positive test results for human T-lymphotropic 1 (HTLV 1) virus

  HTLV testing is required in patients from endemic countries (Japan, countries in the Caribbean basin, South America, Central America, sub-Saharan Africa, and Melanesia)

- Pregnant or lactating
- ECOG performance status greater than 2.
- Participation in another clinical trial with drug intervention within 21 days prior to start of Cycle 1 and during the study
- Patients with SLL/CLL will are excluded during the phase I portion of the study

3.3 IMMUNIZATION DURING B-CELL DEPLETION

To date, no vaccination studies have been performed with obinutuzumab. No vaccination with live virus vaccines should be given to patients treated with obinutuzumab.

4. TREATMENT PLAN

4.1 Phase I

Three dose levels of lenalidomide (10 mg, 15 mg, 20 mg) will be evaluated with a fixed dose of obinutuzumab (1000mg) as outlined in Table 1. (obinutuzumab will be given in divided doses on cycle 1; 100mg IV on day 1, and 900mgIV on day 2, subsequent doses will be given over 1 day) Up to 18 patients may participate in the Phase I component of the study, depending on the level at which toxicity is observed. Subjects will be assigned to a dose level based on the order of study entry and toxicities seen in prior patients. The dose escalation process is described below. There will be no intra-patient dose escalation. DLT will be assessed during the first course of each cohort (28 days), and refers to a medically significant event which meets criteria using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4. (see section 2.3.2)

Table 1. Dose levels to be tested in phase I portion

Dose Level	Lenalidomide Dose (days 2-22 followed by 6 days of no therapy)	Obinutuzumab dose
-1	5 mg	1000mg IV
1	10 mg	
2	15 mg	
3	20 mg	

4. 2 Phase II

Additional pts will be enrolled into two cohorts at the recommended dose level (MTD) established in Phase I up to a maximum of 30 patients each in two independently enrolling cohorts.

Cohort A: 30 patients with relapsed/refractory follicular lymphoma
Cohort B: 30 patients follicular lymphoma, marginal zone lymphoma or SLL

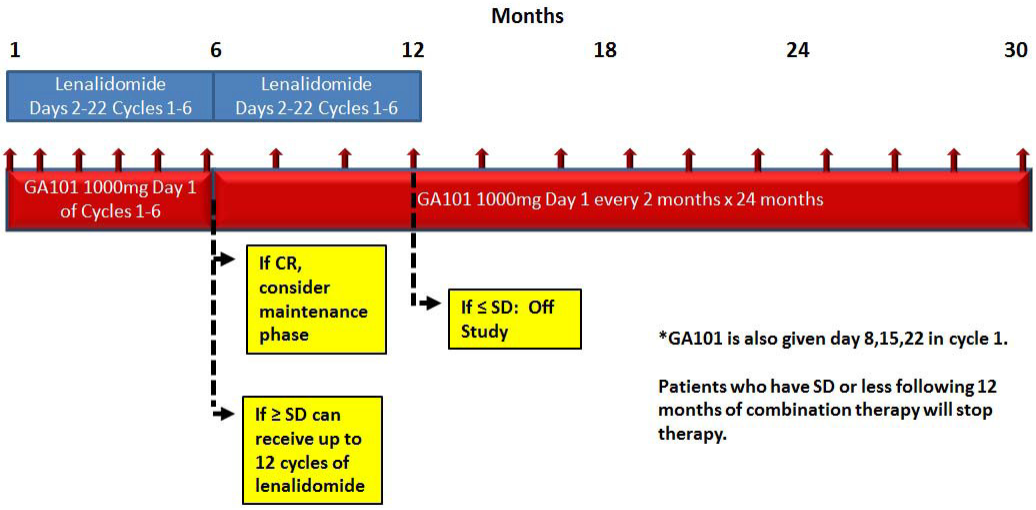
4. 3 Treatment Schedule

Lenalidomide capsules will be taken orally daily each day on days 2 - 22, followed by 6 days of no therapy of each 28-day cycle. Obinutuzumab will be given by intravenous infusion on day 1,,2, 8, 15, and 22 of cycle one and on day 1 of each subsequent cycle up to 6 cycles. Patients who do not progress following 6 cycles and are deriving benefit from the combination in the opinion of the treating physician can receive further cycles of combination up to 12 cycles of lenalidomide therapy. (As long as the patient does not exhibit progression, the decision of how many cycles of combination therapy beyond 6 is at the discrestion of the treating team and investigator).

Extended dosing of obinutuzumab will begin after combination therapy if patients demonstrate at least stable disease on response assessment. In the extended dosing schedule, obinutuzumab will be administered every 2 months, and in the absence of progression, will be dosed for maximum of 30 months (combination + maintenance).

Patients that do not have at least a partial remission following 12 cycles of combination therapy will not continue with extended obinutuzumab treatment.

TREATMENT REGIMEN



*(GA101 will be given in divided doses on first dose in cycle 1; 100mg IV on day 1, and 900mgIV on day 2, subsequent doses will be given over 1 day)

This research study protocol allows the subject to receive up to 21 infusions of obinutuzumab. Even if the treatment is shown to be of benefit, additional infusions of obinutuzumab beyond that allowed in the protocol cannot be given to the subject while they are participating in this study.

Visit schedule and assessments

Screening Assessments and all on study scheduled visits and assessments are outlined in Table of Study Assessments. All timepoints outlined in the Schedule of Assessments allow variation of +/- 3 days.

Due to the drug delivery from an outside facility, clinicians should allow up to 72 hours from patient assessment/evaluation to the start of each cycle.

Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation. In addition to the required pregnancy testing, the Investigator must confirm with FCBP that she is continuing to use two reliable methods of birth control at each visit.

An unscheduled visit can occur at any time during the study. Source must be maintained for these unscheduled visits. The date for the visit and any data generated must be recorded on the appropriate CRF. Source documents for these unscheduled visits must also be maintained.

At treatment discontinuation, subjects will undergo off study evaluations per the Schedule of Assessments, Section 2. In addition, a safety assessment will be done approximately 28 days post the last dose of study drug.

5. STUDY MEDICATION

5.1 OBINUTUZUMAB

Obinutuzumab is provided as a single dose, sterile liquid formulation in 50 mL pharmaceutical grade glass vials containing a nominal 1000 mg of obinutuzumab. The formulated drug product consists of 25 mg/mL drug substance (G3 material) formulated in histidine, trehalose, and poloxamer 188. The vials contain 41 mL (with 2.5% overfill). Genentech will provide obinutuzumab to investigational site as an IMP.

For further details, see the obinutuzumab Investigator's Brochure.

5.1.1 OBINUTUZUMAB DOSE AND SCHEDULE

Obinutuzumab 1000mg will be given IV on day 8, 15, and 22 of cycle one and on day 1 of each subsequent cycle up to 6 cycles during lenalidomide dosing. First dose of 1000mg will be split into day 1 and 2 of cycle 1 as outlined in section
5.1.4. If the patient attains at least stable disease, the patient will receive obinutuzumab 1000mg IV every 2 months for a maximum of 2 years. For dosing instructions, see section 6.2.

