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TITLE:	A Phase II Study of Obinutuzumab and Lenalidomide in Previously Untreated Subjects with Follicular Lymphoma
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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

Abbreviation	Definition
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
FDA	Food and Drug Administration
^{18}F-FDG	^{18}F-fleurodeoxyglucose
FFPE	formalin-fixed paraffin-embedded

Abbreviation	Definition
FISH	fluorescence in situ hybridization
FL	Follicular lymphoma
GCB	germinal center B cell
GCP	Good Clinical Practice
GCSF	granulocyte-colony stimulating factor
GEP	gene expression profiling
G	GA101
G-FC	GA101 in combination with fludarabine and cyclophosphamide
HAHA	human anti-human antibodies
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HD	high dose
HTLV	human T-cell leukemia virus
ICH	International Conference on Harmonisation
Ig	immunoglobulin
IHC	immunohistochemistry

Abbreviation	Definition
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
LVS.D	left ventricular systolic dysfunction
MCL	mantle-cell lymphoma
MRI	magnetic resonance imaging
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

Abbreviation	Definition
ORR	overall response rate
OS	overall survival
PD	progressive disease
PICC	peripherally inserted central catheter
PK	pharmacokinetic
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
TFR	Tumor flare reaction
TLS	tumor lysis syndrome
ULN	upper limit of normal
U.S.	United States
V	valine

• Abbreviation	• Definition
• WHO	• World Health Organization

Introduction

Non-Hodgkin lymphoma

Non-Hodgkin lymphoma (NHL) is the most common hematologic malignancy in adults. The majority of NHL 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.

Early-stage indolent NHL may be effectively treated with radiation therapy, but advanced stages remain incurable and there is no established standard of care for previously untreated follicular lymphoma (Friedberg et al. 2009).

Natural History and Current Management of Indolent Non-Hodgkin Lymphoma

Natural History

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.

Current Management

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). Despite high response rates, and median PFS exceeding 5 years with the addition of maintenance rituximab (Salles et al. 2011), chemoimmunotherapy is not considered curative in FL, as patients continue to relapse. In addition, the side effect profile associated with cytotoxic therapy raises the question, what is the optimal frontline strategy for FL?

Obinutuzumab Background

Structure and Mechanism of Action of Obinutuzumab

Obinutuzumab (GA101, RO5072759), is a glycoengineered, humanized, type II anti-CD20 monoclonal antibody (mAb). Obinutuzumab was derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering leading to the following characteristics (Beers et al. 2010; Mössner et al. 2010): high antibody-dependent cellular cytotoxicity (ADCC); high affinity binding to the CD20 antigen; low complement-dependent cytotoxicity (CDC) activity; and antibody dependent cellular phagocytosis (ADCP) through recruitment of FcγRIII positive immune effector cells such as natural killer (NK) cells, macrophages and monocytes; and high direct cell death induction. Given the direct cell death inducing properties of obinutuzumab and the significantly enhanced ADCC in preclinical assays, it is possible that obinutuzumab may have greater efficacy than the widely used anti-CD20-mAb rituximab (Rituxan®).

Clinical Experience with Obinutuzumab

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). Results from the ongoing studies are described below. For the most up-to-date information on obinutuzumab, please refer to the current version of the Investigator's Brochure.

Tolerability and Efficacy of Obinutuzumab in NHL

Study BO20999 (GAUGUIN; NCT00517530) (Phase I)

BO20999 was an open-label, multicenter, Phase I/II study to explore obinutuzumab safety and activity in relapsed/refractory NHL and CLL. Patients have received obinutuzumab at doses with a range of 400–2000 mg (given as a flat dose) across four cohorts (Morschhauser et al. 2009). There were no dose-limiting toxicities (DLTs) and no requirement for dose reductions. Infusion-related reactions (IRRs) occurred in all CLL patients and were characterized predominantly by National Cancer Institute Common Terminology Criteria (NCI-CTC) Grade 1–2 toxicities: chills, nausea, vomiting, fever, pyrexia, hypertension, hypotension, dyspnea, and dizziness. Two patients experienced four NCI-CTC Grade 3 toxicities: sweats, flushing, asthenia, and hepatic cytolysis.

Although the safety profile appears otherwise similar between NHL and CLL, there was an increase in NCI-CTC v3.0 Grade 3–4 neutropenia noted in CLL patients, which were observed in 9 patients across the four dose levels administered. Five patients experienced NCI-CTC Grade 4 neutropenia and 4 patients experienced NCI-CTC Grade 3 neutropenia as the maximum severity. Of the 9 patients, 7 had one NCI-CTC Grade 3–4 event and 2 patients experienced more than one event. Granulocyte colony-stimulating factor (G-CSF) support was administered to 6 of the 9 patients, and these patients responded quickly to G-CSF support. For the 3 patients who did not receive G-CSF, neutrophil counts normalized spontaneously. Furthermore, it is important to note that these neutropenia events did not appear to be accompanied by a higher incidence of infections. No deaths were reported in Phase I of this study for CLL.

As assessed by the International Workshop on CLL (IWCLL) criteria, the end-of-treatment response rate with obinutuzumab monotherapy was 62% (8 of 13 patients with partial response [PR]) (Morschhauser et al. 2009).

Study BO20999 (GAUGUIN; NCT00517530) (Phase II)

Twenty patients with relapsed/refractory CLL have received 1000 mg of obinutuzumab. The most commonly reported adverse event (AE) during the treatment period was IRR, reported in 19 (95%) of 20 patients. Fifteen patients experienced Grade 3–4 AEs of whom 14 patients had treatment-related Grade 3–4 AEs (investigator assessment). Treatment-related Grade 3–4 AEs were IRR (6 patients), neutropenia (4 patients), lymphopenia (2 patients), thrombocytopenia (2 patients), and anemia, pure red cell aplasia, pancytopenia, febrile neutropenia, herpes zoster, and interstitial lung disease (1 patient each). Eleven serious adverse events (SAEs) in 9 patients were reported during treatment, 9 of which were assessed by the investigator as related to obinutuzumab: IRR (4 patients) and febrile neutropenia, pancytopenia, pure red cell aplasia, interstitial lung disease and pyrexia (1 patient each). Three patients withdrew from further study treatment after the first infusion due to IRR. One death has been reported during follow-up from colon cancer. The most common AE in follow-up was nasopharyngitis, reported in 2 patients. End-of-treatment response assessment showed that four patients (20%) achieved a clinical response, with a best overall response rate (ORR) of 25% in evaluable patients (*Salles* et al. 2011).

Study BO21003 (GAUSS; NCT00576758) (Phase I)

BO21003 is an open-label, dose-escalating, multicenter Phase I/randomized Phase II study in patients with relapsed/refractory CD20+ malignant disease. 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. 2015)

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.

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.

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

Study GAO4753g (GADOLIN) is an 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. Preliminary results have been presented at ASCO and Lugano 2015. The study was terminated early given recommendations from the IDMC as the primary endpoint had been reached with superior PFS with bendamustine plus obinutuzumab vs. bendamustine alone. (Sehn et al. 2015).

Overview of Safety of Obinutuzumab

Obinutuzumab has been administered to approximately 1310 patients with CD20-positive malignancies. Both in patients with NHL and with CLL, IRR was the most common AE in clinical trials conducted to date. They were predominantly associated with the first infusion, generally occurring early during the infusion,

shortly after, or in some cases up to 24 hours after the completion of the infusion with obinutuzumab. The incidence and intensity of IRRs decreased with subsequent infusions of obinutuzumab. In a few patients, concurrent signs of tumor lysis syndrome (TLS) were observed. Other frequently observed AEs include infections and neutropenia. These events appeared to be more common in patients with CLL compared to NHL.

In trials investigating the combination of obinutuzumab and CHOP, FC, chlorambucil or bendamustine, the incidence of AEs in the treatment arms with combined use was consistent with the known safety profiles of the individual study drugs. So far, no maximum tolerated dose, no dose-limiting toxicities, and no clear dose-related trends in the incidence of AEs have been determined.

A pooled analysis of safety data for obinutuzumab collected during the monotherapy studies BO20999 and BO21003 was conducted in patients with NHL (aggressive [aNHL] and indolent []iNHL]) or CLL who participated in those two studies (both Phase I and Phase II) and received monotherapy treatment with obinutuzumab and included a total 205 patients with NHL (49 aNHL and 156 iNHL patients) and 38 patients with CLL.

In the group of 38 patients with CLL treated with obinutuzumab monotherapy, the majority of patients (25 [66%]) were treated for ≥ 4 weeks to < 6 months. Eleven patients (29%) were exposed for 6 to <12 months, and two patients (5%) were exposed for 12 months or longer. Eight of 38 patients (21%) with CLL were withdrawn during the treatment phase; 4 patients (11%) were withdrawn due to AEs, which indicates that AEs were mostly manageable. Almost all patients (37/ 38 [97%]) experienced an IRR. The number of patients with Grade 3–4 IRRs was 11/ 38 (29%). As is typical for patients with CLL, blood and lymphatic system disorders were among the most frequently reported AEs, in particular neutropenia (13/ 38 patients [34%]), febrile neutropenia (5/ 38 patients [13%]), and thrombocytopenia (7/ 38 patients [18%]).