5.1.2 OBINUTUZUMAB PREPARATION

Obinutuzumab drug product intended for IV infusion is prepared by dilution of the drug product into an infusion bag containing 0.9% NaCl to the final drug concentration of 4 mg/mL. Using a 250-mL infusion bag containing 0.9% NaCl, withdraw and discard 40 mL of the NaCl. Withdraw 40 mL of obinutuzumab from a single glass vial and inject into the infusion bag (discard any unused portion of obinutuzumab left in the vial). Gently invert the infusion bag to mix the solution; do not shake.

Do not use obinutuzumab beyond the expiration date stamped on the carton.

5.1.3 OBINUTUZUMAB PRE MEDICATIONS

5.1.3.1 Obinutuzumab Pre-medications

Thirty to 60 minutes prior to all obinutuzumab infusions, the following pre-medications will be given (unless contraindicated):

- Oral acetaminophen (e.g., 650−1000 mg) AND
- An antihistamine such as diphenhydramine (50−100 mg)
- For Cycle 1, prophylactic corticosteroids (e.g., 100 mg IV prednisolone) at least one hour prior to the obinutuzumab infusion. An equivalent

dose of dexamethasone (15-20mg) or methylprednisolone (80mg) is acceptable but hydrocortisone should not be used.

In subsequent cycles, steroids should be given to patients who experienced a severe IRR with the prior infusion of obinutuzumab or who are thought to be at high risk for infusion-related reactions, as assessed by the investigator.

5.1.3.2 Tumor Lysis Syndrome Prophylaxis

Patients who are considered to have a high tumor burden and who are considered to be at risk for tumor lysis by the investigator should additionally receive tumor lysis prophylaxis prior to the initiation of treatment. These patients should be well hydrated starting 1 to 2 days before the first dose of obinutuzumab. In addition, all patients considered to have high tumor burden and who are considered to be at risk for tumor lysis should be treated with allopurinol 300 mg/day orally or a suitable alternative treatment starting 12 to 24 hours prior to treatment on Day 1 of Cycle 1. These patients should continue to receive repeated prophylaxis with allopurinol and adequate hydration prior to each subsequent infusion, if deemed appropriate by the investigator

5.1.4 OBINUTUZUMAB ADMINISTRATION

First Infusions

- First dose of obinutuzumab will be split into two days on cycle 1. Day 1 patient will receive 100mg, day 2 patient will receive 900mg. During cycle 1, rate on day 1 will be 25mg/hr over 4 hours (25ml/hr at 1mg:1ml dilution).
- In the absence of IRRs/hypersensitivity, the rate of the infusion on cycle 1 day 2 will be escalated in increments of 50 mg/hr (14ml/hr) every 30 minutes to a maximum rate of 400 mg/hr(100ml/hr).
- The patient will receive 1000mg of obinutuzumab for the remainder of the cycle 1 infusions (day 8, 15, 22) at the initial rate of 50 mg/hr (12.5 ml/hr) and increased by 50 mg/hr (12.5 ml/hr) increments at 30 minute intervals, as tolerated, to a maximum rate of 400 mg/hr (100 ml/hr).
- If a hypersensitivity or IRR develops, the infusion should be temporarily interrupted or slowed down and concomitant medication may be administered if deemed appropriate by the investigator.
- Upon the resolution of symptoms, the infusion will resume at one-half the previous rate (the rate being used at the time that the hypersensitivity or IRR occurred) and infusion-rate escalation may resume at the increments and intervals described above. If patient does not demonstrate signs of acute infusion reaction hypotension or shortness of breath), the patient can have IV

discontinued prior to 1 hour on second infusion and beyond.

Second cycle and Subsequent Infusions

- If a patient's previous obinutuzumab infusion(s) in cycle 1
- were well tolerated (defined by an absence of Grade ≥2 IRRs during a final infusion rate of ≥100 mg/hr (25cc/hr in standard 4mg:1ml dilution), subsequent infusions beginning with cycle 2 will be administered at an initial rate of 100 mg/hr (25ml/hr) and increased by 100-mg/hr (25ml/hr) increments at 30-minute intervals, as tolerated, to a maximum rate of 400 mg/hr (100ml/hr).
- If a hypersensitivity or IRR develops, the infusion should be temporarily interrupted or slowed down and concomitant medication may be administered if deemed appropriate by the investigator.
- Upon the resolution of symptoms, the infusion will resume at one-half the previous rate (the rate being used at the time that the hypersensitivity or infusion-related reaction occurred) and infusion-rate escalation may resume at the increments and intervals described above.

If the previous infusion rate was not well tolerated, as defined above, instructions for the first cycle infusion rate will be used.

Table 2

Administration of First and Subsequent Infusions of Obinutuzumab

First Infusion (Day 1 of Cycle 1)	Subsequent Infusions
• If a reaction develops, stop or slow the infusion. Administer medications and supportive care in accordance with institutional guidelines. If reaction has resolved, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred).	• If the patient experienced an infusion-related or hypersensitivity reaction during the prior infusion, use full premedication including 100 mg prednisone/prednisolone (or 80mg methylprednisolone equivalent) (until no further IRR occurs), begin infusion at an initial rate of 50 mg/hour (14ml/hr) and follow instructions for first infusion. • If the patient tolerated the prior infusion well (defined by an absence of Grade 2 reactions during a final infusion rate of ≥100 mg/hour (25ml/hr)), begin infusion at a rate of 100 mg/hour (25ml/hr). • If no reaction occurs, increase the infusion rate in 100-mg/hour (25ml/hr) increments every 30 minutes, to a maximum of 400 mg/hour (100ml/hr). If a reaction develops, stop or slow the infusion. Administer medications and supportive care in accordance with used at the time that the reaction occurred).

Obinutuzumab must be administered in a clinical (inpatient or outpatient) setting. Full emergency resuscitation facilities should be immediately available and patients should be under close supervision of the investigator at all times. For the management of IRRs and anaphylaxis, see Section 6.1.1.

Obinutuzumab should be administered as a slow IV infusion through a dedicated line. IV infusion pumps should be used to control the infusion rate of obinutuzumab. Administration sets with polyvinyl chloride, polyurethane, or polyethylene as product contact surface and IV bags with polyolefine, polypropylene, polyvinyl chloride, or polyethylene as product contact surface are compatible and may be used. Do not administer as an IV push or bolus. Do not use an additional in-line filter because of potential adsorption.

After the end of the first infusion, the IV line or central venous catheter should remain in place for greater than or equal to 1 hour to be able to administer IV drugs if necessary. If no adverse events occur after 2 hours, the IV line may be removed or the central venous catheter may be de accessed. For subsequent infusions, the IV line or central venous catheter should remain in place for at least 1 hour after the end of the infusion. If no adverse events occur after 1 hour, the IV line may be removed or the central venous catheter may be de accessed.

5.1.5 OBINUTUZUMAB STORAGE

Obinutuzumab drug product should be stored at 2°C–8°C and protected from light. For the diluted product, chemical and physical in-use stability have been demonstrated at concentrations of 0.2mg/ml-20mg/mL for 24 hours at 2°C–8°C and at ambient temperature and ambient room lighting. The product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C–8°C. Obinutuzumab should not be frozen or shaken. Mix gently. All transfer procedures require strict adherence to aseptic techniques.

For further details, see the obinutuzumab Investigator's Brochure.

5.1.6 OBINUTUZUMAB UNUSED OR EXPIRED DRUG

All unused or expired investigational drug will be destroyed in accordance with institutional policies. Drug accountability records will be emailed to ga101-gsur@gene.com at study closure.

5.2 LENALIDOMIDE

Lenalidomide is available in 2.5 mg, 5mg and 25 mg capsule strengths for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The 5 mg capsule shell

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

5.2.1 Lenalidomide Dose and Schedule

Phase I: In the phase I portion of the study the planned dose of lenalidomide for patients with follicular lymphoma and marginal zone lymphoma (SLL patients not included in phase I portion of study) will be based upon the dose escalation table. (table 1) Patients will receive an oral dose daily on days 2 – 22 followed by 6 days rest (28 day cycle).

Table 3. Dose levels to be tested in phase I portion		
Dose Level	Lenalidomide Dose (days 2-22 followed by 6 days of no therapy)	Obinutuzumab dose
-1	5 mg	1000mg IV
1	10 mg	
2	15 mg	
3	20 mg	

Phase II: Lenalidomide will be administered orally at the maximum tolerated dose (MTD) (as defined by the Phase I portion of the study) on days 2 to 22 of a 28 day cycle in patients with follicular lymphoma and marginal zone lymphoma. Patients with a diagnosis of small lymphocytic lymphoma (SLL) will begin cycle #1 at a maximum dose of 10 mg total daily on days 2 to 22 of a 28 day cycle. This dose will be escalated by 5mg with each cycle up to the MTD if no toxicity is encountered. (see dose modification for lenalidomide table). In the absence of progression or toxicity, patients will remain on lenalidomide treatment for a total of 6-12 months/cycles.

Only one cycle of study drug will be supplied to the patient each cycle.

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

Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately. Subjects experiencing adverse events may need study treatment modifications. See Tables 6 and 7.

Supplier

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

Dosage form
Lenalidomide will be supplied as capsules for oral administration. The capsules are available in 2.5 mg, 5mg and 25mg capsule strengths.

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

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

Unused or Expired Drug
All unused or expired investigational drug will be destroyed in accordance with institutional policies. Drug accountability records will be emailed to ga101-gsur@gene.com at study closure.

Lenalidomide Prescribing Information

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

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

6. DOSE MODIFICATION/TOXICITY MANAGEMENT

A number of measures will be taken to ensure the safety of patients participating in this study. These measures will be addressed through exclusion criteria (see Section 3.2) and routine monitoring as follows.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and during their participation in this study. Safety

evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements. Subjects will be evaluated for adverse events (all grades for phase I section; for phase II portion of study: and all grades for non-hematologic events, grade 3 and 4 only for laboratory abnormalities.), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

6.1 OBINUTUZUMAB

The dose of obinutuzumab generally remains constant throughout the trial. Obinutuzumab infusion should be interrupted for severe reactions, e.g., rapid tumor lysis. Treatment of infusion-related symptoms with diphenhydramine and acetaminophen is recommended. Additional treatment with bronchodilators or IV saline may be indicated. Epinephrine, antihistamines, and corticosteroids should be available for immediate use in the event of a hypersensitivity reaction to obinutuzumab (e.g., anaphylaxis). In most cases, the infusion must be resumed at no greater than 50% of initial rate (e.g., from 100mg/hr to 50mg/hr) when symptoms and laboratory abnormalities have completely resolved. Obinutuzumab can be resumed on the following day if infusion reaction prevented full delivery on day 1.

Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Subjects who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions.

Carriers of hepatitis B and patients with a history of hepatitis B infection or positive serology should be excluded from clinical trials except in situations where the potential benefit is determined to justify the risk of possible hepatitis B reactivation, which can be fatal. Patients with positive serology should have viral DNA levels checked and a gastrointestinal consultation obtained. If treated with obinutuzumab, such patients should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis throughout their study participation.

6.1.1 MANAGEMENT OF INFUSION-RELATED REACTIONS AND ANAPHYLAXIS

Medications (including epinephrine for subcutaneous injections, corticosteroids, diphenhydramine hydrochloride for IV injection) and resuscitation equipment should be available for immediate use at point of infusion. Management of infusion-related symptoms for obinutuzumab is summarized in Table 4. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or an IgE-mediated anaphylactic reaction, obinutuzumab should be discontinued and no additional drug should be administered. Patients who experience any of these reactions should receive aggressive symptomatic treatment and will be discontinued from study treatment.

Patients who experience obinutuzumab -associated, infusion-related temperature elevations of >38.5°C or other minor infusion-related symptoms may be treated symptomatically with acetaminophen (≥500 mg) and/or H_1- and H_2-histamine–receptor antagonists (e.g., diphenhydramine hydrochloride, ranitidine). Serious infusion-related events, manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress, should be managed with additional supportive therapies (e.g., supplemental oxygen, β_2-agonists, epinephrine, and/or corticosteroids) as clinically indicated according to standard clinical practice.

Table 4

Guidelines for Management of Infusion-Related Symptoms Related to Obinutuzumab

Infusion-Related Symptoms [a]	Guidance
Grade 4	• Discontinue infusion immediately, treat symptoms aggressively, and do not resume treatment.
Grade 3	• Hold infusion. • Give supportive treatment. [b] • Upon symptom resolution, may resume infusion rate escalation at the investigator's discretion. [c] • If the same adverse event recurs with the same severity, treatment must be permanently discontinued.
Grade 1–2	• Slow or hold infusion. • Give supportive treatment. [b] • Upon symptom resolution, may resume infusion rate escalation at the investigator's discretion. [c]

[a] Refer to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 for the grading of symptoms. This table does not refer to management of immunoglobulin E–mediated allergic reactions, which should be managed as directed in Section 6.1.1.

[b] Supportive treatment: Patients should be treated with acetaminophen and an antihistamine such as diphenhydramine hydrochloride if they have not been received in the last 4 hours. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, corticosteroids (e.g., 100 mg of intravenous prednisolone or equivalent), and/or bronchodilators. For hypotension, patients may require vasopressors.

[c] Escalation of the infusion rate after re-initiation: Upon complete resolution of symptoms, the infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.

6.1.2 MANAGEMENT OF TUMOR LYSIS SYNDROME

For patients with evidence of TLS, obinutuzumab should be discontinued and the patients 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 as indicated (see Section 5.1.3.2).

6.1.3 CARDIOTOXICITY

Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusion of obinutuzumab. Patients with preexisting cardiac conditions, including arrhythmias and angina, who have had recurrences of these events during obinutuzumab therapy should be monitored throughout the infusion and immediate post-infusion period.

6.1.4 HEPATITIS B VIRUS REACTIVATION

Patients with a history of hepatitis B infection will be excluded from study.