Infections and infestations were common AEs, occurring in 21/ 38 patients (55%). Infections reported in more than one patient were nasopharyngitis (6 patients), bronchitis and sinusitis (4 patients each), influenza and lung infection (3 patients each), and herpes zoster and oral herpes (2 patients each).

Thirteen patients (34%) died, 8 of these due to disease progression. One patient died from an unspecified cause after withdrawal from the study for lack of response. This patient had received subsequent experimental therapies and had stable CLL at the time she died. For 4 additional patients, the cause of death was reported as colon cancer, lung adenocarcinoma, metastasis, and septic shock, and all were considered not to be related to treatment.

In the two studies investigating obinutuzumab as monotherapy, BO20999 and BO21003, patients with CLL appeared to be at a higher risk of experiencing an AE of special interest than patients with NHL. The largest difference in the incidences was seen for neutropenia (occurring in 47%of patients with CLL [18/ 38] vs. 8%of patients with aNHL [4/ 49] and 8%of patients with iNHL [13/ 156]) and treatment-related AEs associated with the infusion (100%[38/ 38] vs. 80%(39/ 49) and 83% [129/ 156]).

To date, a very small number of patients have experienced TLS (six in total); four patients in the aNHL population (population including MCL) and one patient each in the CLL and iNHL populations.

Infections have been reported in 20/ 49 aNHL patients (41%), 74/ 156 iNHL patients (47%), and 21/ 38 CLL patients (55%). One iNHL patient was withdrawn from the

study because of an infection. In addition, one CLL patient and one iNHL patient died from an infection (septic shock in both cases) during survival follow-up 671 days and 494 days after last dose of treatment, respectively.

Three CLL and 3 iNHL patients were withdrawn from treatment due to an AE of special interest, all for IRRs. An additional patient in the iNHL group discontinued treatment because of an infection. This indicates that these events were generally manageable.

Risks Associated with Obinutuzumab Therapy

Hepatitis B *Virus* Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with anti-CD20 antibodies such as obinutuzumab. HBV reactivation has been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation has also occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive, and hepatitis B surface antibody [anti-HBs] positive). HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels and, in severe cases, increase in bilirubin levels, liver failure, and death.

Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with obinutuzumab. For patients who show evidence of hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult physicians with expertise in managing hepatitis B regarding monitoring, and consider HBV antiviral therapy.

Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following treatment with obinutuzumab. HBV reactivation has been reported for other CD20-directed cytolytic antibodies following completion of therapy.

In patients who develop reactivation of HBV while receiving obinutuzumab, immediately discontinue obinutuzumab and any concomitant chemotherapy, and institute appropriate treatment. Resumption of obinutuzumab in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming obinutuzumab in patients who develop HBV reactivation.

Progressive Multifocal Leukoencephalopathy

JC virus infection resulting in progressive multifocal leukoencephalopathy (PML), which can be fatal, was observed in patients treated with obinutuzumab. Consider the diagnosis of PML in any patient presenting with new onset or changes to pre-existing neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture. Discontinue obinutuzumab therapy and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

Infusion-Related Reactions

Obinutuzumab can cause severe and life-threatening IRRs. Two-thirds of patients experienced a reaction to the first 1000 mg of obinutuzumab infusion. IRRs can also occur with subsequent infusions. Symptoms may include hypotension, tachycardia, dyspnea, and respiratory symptoms (e.g., bronchospasm, larynx and throat irritation, wheezing, and laryngeal edema). Other common symptoms include nausea, vomiting, diarrhea, hypertension, flushing, headache, pyrexia, and chills.

Pre-medicate patients with acetaminophen, antihistamine, and a glucocorticoid. Institute medical management (e.g., glucocorticoids, epinephrine, bronchodilators, and/or oxygen) for IRRs as needed. Closely monitor patients during the entire infusion. IRRs within 24 hours of receiving obinutuzumab have occurred.

For patients with any Grade 4 IRRs, including but not limited to anaphylaxis, acute life-threatening respiratory symptoms, or other life-threatening infusion reaction, stop the obinutuzumab infusion. Permanently discontinue obinutuzumab therapy.

For patients with Grade 1, 2, or 3 IRRs, interrupt obinutuzumab for Grade 3 reactions until resolution of symptoms. Interrupt or reduce the rate of the infusion for Grade 1 or 2 reactions and manage symptoms.

For patients with pre-existing cardiac or pulmonary conditions, monitor more frequently throughout the infusion and the post-infusion period because these patients may be at greater risk of experiencing more severe reactions. Hypotension may occur as part of the obinutuzumab IRR. Consider withholding antihypertensive treatments for 12 hours prior to, during, and for the first hour after administration of each obinutuzumab infusion until blood pressure is stable. For patients at increased risk of hypertensive crisis, consider the benefits versus the risks of withholding their hypertensive medication as is suggested here.

Tumor Lysis Syndrome

Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, and/or hyperphosphatemia from TLS can occur within 12–24 hours after the first infusion. Patients with high tumor burden and/or high circulating lymphocyte count ($>25\times10^9$/L) are at greater risk for TLS and should receive appropriate tumor lysis prophylaxis with anti-hyperuricemics (e.g., allopurinol) and hydration beginning 12–24 hours prior to the infusion of obinutuzumab. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

Infection

Serious bacterial, fungal, and new or reactivated viral infections can occur during and following obinutuzumab therapy. Do not administer obinutuzumab to patients with an active infection. Patients with a history of recurring or chronic infections may be at increased risk of infection.

Neutropenia

Obinutuzumab in combination with chlorambucil caused Grade 3 or 4 neutropenia in 34%of patients in clinical trials. Patients with Grade 3 to 4 neutropenia should be monitored frequently with regular laboratory tests until resolution. Anticipate, evaluate, and treat any symptoms or signs of developing infection. Neutropenia can

also be of late onset (occurring more than 28 days after completion of treatment) and/ or prolonged (lasting longer than 28 days).

Patients with neutropenia are strongly recommended to receive antimicrobial prophylaxis throughout the treatment period. Antiviral and antifungal prophylaxis should be considered.

Thrombocytopenia

Obinutuzumab in combination with chlorambucil caused Grade 3 or 4 thrombocytopenia in 12%of patients in clinical trials. In 5%of patients, obinutuzumab caused an acute thrombocytopenia occurring within 24 hours after the obinutuzumab infusion. In patients with Grade 3 or 4 thrombocytopenia, monitor platelet counts more frequently until resolution. Transfusion of blood products (i.e., platelet transfusion) may be necessary.

Summary of Pharmacokinetic and Pharmacodynamic Data for Obinutuzumab

A two- compartment model comprising a time- varying clearance pathway and a linear clearance pathway provides an adequate description of the pharmacokinetics of obinutuzumab following intravenous (IV) administration in Studies BO20999 and BO21003. Following the infusion of obinutuzumab, the elimination appears to be characterized by a clearance pathway that is dependent on time (i.e., starting at a typical value of 630 mL/ day and then gradually decreasing to an asymptote of 60 mL/ day at steady state) and a linear clearance pathway. Tumor burden may potentially contribute significantly to the clearance of obinutuzumab, especially at the beginning of treatment when CD20- positive tumor cells are most abundant. As tumor burden decreases, the clearance reaches an asymptote, which is believed to be primarily a function of the proteolytic metabolic clearance. Consequently, some patients with a high tumor burden may appear to clear the drug from the plasma faster than do 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 obinutuzumab will reduce the quantity of CD20- positive tumor cells. Consequently, the number of obinutuzumab administrations during the first cycle of treatment may be expected to reduce the number of CD20- positive tumor cells, thus minimizing the impact of the time varying clearance pathway on obinutuzumab exposure.

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 and after infusion, but changes have been observed in the levels of interleukin (IL)- 6 and IL- 8 before and after infusion.

lenalidomide BackGround

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 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 $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

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

Lenalidomide is available in 2.5mg,5 mg, 10 mg, 15mg, 20mg, and 25mg 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.

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.

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

Witzig et al reported the Phase II results of lenalidomide monotherapy in patients with relapsed or refractory aggressive NHL. Lenalidomide (25 mg/ d) was administered on days 1 to 21 of a 28-day cycle and continued as tolerated or until disease progression. (Witzig et al 2011) Patients with various aggressive
histologic subtypes (including diffuse large B-cell, grade 3 follicular lymphoma, mantle cell, and transformed NHL) were enrolled. 277 patients were enrolled, the ORR was 35% Clinical responses were observed in all lymphoma subtypes. Median PFS was 3.7 months. The most common adverse event was myelosuppresion with grade 4 neutropenia and thrombocytopenia in 17 and 6% respectively. A multicenter clinical trial has been completed investigating clinical efficacy of single agent lenalidomide vs. investigator's choice in patients with relapsed/ refractory DLBCL and preliminary findings suggest clinically activity of lenalidomide in relapsed/ refractory DLBCL with more pronounced efficacy in ABC DLBCL. (Czucman et al. 2014)

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 three (range 1-4) 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 this basis, a multicenter Phase II trial of lenalidomide in patients with relapsed or refractory MCL after bortezomib was conducted demonstrating an ORR of 28%, median PFS of 4 month, median OS of 19 months, and led to the indication of lenalidomide in relapsed/ refractory MCL. (Goy et al. 2013)

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 conducted a phase II, single arm study with a combination of lenalidomide and rituximab in patients with untreated indolent NHL. (Fowler et al. 2014) Patients receive lenalidomide 20 mg/ day on days 1- 21 of each 28 day cycle. Rituximab was given at 375 mg/ m2 on day 1 of each cycle. We reported high overall response rates, with a complete response rate of 87%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. Hematologic toxicity included 35%≥grade 3 neutropenia and 4%with ≥grade 3 thrombocytopenia. These results were validated by a recently reported Phase II cooperative group study of lenalidomide and rituximab in untreated indolent NHL, demonstrating similar response rates and toxicity. (Martin P, et al ASH 2013).