6.1.5 DOSAGE MODIFICATION DURING MAINTENANCE THERAPY WITH OBINUTUZUMAB

6.1.5.1 Nonhematologic Toxicities

For Grade ≥ 2 nonhematologic toxicities related to obinutuzumab, treatment with obinutuzumab will be delayed for a maximum of 3 weeks until resolution to Grade ≤ 1 or baseline (see Table 4). Resumption of dosing without complete resolution of toxicity may be considered only upon careful weighing of the risks and benefits to the patient by the investigator. It is recommended that cycles be delayed in 1 week increments. If treatment is delayed for more than 3 weeks, study treatment will be discontinued.

There will be no dose reductions of obinutuzumab.

6.1.5.2 Hematologic Toxicity

Note that lymphopenia is not considered to be a hematologic toxicity, because it is an expected outcome of therapy.

For Grade $\geq$3 hematologic toxicities (defined as neutropenia, anemia, or thrombocytopenia), treatment with obinutuzumab will be delayed for a maximum of 3 weeks until resolution to Grade $\leq$2 (see Table 5). Resumption of dosing without complete resolution of toxicity may be considered only upon careful weighing of the risks and benefits to the patient by the investigator. It is recommended that cycles be delayed in 1-week increments. If treatment is delayed for more than 3 weeks, study treatment will be discontinued.

There will be no dose reductions of obinutuzumab.

Table 5
Guidelines for Dose Delay or Modification of Obinutuzumab during Maintenance Therapy

Event	Dose Delay or Modification
Grade 2, 3, or 4 nonhematologic toxicity [a]	• Delay doses of obinutuzumab for a maximum of 3 weeks. • If improvement to Grade ≤1 or baseline, administer full dose of obinutuzumab.
Grade 1 nonhematologic toxicity [a]	• No dose reduction or delay.
Grade 3 or 4 hematologic toxicity	• Delay doses of obinutuzumab for a maximum of 3 weeks. • Administer myeloid growth factors for neutropenia. • Administer RBCs or platelets as required. • If improvement to Grade ≤2, administer full dose of obinutuzumab.
Grade 1 or 2 hematologic toxicity	• No dose reduction or delay.

RBC = red blood cell.
[a] For tumor lysis syndrome or hepatitis B virus reactivation, Section 6.1.2 or 6.1.4, respectively.
[b] Dose delays and interruptions will only occur of toxicity is felt to be related to obinutuzumab per the investigator or treating physician.

6.1.6 Dosage Modification During combination Therapy

For Grade ≥ 3 nonhematologic toxicities felt to be related to obinutuzumab by the investigator or treating physician, treatment with obinutuzumab will be delayed until resolution to Grade ≤ 1 or baseline. Resumption of dosing without complete resolution of toxicity may be considered only upon careful weighing of the risks and benefits to the patient by the investigator.

For Grade ≥ 3 hematologic toxicities (defined as neutropenia, anemia, or thrombocytopenia), treatment with obinutuzumab will be delayed until resolution to Grade ≤ 2. Resumption of dosing without complete resolution of toxicity may be considered only upon careful weighing of the risks and benefits to the patient by the investigator.

Note that lymphopenia is not considered to be a hematologic toxicity, because it is an expected outcome of therapy.

There will be no dose reductions of obinutuzumab.

If a toxicity, hematologic or non-hematologic is felt to be due to either lenalidomide or obinatuzumab, patients safety is considered paramount and either drug can be held at the investigator or treating physicians discretion until the investigator or treating physician feel the causal agent can be restarted safely. In cases of medication hold per physician, redosing must meet all criteria for restarting new cycle (section 6.2.2).

6.2 DOSE MODIFICATION: LENALIDOMIDE

Subjects will be evaluated for AEs at each visit with the NCI CTCAE v4.0, see below for full instruction on initiation of a new cycle of therapy and dose modifications during a cycle of therapy.

Table 6, 7 Lenalidomide dose adjustment steps

Table 6: LENALIDOMIDE Dose Adjustment Steps	
Starting Dose	**MTD mg daily for 21 days every 28 days**
Dose Level –1	MTD -5 mg daily for 21 days every 28 days
Dose Level –2	MTD -10 mg daily for 21 days every 28 days
Dose Level –3	MTD-15 mg daily for 21 days every 28 days

Table 7: LENALIDOMIDE Dose Adjustment Steps in SLL	
Starting Dose	MTD or max of 10 mg daily for 21 days every 28 days
Dose level +1	Starting dose +5 mg daily for 21 days every 28 days
Dose level +2	Starting dose +10mg daily for 21 days every 28 days
Dose level +3	Starting dose +15mg daily for 21 days every 28 days
Dose level -1	Starting dose -5 mg daily for 21 days every 28 days
Dose level -2	Starting dose -10 mg daily for 21 days every 28 days
Dose level -3	Starting dose -15mg daily for 21 days every 28 days

The minimum dose level is 15mg below MTD or 5mg daily for 21 days, (whichever is higher).

Patients who cannot tolerate or require dose reduction below 5mg daily lenalidomide will not receive further doses of lenalidomide.

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f the patient is attaining clinical benefit in the opinion of the treating physician, and has attained at least a partial response, obinutuzumab dosing will continue per study design to a maximum of 21 doses.

The starting dose will be predefined during the phase I portion of the study based upon cohort (see Table 2). In the phase II portion of the study, the starting dose will be the maximum tolerated dose as defined by phase I portion.

6.2.1 INSTRUCTIONS FOR LENALIDOMIDE DOSE MODIFICATIONS OR INTERRUPTION DURING A CYCLE.

Table 8: Dose Modification for Lenalidomide		
NCI CTC Toxicity Grade	**Day 2-14 of Cycle**	**≥Day 15 of Cycle**
Grade 3 neutropenia associated with fever (temperature ≥ 38.5º C) or Grade 4 neutropenia	• Hold (interrupt dose). • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 restart at next lower dose level and continue the cycle until Day 21.	• Omit lenalidomide for remainder of cycle If neutropenia is the only toxicity for which a dose reduction is required. G-CSF may be used and the dose maintained for the next cycle at the investigators discretion.
Thrombocytopenia ≥Grade 3 (platelet count < 50,000/mm³)	• Hold (interrupt dose). • Follow CBC weekly. • If thrombocytopenia resolves to ≤ grade 2 restart at next lower dose level and continue the cycle until Day 21.	• Omit lenalidomide for remainder of cycle
Erythema multiforme ≥ Grade 3	• Discontinue lenalidomide study drug.	• Discontinue lenalidomide study drug.

Sinus bradycardia/ other cardiac arrhythmia **Grade 2** **≥ Grade 3**	• Hold (interrupt) dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21. • Discontinue lenalidomide study drug.	• Omit lenalidomide for the remainder of the cycle. • Discontinue lenalidomide study drug.
Allergic reaction or hypersensitivity **Grade 2-3** **Grade 4**	• Hold (interrupt) dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21. • Discontinue lenalidomide study drug.	• Omit lenalidomide for the remainder of the cycle. • Discontinue lenalidomide study drug
Venous thrombosis/embolism **≥ Grade 3**	• Hold (interrupt) dose and start anticoagulation; restart at investigator's discretion (maintain dose level).	• Omit lenalidomide for remainder of cycle. Anticoagulation measures as described in Conncomitant therapy section below.
other non-hematologic toxicity assessed as Lenalidomide-related≥ Grade 3	• Hold (interrupt) dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 2 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21.	• Omit lenalidomide for remainder of cycle. • Initiate appropriate supportive care, restart lenalidomide next cycle (decrease by one dose level)
Hyperthyroidism or hypothyroidism	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide next cycle (decrease dose by one dose level).	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide next cycle (decrease dose by one dose level).

Dose adjustments/intervention: lenalidomide associated rash:

Grade	**Day 2-14 of Cycle**	**Day ≥ 15 of Cycle**
1-2	• Start supportive	• Start supportive

	measures if grade 2 • No dose adjustment	measures if grade 2 • No dose adjustment
Non-blistering rash Grade 3	• Hold (interrupt) dose. • Start supportive measures. • Evaluate weekly • If rash resolves to ≤ grade 1 prior to day 21 restart at dose level -1 and continue to Day 21. • Restart next cycle at dose level -1.	• Omit lenalidomide for remainder of cycle. • Start supportive measures. • Evaluate weekly until rash ≤ grade 1. • Restart next cycle at dose level -1.
Grade 4*	• Discontinue lenalidomide • Dermatology evaluation • Start supportive measures	• Discontinue lenalidomide • Dermatology evaluation • Start supportive measures
Desquamating (blistering) rash Any Grade*	• Discontinue lenalidomide • Dermatology evaluation • Start supportive measures	• Discontinue lenalidomide • Dermatology evaluation • Start supportive measures

Suggested supportive measures :

1. Initiate daily oral antihistamines
   Examples
   - Loratine 10mg PO daily
   - Ceterizine 10mg PO daily
   - Diphenhydramine 25mg PO daily
2. Short-course low-dose oral steroids
   Example
   - Prednisone 10mg PO x 3 days
   - Hydrocortisone 20mg PO QAM, 10mg PO QPM x 3 days

6.2.2 Instruction for initiation of a New Cycle

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

• The ANC is ≥ 1,000/μL;
• The platelet count is ≥ 50,000/μL;
• Any study drug-related allergic reaction/hypersensitivity or sinus bradycardia/ other cardiac arrhythmia adverse event that may have occurred has resolved to ≤ grade 1 severity;
• Any other study drug-related adverse event that may have occurred has resolved to ≤ grade 2 severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of the combination will not be initiated until the toxicity has resolved as described above. If lenalidomide dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle.

If lenalidomide dosing was omitted for greater than 15 days of the previous cycle or if the new cycle is delayed more than 7 days due to toxicity noted on the scheduled Day 1, then the new cycle will be started with a one-level dose reduction.

Treatment compliance

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

6.3 CONCOMITANT THERAPY

Anti-cancer therapies, including chemotherapy, chemoimmunotherapy, radiation, thalidomide, or any other investigational agents is not permitted while subjects are receiving study drug during the treatment phase of the study.

Patients can receive sargramostim (G-CSF) as treatment for grade 3 or greater neutropenia at the treating physicians discretion. Prophylactic growth factor is not permitted.

It is recommended that patients who are at high risk for a initial or recurrent thromboembolic event (high risk is defined as history of a thromboembolic event and/or taking a concomitant medication associated with an increased risk for a thromboembolic event and/or a known hypercoagulable state regardless of thromboembolic history) receive prophylactic aspirin (70 – 325 mg) daily unless contraindicated. If aspirin is contraindicated, use of low molecular weight heparin or warfarin (or equivalent Vitamin K antagonist) to keep the international normalized ratio (INR) in the range of 2-3, or use of other anti-thrombotic therapy according to hospital guidelines, or physician preference, is acceptable. However, the choice of anticoagulant for prophylaxis for VTE relies upon the investigator's discretion and should be tailored to the subject's individual risk/benefit profile by taking into account the individual thrombotic risk (e.g., history of venous thrombosis), bleeding risk, and the quality of compliance with antithrombotic treatment.

6.4 DISCONTINUATION OF STUDY TREATMENT

Follow-Up

Subjects who discontinue treatment, will be followed for a minimum of 6 months. Patients who die or withdraw consent will not be followed beyond the date of the death or withdrawal of consent. Patients who start alternative therapy will not be followed beyond initiation of next line therapy except for survival. All other patients that remain on study (ie completion of therapy, or drug interruption due to toxicity) will be followed with tumor lesion assessments, imaging, and survival per the schedule of assessments, Section 2.1. Subjects will undergo a safety assessment approximately 28 days post the last dose of study drug. In addition,

off study evaluations, such as recording subsequent therapy, per the Schedule of Assessments will be done. Following completion of chemotherapy, patients will be evaluated every 3 months for one year, then every 6 months for a total of 2 years following completion of therapy with CT of neck, thorax, abdomen and pelvis and other studies as recommend by the treating physician.

7. CRITERIA FOR SUBJECT DISCONTINUATION

7.1 OBINUTUZUMAB-SPECIFIC CRITERIA

Subjects who meet the following criteria should be discontinued from the study:

- Active HBV infection or hepatitis
- Severe or life-threatening anaphylaxis or hypersensitivity reaction

7.2 GENERAL CRITERIA

- Inability of subject to comply with study requirements
- Determination by the investigator that it is no longer safe for the subject to continue therapy

8. CRITERIA FOR STUDY DISCONTINUATION

Treatment will continue for six cycles of combination therapy and 12 cycles (2 years) of maintenance obinutuzumab as per study design, or until the occurrence of any of the following events.

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

- Lack of therapeutic effect
- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug.
- Major violation of the study protocol.
- Withdrawal of consent
- Lost to follow up
- Death
- Suspected pregnancy

9. CLINICAL AND LABORATORY EVALUATIONS

9.1 PRETREATMENT EVALUATIONS

Please see schedule of study assessments for screening evaluations (section 2.1). Screening evaluation will be performed within 30 days of study entry. In the absence of a history of blood transfusion or intravenous drug use in the past 6 months, patients can have hepatitis B/C and HIV testing up to 8 weeks prior to study entry.

9.2 EVALUATIONS DURING TREATMENT

Patients will undergo tumor response assessment including a CT scan of the neck, chest, abdomen, and pelvis, physical exam, and basic laboratory panel during screening, after 3 and 6, 9 and 12 cycles of combination teatment, and every 4 months during maintenance phase with obinutuzumab.

9.3 POST-TREATMENT EVALUATIONS

Subjects who discontinue treatment for any reason, other than completion of therapy, will be followed for a minimum of 6 months from last dose of drug. Subjects will undergo a safety assessment approximately 28 days post the last dose of study drug. In addition, off study evaluations, such as recording subsequent therapy, per the Schedule of Assessments will be done. Following completion of chemotherapy, patients will be evaluated every 3 months for one year, every 6 months for 1 year and then yearly with CT of neck, thorax, abdomen and pelvis and other studies as recommend by the treating physician. When patient starts alternative treatment for lymphoma, they will no longer be followed pre protocol.