Study Rationale

Obinutuzumab Plus Lenalidomide in Untreated Follicular Lymphoma

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 an 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. This dose was also shown to be safe in a recently

presented phase I study of obinutuzumab and lenalidomide in relapsed NHL. (Morschhauser F, et al ASH 2014) In addition, we are conducting a Phase I/II study of obinutuzumab and lenalidomide in relapsed/refractory indolent NHL (NCT01995669). No DLTs were observed in the Phase I dose escalation portion of the study and the Phase II cohort is currently enrolling with obinutuzumab dosed at 1000mg and lenalidomide at 20mg.

Novel Endpoints

With the prolonged natural history of follicular lymphoma, identifying optimal endpoints or surrogates for overall survival for frontline studies is an evolving field. In an analysis of the National LymphoCare Study, previously untreated patients with FL who experienced progressive disease within 2 years of initial treatment were identified as a high risk group, "early progressors". Early progression was dramatically associated with inferior overall survival, 5 year OS estimates of 50%versus 90%in the reference group. (Casulo et al. JCO 2015) After adjusting for FLIPI score, early progression was associated with an increased risk of death (hazard ratio [HR] =6.44 (95%confidence interval [CI] 4.33- 9.58). This suggests that a landmark progression- free survival at 2 years may predict for a high risk population and discern a difference in survival outcomes. Another proposed efficacy endpoint includes the complete response rate at 30 months which has been shown to correlate with PFS in follicular lymphoma (Sargent et al, ASCO 2015). Both approaches serve as surrogate endpoints for overall survival.

We are proposing a novel frontline, open- label, Phase II clinical trial for previously untreated patients with follicular lymphoma, a non- cytotoxic approach based on sound scientific rationale with emerging clinical endpoints. We are proposing the next generation of immune therapy with obinutuzumab in combination with lenalidomide to enhance ADCC and direct cell death to improve outcomes for our patients with an anticipated acceptable toxicity profile. We aim to explore the efficacy and safety of the novel combination of obinutuzumab and lenalidomide in previously untreated patients with follicular lymphoma to influence practice patterns.

Objectives

Primary

The primary objective is to evaluate the efficacy of obinutuzumab combined with lenalidomide in patients with previously untreated follicular lymphoma (determined by PFS at 2 years).

Secondary

The secondary objectives are:

1. To evaluate the safety of obinutuzumab in combination with lenalidomide in patients with untreated follicular lymphoma.
2. To evaluate the efficacy of obinutuzumab in combination with lenalidomide in subjects with follicular lymphoma as assessed by CR at

30 months, ORR, DOR, EFS, and OS

exploratory

The exploratory objective are to evaluate prognostic and predictive biomarkers relative to treatment outcomes.

Study Design

Description of the Study

This is a single center, Phase II, open label study designed to assess the efficacy and safety of obinutuzumab combined with lenalidomide in previously untreated subjects with follicular lymphoma. The study will include approximately 90 subjects in one treatment arm.

Once a patient provides written informed consent, the patient may enter the screening period, which is permitted to last up to 4 weeks. During the screening period, the patient will undergo safety and other assessments to determine eligibility for the study. The patient eligibility will be based on investigator assessment. The patient will enter the treatment period once the patient has fulfilled the required assessment in the screening period. The treatment period for each patients starts with study day 1 of cycle 1. The treatments will be given as described in Section 5. The patients will receive protocol-specified treatments, until:

1) Failure to achieve at least a partial response after 6 cycles of therapy
2) Relapse or progression of disease
3) Withdrawal of consent,
4) Unacceptable toxicity, or
5) End of study.

Upon completion of the required treatments, the patient will enter the follow-up period. During the follow-up period, patients will be followed for disease progression, next lymphoma treatment, and OS.

Study Endpoints

Primary Efficacy Outcome Measure

Progression-free survival (PFS) at 2 years as assessed by the investigator

Secondary Efficacy Outcome Measures

- Complete response rate ([CR], based on Cheson, Lugano classification 2014) at 30 months or 120 weeks as assessed by the investigator
- Overall response rate ([ORR] CR + partial response [PR]) based on Cheson, Lugano 2014 as assessed by the investigator
- ORR, CR, and PR based on Cheson 2007.
- Duration of response (DOR)

- Event free survival (EFS)
- Overall survival (OS)

Safety Outcome Measures

- Frequency, severity, and relatedness of treatment-emergent adverse events (AEs)
- Frequency of treatment-emergent AEs requiring discontinuation of study drug or dose reductions

Exploratory Endpoints

- Immunophenotyping of PBMCs to determine alteration in immune cell subsets
- Identification of signaling pathways or biomarkers that predict sensitivity or resistance by gene expression profiling

Evaluation of response

Response assessment will be completed by the Principal Investigator using Cheson 2014 Lugano Criteria. At screening, up to 6 target lesions will be selected and followed for the duration of the study as outlined in Section 7.7.8. Information on extranodal involvement can also be recorded. The best response will be documented.

Safety plan

This study will be monitored by the Principal Investigator and in accordance with all FDA safety reporting requirements. AEs and SAEs will be reviewed on an ongoing basis to identify potential safety concerns. The Investigator will record the action taken with the study drugs as a result of an AE or SAE, as applicable (e.g., discontinuation, interruption, or reduction of study drugs, as appropriate) and report if concomitant and/ or additional treatments were given for the event. The principal Investigator is required to notify his/ her Institutional Review Board (IRB) of a serious adverse event according to institutional policy. Enrolled subjects will be evaluated clinically including vital signs and standard laboratory test assessment.

Statement of compliance

The study will be conducted in compliance with this protocol, principles of International Conference on Harmonization (ICH), Good Clinical Practice (GCP), Declaration of Helsinki, and all applicable national and local regulations governing clinical studies.

Study Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. A diagnosis of follicular lymphoma (grades 1, 2, or 3a), untreated

2. Able and willing to provide written informed consent and to comply with the study protocol
3. Must be ≥18 years of age
4. Bi- dimensionally measurable disease, with at least one mass lesion ≥ 2 cm in longest diameter by CT, PET/ CT, and/ or MRI.
5. Must be in need of therapy as evidenced by at least one of the following criteria:
    a. Bulky disease defined as:
        i. A nodal or extranodal (except spleen) mass > 7 cm in its greater diameter or,
        ii. At least 3 nodal or extranodal sites ≥ 3 cm in diameter
    b. presence of at least one B symptom:
        i. fever (>38 C) not due to infectious etiology
        ii. night sweats
        iii. weight loss >10%in the past 6 months
    c. Fatigue due to lymphoma
    d. Splenomegaly (>13 cm)
    e. Compression syndrome (ureteral, orbital, gastrointestinal)
    f. Any of the following cytopenias due to lymphoma:
        i. Hemoglobin ≤ 10 g/ dL
        ii. Platelets ≤ 100 x 10^9/ L
        iii. absolute neutrophil count (ANC) < 1.5x10^9/ L
    g. Pleural or peritoneal effusion
    h. LDH > ULN or β2 microglobulin > ULN
6. Stage II, III, or IV disease
7. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2

8. Adequate hematologic function defined as follows:
    a. Absolute neutrophil count (ANC) >1.0x10^9/ L
    b. Platelet count > 75x10^9/ L
9. Adequate organ function, including:
    a. Serum aspartate transaminase (AST) and alanine transaminase (ALT) < 3 x upper limit of normal (ULN)
    b. Creatinine clearance >30 ml/ min calculated by modified Cockcroft- Gault formula.
    c. Bilirubin < 1.5 x ULN unless bilirubin is due to Gilbert's syndrome, documented liver involvement with lymphoma, or of non- hepatic origin, in which case bilirubin should not exceed 3g/ dL.
10. Women of childbearing potential and men who are sexually active must practice reliable contraceptive measures started at least 4 weeks before study therapy and continued for at least 18 months for female subjects and 6 months for male subjects following discontinuation of therapy. Females of childbearing potential must either completely abstain from heterosexual sexual contact or must use 2 methods of reliable contraception. Reliable contraceptive methods include 1 highly effective method [intrauterine device, birth control pills, hormonal patches, injections, vaginal rings, or implants] and at least 1 additional method [condom, diaphragm, or cervical cap] every time they have sex with a male. Males who are sexually active must be practicing complete abstinence or agree to a condom during sexual contact with a pregnant female or female of child bearing potential. Men must agree to not donate sperm during and after the study.
11. Women of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [β- hCG]) pregnancy test at screening. Women who are pregnant or breastfeeding are ineligible for this study.

a. Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.

12. All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the REMS® program.
13. Sign (or their legally-acceptable representatives must sign) an informed consent document indicating that they understand the purpose of and procedures required for the study, including biomarkers, and are willing to participate in the study.

Exclusion Criteria

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

1. Known active central nervous system lymphoma or leptomeningeal disease.
2. Follicular lymphoma with evidence of diffuse large B-cell transformation
3. Grade 3b follicular lymphoma
4. Any prior history of other malignancy besides follicular lymphoma, unless the patient has been free of disease for ≥ 5 years and felt to be at low risk for recurrence by the treating physician, except:
    a. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
    b. Adequately treated cervical carcinoma in situ without evidence of disease.
5. Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of lenalidomide capsules, or put the study outcomes at undue risk
6. Known history of human immunodeficiency virus (HIV), active Hepatitis C Virus, active Hepatitis B Virus infection, or any uncontrolled active systemic infection
    a. Patients with inactive hepatitis B infection must adhere to hepatitis

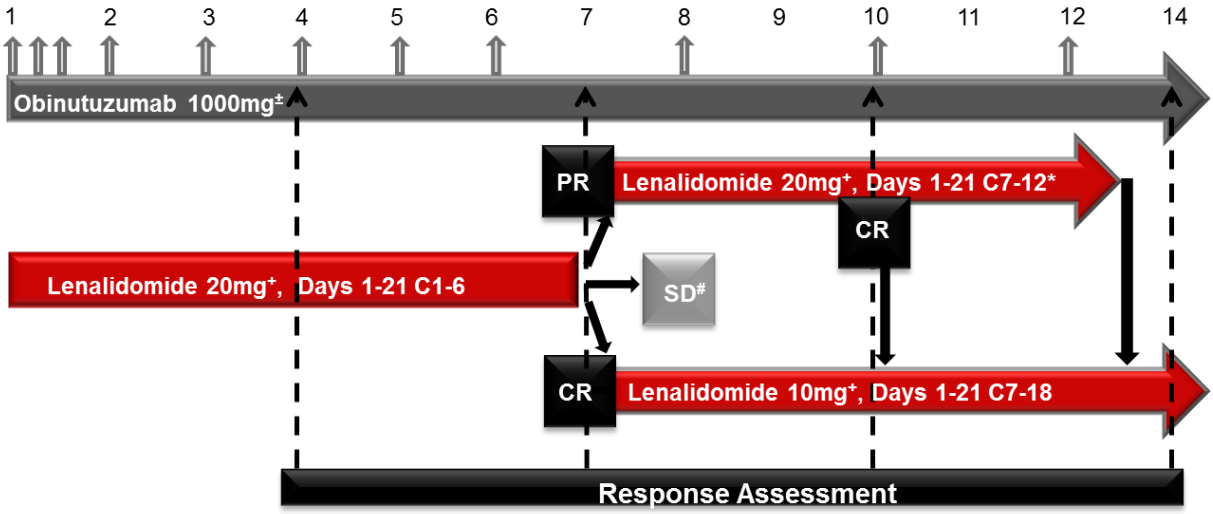
B reactivation prophylaxis unless contraindicated.

7. Prior use of lenalidomide
8. Concurrent systemic immunosuppressant therapy (e.g., cyclosporine, tacrolimus, etc., or chronic administration glucocorticoid equivalent of >10mg/ day of prednisone) within 28 days of the first dose of study drug
9. Known anaphylaxis or IgE- mediated hypersensitivity to murine proteins or to any component of rituximab
10. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification.
11. Significant screening electrocardiogram (ECG) abnormalities including left bundle branch block, 2nd degree atrioventricular (AV) block, type II AV block, or 3rd degree block. QT prolongation is not a significant ECG abnormality that would warrant exclusion.
12. Vaccinated with live, attenuated vaccines within 4 weeks of study entry
13. Lactating or pregnant subjects
14. Administration of any investigational agent within 28 days of first dose of study drug.
15. Patients who have undergone major surgery within 14 days.
16. Patients with the following:
    a. bleeding diathesis or patients in whom prophylactic antithrombotic therapy is otherwise contraindicated
    b. patients with prior DVT, PE, or arterial thromboembolism
    c. patients with ischemic stroke or TIA

Treatment of subjects

enrollment and blinding

This is an open- label, Phase II study with one treatment arm. Subjects will not be blinded to study drug nor will they be randomized. Enrolled subjects will receive open- label capsules of lenalidomide in combination with IV obinutuzumab.



treatment schedule

± After cycle 6, obinutuzumab will be administered every 2 cycles until cycle 30 (8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30)

+ For subjects with CrCL >60mL/ min, see Table 2 for dose modification for CrCL≤60 mL/ min.

* For subjects who achieve a CR prior to cycle 12, these subjects will proceed to 10mg of lenalidomide, days 1- 21 for the remainder of 18 cycles. For subjects who maintain a PR, after 12 cycles, they will receive 10mg of lenalidomide for the remainder of 18 cycles.

For subjects who fail to achieve at least a partial response after 6 cycles of therapy, they will discontinue study drug. Subjects with earlier evidence of nonresponse that warrants change in therapy in the opinion of the treating physician will discontinue study drug.

- Lenalidomide dosing:
  - Patients will receive a maximum of 18 cycles of lenalidomide.
  - Cycles 1- 6:
    - Patients with a CrCl >60 mL/ min, will receive 6 cycles of lenalidomide, 20mg daily on days 1- 21 of a 28 day cycle (± 2days). For patients with a CrCl ≤ 60

mL/ min, see Section 5.3.2.1 / Table 1 for dose adjustment for renal impairment.

- Cycles 7- 18:
  - Patients with a CrCl >60 mL/ min exhibiting a CR after six cycles will then receive 12 additional cycles of 10mg of lenalidomide daily on days 1- 21 every 28 days (± 2days) for a total of 18 cycles.
  - Patients who fail to achieve at least a PR after 6 cycles will discontinue study drug.
  - Patients with a CrCl >60 mL/ min with a PR after six cycles will continue 20mg of lenalidomide on days 1- 21 every 28 days (± 2days) for 3 to 6 more cycles until they achieve a CR at which time they will receive 10mg lenalidomide on days 1- 21 every 28 days (± 2days) for the remainder of 18 cycles.
  - Patients with a CrCl >60 mL/ min with a PR after 12 cycles will then receive 10mg of lenalidomide on days 1- 21 every 28 days (± 2days) for the remainder of 18 cycles.

- Obinutuzumab dosing:
  - Cycle length is 28 days.
  - Cycles 1- 6:
    - Patients will receive obinutuzumab, 1000 mg on days 1, 8 (± 2days), and 15 (± 2days) of cycle 1, and day 1 (± 2days) of cycles 2 through 6.
    - Patients who fail to achieve at least a PR after 6 cycles will discontinue study drug.
  - Cycles 7- 30:
    - Patients will receive 1000mg of obinutuzumab on day 1 (± 2days) of cycle 8, 10, and 12.
    - Patients will receive obinutuzumab, 1000 mg on day 1 (± 7 days) of cycle 14, 16, 18, 20, 22, 24, 26, 28, and 30.
    - Obinutuzumab is continued for 30 cycles or until disease progression, unacceptable toxicity, or voluntary withdrawal whichever occurs first.

dosage and administration

Below are specific administration instructions for drugs used within this study.

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). Obinutuzumab will be supplied to research subjects by Genentech for the duration of this trial at no charge to participants or their insurance providers.

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.

Obinutuzumab Administration

Obinutuzumab 1000mg will be given as outlined in Section 5.2.

First Infusion of obinutuzumab:

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

- Oral acetaminophen (1000 mg) AND
- An antihistamine such as diphenhydramine (50−100 mg)
- For Cycle 1, day 1 prophylactic corticosteroids (e.g., 20 mg IV dexamethasone) at least one hour prior to the obinutuzumab infusion. An equivalent dose of methylprednisolone (80mg) is acceptable but hydrocortisone should not be used.

Obinutuzumab will be administered at an initial rate of 12.5mL/ hr (50mg/ hr) for 60 minutes, and then the infusion rate may be escalated by 12.5mL/ hr increments every 30 minutes to a maximum of 100mL/ hr as tolerated. If hypersensitivity or an infusion reaction develops, the infusion should be interrupted until symptoms resolve or improve, see Section 6.4, Table 4. For management of infusion reaction, please refer to the institution's hypersensitivity reaction order sheet. The infusion can continue at one- half the previous rate upon improvement in symptoms, and the escalation of 12.5mL/ hr increments every 30 minutes resumes to a maximum rate of 100mL/ hr.

After the end of the first infusion, the IV line or central venous catheter should remain in place for ≥ 1 hour to be able to administer IV drugs if necessary. If no adverse events occur after 1 hour, the IV line may be removed or the central venous catheter may be de accessed.