10. EVALUATION OF RESPONSE

Response criteria for patients enrolled onto the study will follow the guidelines recommended by the1999 International Workshop on Response Criteria for NHL (Cheson et al.1999) All responses will be characterized as either complete remission (CR), unconfirmed complete remission (CRu), partial remission (PR), stable disease (SD), or progression of disease (POD). Response will be assessed after every three cycles of therapy and at the completion of lenalidomide treatment. Response will be assessed every 4 months thereafter while the patient receives obinutuzumab.

11. STATISTICAL CONSIDERATIONS

This is a single-center, open label, phase I/II study in patients with refractory or relapsed indolent lymphoma. The feasibility of administrating lenalidomide in combination with obinutuzumab and the MTD of the combination will be determined in the phase I part of the study. When the MTD has been established, the efficacy of the combination will be further evaluated in the phase II part of the study in two patient cohorts simultaneously. The two patient cohorts are the patients with follicular lymphoma (grade 1-3a) and the patients with either follicular lymphoma, marginal zone lymphoma, or SLL. A maximum of 72 patients (18 in phase I and 60 in phase II (30 patients each cohort); the patients treated at the MTD in phase I will be counted as the first group of patients treated in phase II) will be enrolled in this study on an intent-to-treat basis.

11.1 STATISTICAL/STUDY DESIGN

11.1.1 Phase I

The primary objective of the phase I part of the study is to determine the maximum tolerated dose (MTD) of lenalidomide when given in combination with obinutuzumab for subsequent testing in the phase II part of the trial. There are three predefined dose levels for lenalidomide (10 mg, 15 mg, 20 mg) with a fixed dose of obinutuzumab (1000mg) as outlined in Table 2.

Dose limiting toxicity (DLT) will be assessed during the first course of each cohort (28 days), and refers to a medically significant event which meets one of the following criteria using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4:

- Grade 3 or higher non-hematologic AE which is felt to be related to the study drug by the investigator with the exception of the following:
- Transient grade 3 or more infusion reaction that completely resolves within 24 hours.
- Grade 4 hematologic toxicity (Platelet count is defined as <25,000 for the purposes of determining DLT.
- Grade 3 neutropenia with elevated temperature (defined as >/= 101 degrees F to be confirmed on two occasions).
- Grade 3 thrombocytopenia with bleeding.
- Treatment delay of greater than 2 weeks due to treatment related toxicity.

The target rate of DLT is 30%. The standard '3+3' design will be used. Applying the 3+3 design, the first cohort of 3 patients will be treated at dose level 1 and evaluated at the end of 28 days. The algorithm is as follows: (1) If 0 out of 3 patients experiences DLT, the next cohort of 3 patients will be

treated at the next higher dose level. (2) If 1 out of 3 patients develop DLT, additional 3 patients will be treated at the same dose level. If no more DLT develops at the dose, i.e. 1 out of a total of 6 patients develops DLT, the dose escalation continues for the next cohort of 3 patients. (3) At any given dose, if greater than 1 out 3 patients or 1 out of 6 patients experience DLT, the dose level exceeds the MTD and 3 more patients will be treated at the next lower dose if there are less than 6 patients already treated at that dose. Following the above scheme, MTD is defined as the highest dose level in which 6 patients have been treated with less than 2 instances of DLT. Given 3 dose levels, it is anticipated that up to 18 eligible patients are required for the phase I part of the study.

Safety parameters and DLTs will be summarized and listed by each dose level.

Prior to advancing/changing dose levels a cohort summary will be completed and submitted to the Clinical Research Monitor in the IND Office.

11.1.2 Phase II

The primary objective for the phase II part is to further evaluate the safety and efficacy of lenalidomide when given in combination with obinutuzumab at the MTD of lenalidomide determined in phase I. The maximum number of patients that will be recruited for the phase II part is 60 (include additional 54 and the 6 patients treated at the MTD in phase I) with 30 for each of the two patient cohorts: the patients with follicular lymphoma (grade 1-3a) and the patients with either follicular lymphoma, marginal zone lymphoma or SLL. The patients who are treated at the MTD in the phase I part will be included in phase II (in relevant cohort). The objective response (complete response + partial response) after 6 cycles and DLT after 1 cycle will be monitored simultaneously using the Bayesian approach of Thall, Simon, Estey (1995, 1996) as extended by Thall and Sung (1998).

Cohort A: **Patients with Follicular lymphoma**

Historical data on 43 patients (Witzig, 2009) with relapsed or refractory indolent non-Hodgkin's lymphoma treated with lenalidomide show an objective response (OR) rate of 23% and DLT rate of under 30%. Independence was assumed between OR and DLT. It is expected for the current trial that the two-drug combination will improve the OR rate by 20% to 43% while the DLT rate is maintained at or below 30%. A sample size of 30 patients ensures that, if the trial is not terminated early, a posterior 90% credible interval for OR rate will have width of 0.283 at most, under the assumption of a 43% of OR rate. We will claim that the regimen is worth of further investigation if the lower limit of the posterior 90% credible interval for OR rate is higher than 0.23. The probabilities of OR and DLT for the historical data are modeled by beta distributions (*Beta* (9.89, 33.11) and *Beta* (12.9, 30.1), respectively). The prior probabilities of OR and DLT for the experimental regimen are also modeled by beta distributions (*Beta* (0.46, 1.54) and *Beta* (0.6, 1.4), respectively), which have the same *means* as the corresponding beta distributions for the historical data.

Denoting the historical probabilities of objective response rate and DLT rate by {p(OR,H) , p(DLT,H)}, the following decision criteria will be applied:

1) Let E correspond to the experimental treatment, stop if
   Prob{p(OR,H) + δ_{OR} > p(OR,E) | data} > 0.95, where δ_{CR} =0.20

2) Stop if Prob{p(DLT,H) + δ_{TOX} < p(DLT,E)| data}>0.95, where δ_{DLT} =0

Patients will be monitored in cohorts of 10 according to the following stopping boundaries for overall response and toxicity.

Number of patients evaluated	Recommend stopping if ≤ OR observed	Recommend stopping if ⩾ DLT observed
10	1	7
20	4	11
30	7	15

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

True DLT Rate	True OR Rate	Prob(stop the trial early)
0.10	0.13	0.9047
	0.23	0.5420
	0.33	0.2014
	0.43	0.0491
	0.53	0.0082
0.20	0.13	0.9048
	0.23	0.5426
	0.33	0.2025
	0.43	0.0503
	0.53	0.0095
0.30	0.13	0.9069
	0.23	0.5528
	0.33	0.2203
	0.43	0.0715
	0.53	0.0316

0.40	0.13	0.9186
	0.23	0.6087
	0.33	0.3177
	0.43	0.1875
	0.53	0.1526
0.50	0.13	0.9461
	0.23	0.7410
	0.33	0.5485
	0.43	0.4623
	0.53	0.4392

Cohort B: **Patients with follicular lymphoma, marginal zone lymphoma or small lymphocytic lymphoma.**

Historical data on 44 patients (Ferrajoli, 2008) with relapsed or refractory chronic lymphocytic leukemia treated with lenalidomide show an objective response (OR) rate about 30% and DLT rate of under 30%. Independence was assumed between OR and DLT. It is expected for the current trial that the two-drug combination will improve the OR rate by 20% to 50% while the DLT rate is maintained at or below 30%. A sample size of 30 patients ensures that, if the trial is not terminated early, a posterior 90% credible interval for objective response rate will have width of 0.287 at most, under the assumption of a 50% of objective response rate. We will claim that the regimen is worth of further investigation if the lower limit of the posterior 90% credible interval for OR rate is higher than 0.30. The probabilities of OR and DLT for the historical data are both modeled by beta distributions (*Beta* (13.2, 30.8)) since the historical rates are same for both. The prior probabilities of OR and DLT for the experimental regimen are then also modeled by beta distributions (*Beta* (0.6, 1.4)), which have the same *mean* as the corresponding beta distribution for the historical data.