Subsequent infusions of obinutuzumab:

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

- Oral acetaminophen (1000 mg) AND
- An antihistamine such as diphenhydramine (50−100 mg)

In subsequent cycles, steroids (dexamethasone 20mg IV 30-60 minutes before obinutuzumab) should be given to patients who experienced a severe IRR (≥ grade 3) with the prior infusion of obinutuzumab or who are thought to be at high risk for infusion-related reactions, as assessed by the investigator.

If subjects tolerated the previous infusion well, the subsequent infusions can start at an initial rate of 25mL/hr and increase by 25mL/hr increments every 30 minutes to a maximum of 100mL/hr as tolerated. If subjects did not tolerate the first infusion well, follow the guidelines for the first infusion.

If hypersensitivity or an infusion reaction develops, the infusion should be interrupted until symptoms resolve or improve, see Table 4. For management of infusion reaction, please refer to the institution's hypersensitivity reaction order set. The infusion can continue at one-half the previous rate upon improvement in symptoms, and the escalation of 25mL/hr increments every 30 minutes resumes to a maximum rate of 100mL/hr.

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.

Obinutuzumab Storage

The recommended storage conditions for the obinutuzumab drug product are between 2°C and 8°C, protected from light. Chemical and physical in-use stability for obinutuzumab dilutions in 0.9%sodium chloride (NaCl) at concentrations of 0.2 – 20 mg/mL have been demonstrated for 24 hours at 2°C – 8°C and an additional 24 hours at ambient temperature and ambient room lighting. The prepared diluted product should generally be used immediately. If not used immediately, the infusion should be stored under refrigerated conditions due to microbiology stability and should not be longer than 24 hours at 2°C – 8°C unless reconstitution/dilution has taken place in controlled and validated aseptic conditions. Obinutuzumab should not be frozen or shaken. Mix gently. All transfer procedures require strict adherence to aseptic techniques.

All unused or expired investigational drug will be destroyed in accordance with institutional policies.

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

Lenalidomide

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the Celgene Corporation's 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 the Revlimid REMS® program.

Further information about the Revlimid REMS® program is available at www.celgeneriskmanagement.com.

Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site for IND studies. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

Lenalidomide administration

Patients with creatinine clearance (CrCl) >60 mL/ min as determined by modified Crockcroft- Gault (see Appendix 2) will receive a total of 18 cycles as outlined in Section 5.2.

Lenalidomide Dose Adjustment for Renal Impairment

Subjects with renal impairment (CrCl ≤ 60 ml/ min) will be dosed based on Table 1. CrCL assessment will occur on: Day 1, 8, and 15 for cycle 1 and Day 1 of cycles 2- 18. However, if a subject has a creatinine obtained at any time during the administration of lenalidomide on study because it was clinically indicated, a dose reduction based on CrCL and Table 1 should be performed.

Subjects with moderate renal impairment, CrCL of 30- 60mL/ min, will initiate 10mg of lenalidomide daily on days 1- 21 of a 28 day cycle. Subjects with severe renal impairment, CrCL of <30 mL/ min, will initiate 15mg of lenalidomide every 48 hours on days 1- 21 of a 28 day cycle.

For subjects with renal impairment (CrCl ≤ 60 ml/ min) necessitating dose adjustment on Day 1 of a cycle according to Table 1, but then stably improves, a dose increase based on CrCL will not occur until day 1 of the next cycle. At any point, should a patient require dose reduction due to reduced CrCl, and the CrCl then stably improves, dose escalation will not occur until day 1 of the next cycle.

Table 1. Lenalidomide Dose Adjustment for Patients with Renal Impairment

Category	Renal Function (modified Cockcroft-Gault)	Cycles 1-6	Cycles 7-18
Mild or no renal Impairment	CrCl > 60 mL/min	20 mg once daily	10 mg once daily for subjects with a CR after 6 cycles OR 20mg once daily for subjects with PR after 6 cycles
Moderate renal impairment	CrCl 30-60 mL/min	10 mg every 24 hours*	5mg every 24 hours
Severe renal impairment	CrCl <30mL/min (not requiring dialysis)	15 mg every 48 hours*	10mg every 48 hours

* If CrCl is ≤ 60 ml/ min necessitating dose reduction of lenalidomide but then stably improves to >60 mL/ min, proceed to lenalidomide 20 mg once daily with subsequent cycle, day 1.

Lenalidomide should be taken orally at about the same time each day, either with or without food. Lenalidomide capsules should be swallowed whole with water, and should not be opened, broken, or chewed. If a dose is missed, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. No extra capsules to make up the missed dose should be taken. Females of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves.

Additional prescribing information can be found at www.revlimid.com/wp-content/uploads/2013/11/PI.pdf

Lenalidomide Storage

Lenalidomide is available in capsule doses of 2.5mg, 5mg, 10mg, 15mg, 20mg, and 25mg. Lenalidomide should be stored as directed on the respective package labels. Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

All unused or expired investigational drug will be destroyed in accordance with institutional policies.

Dose Reduction, Delay and Discontinuation

Toxicity necessitating dose modification or delay is based on NCI CTCAE v 4.03 Toxicity Grade. The Principal Investigator will assess whether each AE is related or not to each of the study drugs. Events that are judged definitely, probably or possibly related are considered related AEs. Events that are considered unlikely or definitely not related are considered not related AEs. Factors to be taken into consideration include the temporal relationship between administration of study drug and the onset of the AE, other potential causes of the AE including the subject's underlying medical condition and concomitant medications, whether the AE is consistent with known AEs previously attributed to a study drug, whether the AE decreases or resolves upon withholding or reducing the dose of the study drug, or whether the AE recurs upon reintroduction of the study drug. AEs defined below (Sections 5.4.1), unless the Principal Investigator considers the event clearly unrelated to study drug, will be considered a toxicity that necessitates dose modification or delay.

Toxicities Necessitating Dose Modification or Delay

Toxicities necessitating dose modification or delay will be defined as any non-hematologic or hematologic toxicity listed below. Study treatment should be discontinued in the event of a toxicity lasting more than 28 days despite appropriate medical management, unless reviewed and approved by the Principal Investigator. The action in Table 2 should be taken for the following toxicities:

Non-hematologic toxicity will be defined as any of the following:

- Any unmanageable Grade 3 or 4 non-hematologic toxicity with failure to improve (< Grade 2) or recover to baseline within 14 days of withholding drug
- Grade 3 non-blistering rash that does not resolve to < Grade 2 within 14 days
- Any desquamating (blistering) or grade 4 rash
- Any grade Stevens-Johnson syndrome or toxic epidermal necrolysis
- Grade 3 or 4 thrombosis/ embolism
- Grade 3 or 4 peripheral neuropathy which began or worsened while on study

Hematologic toxicity will be defined as any of the following:

- Grade 3 neutropenia with infection or fever (single temperature of > 38.3 ºC, or with a sustained temperature of ≥ 38 º C lasting > 1 hour).
- Grade 4 neutropenia (ANC<500/ µL) lasting > 7 days.
- Grade 4 thrombocytopenia (<25,000/ µL)

The following action in Table 2 should be taken for any unmanageable toxicity that is consistent with the rules outlined above:

Table 2. Dose Modification for Toxicity

Toxicity Grade	Action to be Taken
Grade 3 neutropenia associated with fever (single temperature of > 38.3 ºC, or with a sustained temperature of ≥ 38 º C lasting > 1 hour) OR Grade 4 neutropenia lasting > 7 days.	•Hold lenalidomide. •Follow CBC weekly. •If neutropenia has resolved to < Grade 2 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level, (see Table 3) and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. •Withhold obinutuzumab until recovery to < Grade 2 or baseline. •Omitted doses are not made up. •G-CSF may be used.
Grade 3 thrombocytopenia	• Follow CBC weekly. • Hold prophylactic anti-coagulation including aspirin, if applicable. • Restart prophylactic anti-coagulation and/or aspirin when platelet count is ≥ 50,000/ mm^3.
≥ Grade 4 thrombocytopenia	• Hold lenalidomide. • Follow CBC weekly. • If thrombocytopenia resolves to < Grade 2 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. • Withhold obinutuzumab until recovery to < Grade 2 or

	baseline. • Omitted doses are not made up. • Hold prophylactic anti-coagulation including aspirin, if applicable. • Restart prophylactic anti-coagulation and/or aspirin when platelet count is ≥ 50,000/mm³.
Non-blistering rash Grade 3	• If Grade 3, hold lenalidomide. • Follow weekly. • If the toxicity resolves to < Grade 2 prior to Day 21 of the current cycle, restart lenalidomide at original dose level (for first occurrence) and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle. • Omitted doses are not made up. • For the second occurrence of Grade 3, hold lenalidomide, and follow weekly. If the toxicity resolves to ≤ Grade 2 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. • Treatment with 10mg of prednisone or equivalent for 10 days (with or without taper) and/or antihistamines PO daily is recommended. • If Grade 3 rash has not improved to at least Grade 2 within 14 days of drug being withheld and administration of 10mg of steroids and/or antihistamines daily, the subject will discontinue study treatment.
Desquamating (blistering) rash	• Discontinue study drugs. Remove patient from study.