Denoting the historical probabilities of objective response rate and DLT rate by {p(OR,H) , p(DLT,H)}, the following decision criteria will be applied:

1) Let E correspond to the experimental treatment, stop if Prob{p(OR,H) + δ_{OR} > p(OR,E) | data} > 0.95, where δ_{CR} =0.2
2) Stop if Prob{p(DLT,H) + δ_{DLT} < p(DLT,E)| data}>0.95, where δ_{DLT} =0

Patients will be monitored in cohorts of 10 according to the following stopping boundaries for overall response and DLT.

Number of patients evaluated	Recommend stopping if ≤ OR observed	Recommend stopping if ⩾ DLT observed
10	2	7
20	6	11
30	9	15

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

True DLT Rate	True OR Rate	Prob(stop the trial early)
0.10	0.30	0.6491
	0.40	0.3014
	0.50	0.0889
	0.60	0.0164
	0.70	0.0018
0.20	0.30	0.6496
	0.40	0.3023
	0.50	0.0901
	0.60	0.0176
	0.70	0.0031
0.30	0.30	0.6574
	0.40	0.3179
	0.50	0.1104
	0.60	0.0395
	0.70	0.0253

0.40	0.30	0.7002
	0.40	0.4031
	0.50	0.2216
	0.60	0.1596
	0.70	0.1471
0.50	0.30	0.8016
	0.40	0.6050
	0.50	0.4848
	0.60	0.4438
	0.70	0.4355

11.2 Analysis Plans

Phase I:
Toxicity type and severity by dose level will be summarized using frequency tables.

Phase II:
The analysis for phase II will include the patients who are treated at the MTD in phase I.
Toxicity type and severity will be summarized for each patient cohort using frequency tables.
Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize categorical variables. The overall response rate for each patient cohort will be calculated and the Clopper Pearson confidence interval will be provided. Chi square test or Fisher's exact test will be used to evaluate the association between patient prognostic factor and response. The distribution of time-to-event endpoints including overall survival and progression free survival will be estimated using the method of Kaplan and Meier.
Comparison of time-to-event endpoints by important subgroups will be made using the log-rank test.
For the toxicity endpoint, per-treated analysis will be performed to include any patient who received the treatment regardless of the eligibility nor the duration or dose of the treatment received. For the efficacy endpoints, intend-to-treat analysis will be applied to the eligible patients.

12. REPORTING OF ADVERSE EVENTS

12.1 ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern.

12.1.1 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 subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with non-Hodgkin's lymphoma 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.

12.1.2 SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) Reporting Requirements for M D Anderson Sponsor Single Site 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 event
- 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 IND 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 on Reporting Adverse Events for Drugs and Devices”.
- 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.
- All SAEs, expected or unexpected/ initial or follow up, must be reported to the IND Office within 5 working days of knowledge of the event regardless of the attribution.
- Death or life-threatening events that are unexpected, possibly, probably or definitely related to drug must be reported (initial or follow up) to the IND Office within 24 hours of knowledge of the event
- Additionally, any serious adverse events that occur after the 30 day timeline that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.
- The electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MD Anderson IRB.
- All events reported to the supporting company must also be reported to the IND Office

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor 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.

12.2 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 FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

12.2.1 ADVERSE EVENT REPORTING PERIOD

The study period during which all AEs and SAEs must be reported begins after the first protocol intervention. 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.

12.2.2 ASSESSMENT OF ADVERSE EVENTS

All AEs and SAEs whether volunteered by the subject, 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 {study drug} (see following guidance), and actions taken.

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

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

Attribution - the determination of whether an adverse event is related to a medical treatment or procedure:

- Definite - the adverse event is clearly related to the investigational agent(s).
- Probable - the adverse event is likely related to the investigational agent(s).
- Possible - the adverse event may be related to the investigational agent(s).
- Unlikely - The adverse event is doubtfully related to the investigational agent(s).
- Unrelated - The adverse event is clearly NOT related to the investigational agent(s).

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

Unexpected adverse events are those not listed in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.
Protocol specific data and adverse events will be entered into PDMS/CORE. PDMS/CORE will be used as the electronic case report form for this protocol.

12.3 PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

12.3.1 ELICITING ADVERSE EVENTS

A consistent methodology for eliciting AEs at all subject evaluation time points 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?"

12.3.2 SPECIFIC INSTRUCTIONS FOR RECORDING AES

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

a. Diagnosis vs. 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.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 12.2.1), 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”.

c. 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”).

d. 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 subject 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 subject 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.

Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v4.0.
The severity of the adverse events (AEs) will be graded according to the U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

Events not included in the NCI CTCAE will be scored as follows:

- Grade 1: Mild: discomfort present with no disruption of daily activity, no treatment required beyond prophylaxis.
- Grade 2: Moderate: discomfort present with some disruption of daily activity, require treatment.
- Grade 3: Severe: discomfort that interrupts normal daily activity, not responding to first line treatment.
- Grade 4: Life Threatening: discomfort that represents immediate risk of death

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events, assigning the attribution and assessing the severity of the AE, the causal relationship between any events and the clinical study procedure, activities or device. Additionally, the Investigator is responsible for providing appropriate treatment for the event and for adequately following the event until resolution for all adverse events for subjects enrolled.

Pregnancy

If a female patient becomes pregnant while receiving obinutuzumab or within 18 months after the last dose of obinutuzumab, or the partner of a male patient becomes pregnant while receiving therapy or within 6 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 subject exposed to obinutuzumab should be reported as an SAE.

Pregnancies occurring while the subject is on lenalidomide or within 4 weeks after the subject's last dose of lenalidomide are considered expedited reportable events. If the subject is on lenalidomide, it is to be discontinued immediately and

the subject is to be instructed to return any unused portion of lenalidomide to the Investigator. The pregnancy must be reported by the investigator to MDACC IRB and IRB OFFICE AND to Celgene Corporation Worldwide Drug Safety Surveillance (WWDSS) within 24 hours of the Investigator's knowledge of the pregnancy by phone and facsimile using the SAE Form.

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

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

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

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

In the case of a live "normal" birth, Celgene Corporation Worldwide Drug Safety Surveillance (WWDSS), MDACC IRB AND IRB OFFICE should be advised as soon as the information is available.

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

Post-Study Adverse Events
The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior obinutuzumab or lenalidomide exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject, including pregnancy occurring in the partner of a male study subject who participated in the study, this should be reported as an SAE adequately to Genentech drug Safety during follow up period

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.