Any grade Or grade 4 rash	• Start supportive care: daily antihistamine, 10mg or higher of prednisone or corticosteroid equivalent as clinically indicated
≥ Grade 3 thrombosis/ embolism	•Hold lenalidomide and start therapeutic anticoagulation. •Restart lenalidomide at investigator's discretion (maintain dose level) after anticoagulation is initiated. •See anticoagulation considerations, Section 6.2.
Peripheral neuropathy Grade 3 Grade 4	•If Grade 3, hold lenalidomide dose. Follow at least weekly. •If the toxicity resolves to ≤ grade 1 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. •If Grade 4, discontinue lenalidomide. Remove patient from study.
Other non- hematologic toxicity ≥ Grade 3	• Hold lenalidomide. Follow at least weekly. • If the toxicity resolves to < Grade 2 prior to Day 21 of the current cycle, restart lenalidomide and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle. Omitted doses are not made up. For toxicity attributed to lenalidomide, reduce the lenalidomide dose by 1 dose level when restarting lenalidomide. • Withhold obinutuzumab until recovery to < Grade 2 or baseline.

Obinutuzumab Dose Reduction or Delay

The obinutuzumab dose should be held for any unmanageable toxicity that is consistent with the rules outlined in Table 2. A missed dose of obinutuzumab on the weekly schedule for any

reason will not be made up (the visit window for this visit and Day 1 of Cycles 2 - 12 is ±2 days, and ±7 days for cycles 14- 30).

Lenalidomide Dose Reduction or Delay

The lenalidomide dose should be held for any unmanageable toxicity that is consistent with the rules outlined in Table 2.

The dose of lenalidomide may be reduced successively by one level from starting dose, Table 3. Once a patient's dose has been reduced, no dose re- escalation is permitted. Patients who cannot tolerate the lowest applicable dose level are to be discontinued from the Treatment Phase. Dose modification should also meet the specifications outlined for those subjects with renal insufficiency as outlined in Table 1. If patients with renal impairment are currently receiving 10mg every 24 hours and need a dose modification, they will then be dose reduced to 15mg every 48 hours. If they need further dose reduction due to toxicity, they will be discontinued due to being unable to tolerate the lowest applicable dose. Similarly, patients starting at 15mg every 48 hours who need further dose reduction will be discontinued due to being unable to tolerate the lowest applicable dose.

Table 3. Dose Reduction Levels for Lenalidomide

Dose Level	Lenalidomide 10 mg starting dose*	Lenalidomide 20 mg starting dose
Level - 1	5mg daily on Days 1- 21, every 28 days	15mg daily on Days 1- 21, every 28 days
Level - 2	Discontinue Lenalidomide	10mg daily on Days 1- 21, every 28 days
Level - 3	Discontinue lenalidomide	5mg daily on Days 1- 21, every 28 days

- If patients with renal impairment are currently receiving 10mg every 24 hours and need a dose modification, they will then be dose reduced to 15mg every 48 hours. If they need further dose reduction due to toxicity, they will discontinue lenalidomide.

Overdose Instruction

Overdose, as defined for this protocol, refers to obinutuzumab and lenalidomide dosing only.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of obinutuzumab and lenalidomide assigned to a given patient, regardless of any associated adverse events or sequelae.

PO any amount over the protocol- specified dose
IV 10%over the protocol- specified dose
SC 10%over the protocol- specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form

Permanent Discontinuation of Study Drug

Investigators are encouraged to keep a subject who is experiencing a clinical benefit on study unless significant toxicity puts the subject at risk or routine noncompliance puts the study outcomes at risk. If a subject meets any of the following criteria, then withdrawal from the study treatment is mandatory:

- Subject has failed to achieve at least a partial response (PR) after 6 cycles of therapy. Subjects with earlier evidence of nonresponse that warrants change in therapy in the opinion of the treating physician will discontinue study drug at any time.
- Subject has confirmed progressive disease (PD)
- Subject has an intercurrent illness or AE that prevents further treatment administration beyond 28 days
- Subject decides to withdraw from study
- Subject becomes pregnant
- Subject is routinely noncompliant with study procedures and/or scheduled evaluations
- Subject requires a prohibited concomitant medication
- Investigator considers withdrawal to be in the best interest of the subject.

A safety follow up visit is required for all subjects except those who have withdrawn full consent.

Concomitant medications

permitted supportive care

Supportive medications (such as for emesis, diarrhea, constipation, etc.) should be delivered in accordance with standard practice. Use of neutrophil growth factors (granulocyte colony-stimulating factor [G-CSF] such as filgrastim or pegfilgrastim) is permitted for management of neutropenia in accordance with the American Society of Clinical Oncology (ASCO) guidelines. Preemptive or prophylactic G-CSF during cycle 1 is not required, but can be used at the discretion of the investigator if the subject is felt to be of high risk according to the current ASCO guidelines.

Transfusions may be given in accordance with institutional policy. Short courses of corticosteroids (<14 days) for treatment of non-lymphoma related medical reasons (e.g. rash, arthritis, asthma) or for tumor flare reaction (TFR) at doses that do not exceed 10mg per day of prednisone or equivalent are permitted. However, if clinically indicated, higher doses of corticosteroids (>10mg per day) are permissible.

Thromboembolism prophylaxis

It is recommended that patients receive prophylactic aspirin (81mg) 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 patient'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. In the setting of thrombocytopenia, thromboembolism prophylaxis should be held in accordance with the guidelines established in Table 2.

All patients who develop a deep venous thromboembolism in any location must be treated appropriately with low molecular weight heparin. Heparin should continue for at least 3 months, however treating physician discretion is allowed. Study treatment is to continue during heparin use. For subjects in whom low molecular weight heparin is contraindicated (i.e., renal impairment), a vitamin K antagonist anti-coagulant can be used instead where medically appropriate.

Tumor lysis prophylaxis

Patients with high tumor burden or those considered to be high risk for tumor lysis by the investigator should receive TLS prophylaxis (allopurinol, rasburicase or equivalent as per institutional guidelines) during the first cycle of lenalidomide administration or as clinically indicated. To monitor for TLS, the patients will have chemistries drawn on Days 1, 8, and 15 of the first cycle and additionally as clinically indicated.

Obinutuzumab pre-medication

Premedication consisting of acetaminophen and an antihistamine should be administered before each obinutuzumab infusion as outlined in Section 5.3.1.1. Steroids (dexamethasone or prednisone) can also be administered as clinically indicated before obinutuzumab.

Management of infusion-related symptoms for obinutuzumab is summarized in Table 4 and in accordance with institution policy outlined in the hypersensitivity order set. 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.

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 as outlined in 5.3.1.1.[c] • If the same adverse event recurs with the same severity despite aggressive supportive treatment, treatment must be discontinued. Retreatment at the
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.

[b] Supportive treatment: Please refer to hypersensitivity order set

[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 12.5mL/hr (or 25mL/hr for subsequent infusions) every 30 minutes to a maximum rate of 100mL/hr.

Hepatitis B Prophylaxis

Patients with inactive hepatitis B infection must adhere to hepatitis B reactivation prophylaxis unless contraindicated.

prohibited concomitant therapy

Systemic corticosteroid use at doses above 10 mg / day (prednisone or equivalent) is prohibited during the Treatment Phase. For patients receiving systemic corticosteroids at doses above 10 mg/day (prednisone or equivalent), a 28 day washout period prior to Cycle 1 Day 1 study drug dosing is required. Systemic doses above 10 mg/day (prednisone or equivalent) are allowed for the exceptions of tumor flare reaction (TFR) treatment at any time, for obinutuzumab cytokine release syndrome prophylaxis on C1D1, and treatment of infusion related reactions at any time.

Experimental therapy or radiotherapy is prohibited during the Treatment phase.

Study procedures

Before study entry (Screening Phase), throughout the Treatment Phase, and during Follow-up, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these measurements is to ensure adequate safety and tolerability. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Study Flow Chart is provided in Appendix 1.

screening Phase

Screening procedures will be performed up to 28 days before Cycle 1 Day 1, unless otherwise specified. All subjects must first read, understand, and sign the IRB-approved informed consent form (ICF) before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to signing the ICF and are considered standard of care may be used as screening assessments if they fall within the 28 day screening window.

The following procedures will be performed during the Screening Phase:

- Informed consent
- Review of eligibility criteria
- Medical history and demographics
- Record the Follicular Lymphoma International Prognostic Index (FLIPI) score (Appendix 3) and tumor burden (Appendix 4)
- Review of AEs and concomitant medications
- Complete physical exam
- ECOG performance status
- Vital signs, weight, and height
- 12 lead ECG
- Imaging by CT/ PET/ or MRI
- Bone marrow aspirate and biopsy (can be done within 90 days of study entry)
- Clinical laboratory tests for:
    - Hematology (CBC with differential)
    - Serum chemistry (electrolytes [Na, K, Cl, bicarbonate, Ca], glucose, blood urea nitrogen [BUN], creatinine, alkaline phosphatase, AST, ALT, total protein, albumin, total bilirubin, lactate dehydrogenase [LDH], β2-microglobulin), uric acid

- Coagulation (PT/ INR, aPTT)
- Serum pregnancy test (for women of childbearing potential only) will be performed 10- 14 days and again 24 hours prior to writing an initial prescription for lenalidomide.
- Hepatitis serologies (hepatitis B surface antigen [HBsAg], hepatitis B core antibody [anti- HBc, hepatitis C antibody])
- HIV 1 and 2 antibody
- TSH

- Optional core needle or fine needle aspiration (FNA) biopsy will be obtained by Interventional Radiology from an accessible lymph node under ultrasound or CT- scan guidance within 28 days prior to the first infusion of obinutuzumab.
- Optional research blood sample, 10ml EDTA tube to be collected prior to infusion of obinutuzumab.
- Determination of creatinine clearance (modified Cockcroft- Gault estimate, Appendix 2) utilizing actual body weight

Treatment phase

Cycle 1/Day 1

Subjects who are deemed eligible will return to the clinic on Cycle 1, Day 1. The following procedures will be performed on Day 1:

Pre- Dose

- Confirmation of eligibility
- Complete physical exam
- ECOG performance status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
  - Determination of creatinine clearance (modified Cockcroft- Gault estimate) utilizing actual body weight
- Review of AEs and concomitant medications
- Dispense lenalidomide

Dosing

- In- clinic administration of obinutuzumab

Cycle 1/Day 8

The following procedures will be performed on Cycle 1, Day 8 (±2 days):

Pre- Dose

- Complete physical exam
- ECOG performance status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
- Optional research blood draw, 10 ml EDTA tube
- Optional research FNA of an accessible lymph node
- Determination of creatinine clearance (modified Cockcroft- Gault estimate) utilizing actual body weight
- Review of AEs and concomitant medications

Dosing

- In- clinic administration of obinutuzumab

Cycle 1/Day 15

The following procedures will be performed on Cycle 1, Day 15 (±2 days):

Pre- Dose

- Complete physical exam
- ECOG performance status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
  - Determination of creatinine clearance (modified Cockcroft- Gault estimate) utilizing actual body weight
- Review of AEs and concomitant medications

Dosing

- In- clinic administration of obinutuzumab

Cycle 2/Day 1and every 4 weeks until Cycle 18 or Treatment Termination

Visits will be performed every 4 weeks (± 2 days) starting at Cycle 2, Day1. Visit windows are relative to Day 1 visit date. The following procedures will be performed:

Pre- Dose

- Complete physical exam
- ECOG performance status
- Vital signs and weight

- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
  - Determination of creatinine clearance (modified Cockcroft- Gault estimate) utilizing actual body weight
- Review of AEs and concomitant medications
- Drug accountability
- Dispense lenalidomide
- CT/ PET/ or MRI on Cycle 4/ Day 1, Cycle 7/ Day 1, Cycle 10/ Day 1 only, Cycle 14/ Day 1
- Optional research blood draw on Cycle 4/ Day 1 only, 10 ml EDTA tube

Dosing

- In- clinic administration of obinutuzumab on Day 1 of Cycle 2, 3, 4, 5, 6, 8, 10,12, 14, 16, 18

Cycle 20/Day 1 and every 4 weeks until Cycle 30 or Treatment Termination

Visits will be performed at Cycle 20, Day 1, Cycle 22, Day 1, Cycle 24, Day 1, Cycle 26, Day 1, Cycle 28, Day 1, Cycle 30, Day 1 (± 7 days). Visit windows are relative to Day 1 visit date. The following procedures will be performed:

Pre- Dose

- Complete physical exam
- ECOG performance status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
- Review of AEs and concomitant medications
- CT/ PET/ or MRI on Cycle 14/ Day 1, Cycle 20/ Day 1, and Cycle 26, Day1 only

Dosing

- In- clinic administration of obinutuzumab on Day 1 of Cycle 14, 16, 18, 20, 22, 24, 26, 28, and 30.

End of Treatment Visit

The end of treatment visit will occur approximately 4 weeks (±14 days) from last dose of study drug (end of cycle 30) for patients who complete the planned study treatment. If the subject comes in for a regular study visit and the investigator suspects PD, or if the subject wants to discontinue treatment for any other reason outlined in Section 5.6, the regular visit will

become the termination visit. Adverse events and hospitalizations will be recorded up to 30 days after the last dose of study drugs.

The following procedures will be performed:

- Complete physical exam
- ECOG performance status
- Vital signs
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
  - TSH
- For consenting patients and those undergoing a biopsy at PD as part of standard of care, a research sample will also be collected
- Optional research blood draw at the time of PD only, 10 ml EDTA tube
- Review of AEs and concomitant medications
- Drug accountability
- CT/ PET/ or MRI

Response evaluation

Response Evaluation visits will be performed at the following timepoints:

- At approximately cycle 4, day 1, cycle 7, day 1, cycle 10, day 1, cycle 14, day 1, cycle 20, day 1, cycle 26, day 1 (±7 days).
- At the End of treatment visit (±2 weeks), this will also serve as the 120 week response assessment.
- Every 24 weeks during the follow up phase for 3 assessments, then annually until the subject exhibits disease progression (± 4 weeks).
- If clinical suspicion for PD is raised at any time outside of a pre- determined response evaluation, imaging can be requested at the discretion of the investigator.

The following procedures will be performed in conjunction with standard visits as follows:

- Radiologic exam by CT, PET/ CT, or MRI scan
- Bone marrow biopsy and/ or aspirate, to be done once to confirm CR if marrow was involved with lymphoma at screening
- Overall response assessment

follow up phase

The follow up period will start at the end of treatment visit (after cycle 30) Patients will be assessed every 24 weeks (± 4 weeks) for 3 assessments, and then annually (± 4 weeks) up to the end of the follow up period, 2 years after the last subject's last study drug dose.

For patients who have completed treatment the follow up assessments will include:

- Physical exam including vital signs and ECOG PS

- Clinical laboratory tests for hematology and serum chemistry
- Second primary malignancy (SPM)
- Adverse events and hospitalization up to 30 days after last study drug
- Overall survival
- Radiologic assessment (CT, PET/ CT, or MRI)

For patients who discontinue treatment due to progressive disease or relapse, follow up assessments will include:

- Overall survival
- Subsequent anti- lymphoma therapy (including the time of initiation of therapy and best response to first subsequent anti- lymphoma treatment utilized after discontinuation from this study)
- Adverse events and hospitalization up to 30 days after last study drug (Safety visit)
- SPM

Survival Follow up

Once subject progresses or starts use of alternative antineoplastic therapy (for subjects who have not withdrawn consent), they will be contacted approximately q 12 weeks (± 2 weeks) for 1 year and then q 24 weeks (± 4 weeks) from the last dose of study drug by clinic visit or telephone to assess survival and the use of alternative antineoplastic therapy and stem cell transplant. Subjects will be contacted until: death, consent withdrawal, lost to follow up, or study termination, whichever comes first.

Missed evaluations

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the opinion of the investigator, medically unnecessary or unsafe. In that case the missed evaluation should be abandoned.

Description of Procedures

Medical History

The subject's medical history through review of the medical records and by interview will be collected and recorded. A disease history including date of initial diagnosis and baseline symptoms and severity should be recorded.

Physical Examination

The physical exam should include the general state of the subject, examination of the skin, eyes, ear, nose, throat, lungs, heart, abdomen, extremities, lymphatic system. Nervous system should be included if clinically indicated.

Vital Signs

Vital signs including weight, blood pressure, heart rate, respiratory rate, and temperature will be recorded. Height will only be recorded during the screening phase, Visit 1.

ECOG PS

Table 5: Performance status definitions

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

Concomitant Medications

All concomitant medications including over the counter medications and supplements should be recorded starting during the screening phase and continued through the treatment phase as well as up to 30 days after last study drug dose. Concomitant medications will be captured in the electronic medical record.

Adverse Events

Only laboratory abnormalities which result in signs or symptoms that require intervention or follow up and are considered clinically significant should be recorded as AEs. See Section 10 for more details. All other AEs whether serious or non-serious will be entered in RedCap/ CORe (the electronic case report form) from the time of first protocol intervention up until 30 days after the last dose of study drugs. The Principal Investigator or designee will be responsible for assigning attribution to the study drugs.

CT, PET/CT, MRI scans

A CT scan (with contrast unless contraindicated) of the neck, chest, abdomen and pelvis are required for disease assessment. A "diagnostic quality" combined PET/ CT with IV and PO (or water) contrast is an acceptable alternative to CT scans. In addition, if independent CTs are performed, a PET can also be used to augment tumor assessment. In the case where a CT with contrast is contraindicated, an alternative would be an MRI of the chest, abdomen, and pelvis.

In general, follow-up assessments will be done by CT scans. PET-CT scan is encouraged and should be done at baseline and repeated to confirm complete remission and/ or at treatment discontinuation, unless the subject's insurance will not cover a PET as part of standard of care. In this situation, CTs are acceptable alternatives. For lymphomas that are not FDG-avid at screening, PET does not need to be repeated in subsequent assessments.

Response Assessment

Response assessment will be completed by the Principal Investigator using Cheson 2014 Lugano Criteria. At screening, up to 6 target lesions will be selected and followed for the duration of the study. Information on extranodal involvement can also be recorded. The best ORR will be documented.