AEs of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

Adverse events of special interest for this study include the following:

- 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:
- 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
- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), 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 a contamination of the study drug is suspected.

The obinutuzumab Events of Special Interest are:

- TLS (all grades)
- Second malignancy

Other Special Situations Reports

The following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech:

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
- In addition, reasonable attempts should be made to obtain and submit the age or

age group of the patient, in order to be able to identify potential safety signals specific to a particular population

Product complaints

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

Exchange of Single Case Reports with Genentech

The principal Investigator will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, AESIs and Product Complaints with an AE where the patient has been exposed to the Product. The completed MD Anderson SAE form should be sent to the Genentech contact specified below. Transmission of these reports (initial and follow-up) will be either electronically via email or by fax and within the timelines specified below:

Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

All Product Complaints *without* an AE should call via:
PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

Serious Adverse Drug Reactions (SADRs)	*15 calendar days of the awareness date*
Other SAEs	30 calendar days of the awareness date.
Special Situation Reports (Pregnancy) Special Situation Reports (Other)	30 calendar days of the awareness date. 30 calendar days of the awareness date.
Product Complaints	15 calendar days of the awareness date.
AESIs	15 calendar days of the awareness date.

- **Serious Adverse Drug Reactions (SADRs)**

Serious AE reports that are related to the Product or where the causality is assessed as unknown or not provided shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.

- **Other SAEs**

Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

- **Special Situation Reports**
  - **Pregnancy reports**

While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed-up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 180 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to Genentech within thirty (30) calendar days of the awareness date.

  - **Other Special Situation Reports**, as defined above, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

- **Product Complaints**

All Product Complaints (with or without an AE) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

- **AESIs**

AESIs requiring expedited reporting (related or possibly related to Genentech product or where the causality is assessed as unknown or not provided) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date. Others (non-related to product) shall be sent within thirty (30) calendar days.

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

Case Transmission Verification of Single Case Reports

The Principal Investigator (PI) agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via Principal Investigator emailing Genentech a Quarterly line-listing documenting single case reports sent by MD Anderson Cancer Center to Genentech in the preceding time period.
The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Principal Investigatorand 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. The PI shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by the PIto Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech.

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

- Adding to the original MDACC Internal SAE Report Form for Prompt Reporting and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MDACC Internal SAE Report Form for Prompt Reporting
- 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 adverse event 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 adverse event 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.

MEDWATCH 3500A REPORTING GUIDELINES

The below guidelines must also be followed when completing SAE forms different to MEDWATCH 3500A:

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Section C & D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-Up Information

- Additional information may be added to a previously submitted report by any of the following methods:
- Adding to the original MedWatch 3500A report (or MDACC SAE form) and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original
  MedWatch 3500A form (or MDACC SAE 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 adverse event 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)

MedWatch 3500A (Mandatory Reporting) form is available at https://www.fda.gov/media/69876/download

The Principal Investigator will be responsible for the expedited reporting of safety reports originating from the Study to the Ethics Committees and Institutional Review Boards (IRB), where applicable.

MD Anderson Cancer Center will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

12.3.3 ADDITIONAL REPORTING REQUIREMENTS FOR IND

For Investigator-Sponsored IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:
The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of obinutuzumab. An unexpected adverse event is one that is not already described in the obinutuzumab Investigator Brochure. Such reports

are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of obinutuzumab. An

unexpected adverse event is one that is not already described in the obinutuzumab investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a Medwatch 3500 form, but alternative formats are acceptable (e.g., MDACC Internal SAE Report Form for Prompt Reporting, summary letter).

FDA fax number for IND Safety Reports:
Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA must also be faxed to Genentech Drug Safety:
Fax: (650) 225-4682 or (650) 225-4630
Email: usds_aereporting-d@gene.com

And to the Site IRB:
U.T. MD Anderson Cancer Center
Institutional Review Board
1400 Pressler, Unit 1437
Houston, TX 77030
(713)792-2933 phone
(713) 794-4589 fax

For questions related to safety reporting, please contact Genentech Drug Safety:
Tel: (888) 835-2555
Fax: (650) 225-4682 OR (650) 225-4630

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

12.3.4 IND Annual Reports

Copies to Genentech:
All IND annual reports submitted to the FDA by the Sponsor should be copied to Genentech.

Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mail box: ctvist_drugsafety@gene.com

12.4 STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

Obinutuzumab Protocols
Email: ga101-gsur@gene.com

And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

13. MD ANDERSON REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND DOSE LIMITING TOXICITIES:

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Expedited Reporting by Investigator to Celgene
Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form, MDACC SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s),. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (RV-
XX-PI-###) 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.
If this is a multicenter trial, suggest including language indicating that participating study sites must report SAEs to Celgene as described and within 24 hours of awareness. Participating sites should also report SAEs to the primary study site.

14. RETENTION OF RECORDS

U.S. FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, subject records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

For studies conducted outside the United States under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the U.S. FDA IND regulations and the relevant national and local health authorities, whichever is longer.

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APPENDIX D
Calculation of Creatinine Clearance Using the Cockcroft–Gault Formula

$$\text{Creatinine Clearance (men)} = \frac{(140\text{-Age}) \times \text{Lean Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

$$\text{Creatinine Clearance (women)} = 0.85 \times \frac{(140\text{-Age}) \times \text{Lean Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

Reference:

Gault MH, Longerich LL, Harnett JD, et al. Predicting glomerular function from adjusted serum creatinine (editorial). Nephron 1992;62:249.

APPENDIX E
SAFETY REPORTING FAX COVER SHEET

GENENTECH SUPPORTED RESEARCH

AE / SAE FAX No: (650) 225-4682

Alternate Fax No: (650) 225-5288

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Safety: (888) 835-2555

PLEASE PLACE MD ANDERSON SAE REPORTING FORM BEHIND THIS COVER SHEET

APPENDIX F: CURRENT NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)

Please refer to the following web link:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

APPENDIX G: GUIDELINES FOR OBINUTUZUMAB PREPARATION AND ADMINISTRATION

Reconstituted obinutuzumab drug product intended for IV infusion is prepared by dilution of the drug product into an infusion bag containing 0.9% sodium chloride, to the final drug concentration of 4 mg/mL. Using a 250-mL infusion bag containing 0.9% sodium chloride, withdraw and discard 40 mL of the sodium chloride. Withdraw 40 mL of obinutuzumab from a single glass vial and inject into an infusion bag (discard any unused portion of obinutuzumab left in the vial). Gently invert the infusion bag to mix the solution; do not shake.

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

Risks Associated with Pregnancy

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

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

Females of childbearing potential (FCBP)[†] must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; and 3) for at least 28 days after discontinuation from the study. The two methods of reliable contraception must include one highly effective method (i.e. intrauterine device (IUD), hormonal [birth control pills, injections, or implants], tubal ligation, partner's vasectomy) and one additional effective (barrier) method latex condom, diaphragm, cervical cap). FCBP must be referred to a qualified provider of contraceptive methods if needed.

Before starting study drug:

Female Subjects:

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

[†] 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).

Male Subjects:

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

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

All Subjects:

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

Female Subjects:

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

Male Subjects:

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