Hematology

Hematology studies must include a complete blood count (CBC) with differential. Coagulation studies performed at screening will include a PT and PTT.

Serum Chemistry

Chemistry must include electrolytes (sodium, potassium, chloride, bicarbonate), blood urea nitrogen, creatinine, glucose, calcium, alkaline phosphatase, ALT, AST, total bilirubin, albumin, total protein, LDH, β2-microglobulin), and uric acid.

Coagulation Studies

Coagulation studies performed at screening will include PT/ INR and activated PTT.

Hepatitis Serologies

Hepatitis serologies include Hepatitis C antibody, Hepatitis B surface antigen, Hepatitis B core antibody. For patients with a positive Hepatitis C antibody, Hepatitis C viral PCR should be performed to evaluate for active infection.

HIV serologies

HIV serologies include antibodies to HIV 1 and 2.

Creatinine Clearance

Determination of creatinine clearance using the modified Cockcroft-Gault estimate (utilizing actual body weight) should be calculated during the Screening phase and at the start of each cycle to determine dose of lenalidomide (Section 5.4.3).

Pregnancy Test

During screening, two serum pregnancy tests will be required for women of childbearing potential. Females of childbearing potential are defined as: all females who are menstruating, amenorrheic from previous treatments, under 50 years of age, and/or perimenopausal, and do not qualify for the females not of reproductive potential category.

Females not of reproductive potential are defined as: females who have been in natural menopause for at least 24 consecutive months, or who have had a hysterectomy and/or bilateral oophorectomy, or female children who have not started menstruating.

Females of reproductive potential must also adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.
Urine pregnancy tests should be performed as clinically indicated for women of childbearing potential.

Bone Marrow Biopsy and Aspirate

An unilateral bone marrow biopsy and aspirate will be done at screening or up to 90 days before the first dose of study drug. Thereafter, bone marrow biopsy and aspirate will only be required to confirm CR if it was positive at screening.

ECG

An electrocardiogram will be conducted during screening to evaluate for clinically significant cardiac arrhythmias.

Determination of FLIPI Score

During the screening phase, subject's FLIPI score will be calculated and recorded as outlined in Appendix 3.

Determination of Tumor Burden Status

During the screening phase, subject's tumor burden, either high or low will be determined using the GELF criteria as outlined in Appendix 4.

Blood Sampling and Tumor Tissue Collection for Correlative Studies

Blood and tumor sample collection for biomarker studies is optional. In consenting subjects, 10 ml of blood sample (purple top, EDTA) will be collected within 28 days prior to the first infusion of obinutuzumab, C1D8 (± 2 days), C4D1 (± 2 days), and at the time of disease progression (±14 days). These samples will be transported within 6 hours of collection to Dr. Neelapu's laboratory for processing at the South Campus Research Building I, Room 4.3206, at M. D. Anderson Cancer Center (MDACC).

In consenting patients, core needle biopsies and FNA will be obtained by Interventional Radiology from an accessible lymph node under ultrasound or CT-scan guidance within 28 days prior to the first infusion of obinutuzumab, on C1D8 (±2 days), and at the time of disease progression (±14 days). Whenever feasible, up to 3 cores will be obtained using 18 or 20 gauge needles as deemed appropriate by an Interventional Radiologist. The three cores will be placed into normal saline and transported within 6 hours of collection on ice to Dr. Neelapu's laboratory for processing at the South Campus Research Building I, Room 4.3206, at MDACC. The cores will be processed as follows: i) the first core will be disaggregated and analyzed by flow cytometry and single cell RNA sequencing, ii) second core will be formalin-fixed and paraffin-embedded for IHC, iii) third core will be snap frozen for DNA, RNA, or protein isolation. If fresh biopsies are not feasible, archival tissue from prior tumor biopsy may be used for biomarker studies.
Samples will be maintained until the study has been terminated.

SUBJECT COMPLETION AND WITHDRAWAL

Completion

A subject will be considered to have completed the study if he or she has died before the end of the study, has not been lost to follow up, or has not withdrawn consent before the end of the study.

Treatment Discontinuation

Study treatment will be discontinued in any of the following events:

- SD after 6 cycles of therapy.
- Confirmed PD
- Unacceptable toxicity: an intercurrent illness or AE that prevents further study drug administration beyond 28 days
- Treatment discontinuation by subject beyond 28 days
- Investigator decision
- Subject becomes pregnant

All subjects, regardless of reason for discontinuation of study treatment will undergo a treatment termination visit and followed for progression and survival.

Study Exit/Withdrawal

Exit from study (including all follow up) will occur under the following circumstances:

- Withdrawal of consent for follow-up observation by the subject
- Lost to follow up
- Study termination by the Investigator
- Death

If a subject is lost to follow up, every reasonable effort should be made by the study personnel to contact the subject. The measures taken should be documented.

When a subject withdraws before the completing the study, the following information should be documented:

- Reason for withdrawal

Whether the subject withdraws full consent (withdraws consent for treatment and all follow up including further contact) or partial consent (withdraws consent to treatment but agrees to participate in follow up visits).

Statistical

General Considerations

This is an open-label, Phase II study investigating the efficacy and safety of obinutuzumab and lenalidomide in previously untreated subjects with FL. The study will include 90 subjects in one treatment arm.

Response Assessment

Response assessments will be done and recorded by the Principal Investigator. The response criteria are based on the revised criteria for malignant lymphoma described in the Lugano Criteria, international Working Group for NHL (Cheson 2014). In addition, will examine response assessment based on the Cheson 2007 response criteria for historical comparison.

Safety Monitoring

The Principal Investigator or a physician designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart, Appendix 1 and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.03. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment. The study investigators and data coordinators are

responsible for entering the data and safety for this study including causality. For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

Safety data will be monitored by the Principal Investigator and in accordance with institutional policies. The Investigator will record the action taken with the study drugs as a result of an AE or SAE, as applicable (e.g., discontinuation, interruption, or reduction of study drugs, as appropriate) and report if concomitant and/ or additional treatments were given for the event. AEs and SAEs will be reviewed on an ongoing basis to identify safety concerns.

For subjects with a history of Hepatitis B or C, standard of care monitoring for viral reactivation will be conducted. Subjects with a history of Hepatitis B will be required to undergo hepatitis B reactivation prophylaxis unless contraindicated.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered or death (due to the SAE).

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

Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected, any changes on the investigational brochure or any other safety information that changes the risk/ benefit profile of obinutuzumab or lenalidomide during the conduct of the study; any finding from tests in laboratory animals that suggests a significant risk for human subjects; including reports of mutagenicity, teratogenicity, or carcinogenicity. The Principal Investigator shall notify his/ her IRB promptly of these new serious and unexpected AEs or significant risks to subjects. The Investigator must keep copies of all AE information, including correspondence with Genentech, Celgene, and the IRB, on file.

Definition of Analysis Populations

The following definitions will be used for the efficacy and safety analysis:

All treated population: The subjects who enrolled in the study and had at least 1 dose of study drug.

Response evaluable population: The subjects in the all treated population who have measurable disease at baseline and have at least one adequate post-treatment disease assessment by the investigator.

Safety analysis population: All enrolled subjects who receive at least 1 dose of study drug (same as the all treated population).

The all treated population will be used for analyzing efficacy endpoints unless specified otherwise. The response evaluation population will be used for sensitivity analysis of efficacy endpoints. The safety population will be used for safety analysis.

Endpoint Data Analysis

Baseline Characteristics

Subject demographics (age, sex, race/ ethnicity) and other baseline characteristics (ECOG PS, tumor burden, FLIPI score) will be summarized. Summary statistics will include means, standard deviations, and medians for continuous variables and proportions for categorical variables. Compliance parameters including number of completed cycles, number of dose modifications, and reasons for discontinuation will also be similarly summarized.

Primary Efficacy Endpoint

The primary efficacy endpoint is PFS rate at 2 years. Response will be assessed by the investigator based on the 2014 Cheson Lugano criteria. The 2-year PFS rate will be calculated and corresponding 95%CI will be derived.

Analysis Methods

The primary analysis for all efficacy endpoints will be conducted based on the all treated population. PFS is defined as the time from the treatment start date (Cycle 1, Day 1) until the first date of objectively documented progressive disease or date of death from any cause. Patients will be censored at the last follow-up date if progression or death has not occurred during follow-up. If a patient has missing data (incomplete CT scan), all other available CT, PET/ CT or MRI of the patient will be used for the analysis. Kaplan-Meier method will be used to estimate the PFS. Corresponding 95%CI will be summarized. Cox proportional hazards models will be used to assess the effects of patient prognostic factors on time-to-event endpoints. The final analysis will be performed when the last patient is followed for 3 years after last study drug dose.

Secondary Efficacy Endpoints

CR rate at 120 weeks (± 4 weeks) will be determined by the PI (Cheson, Lugano classification 2014). The number and percentage of subjects with a CR at 120 weeks will be tabulated.

ORR (CR + PR) will be assessed by the investigator based on Cheson, Lugano 2014. The number and percentage of subjects with an ORR will be tabulated. The best ORR will be recorded.

DOR will be measured from the time by which measurement criteria for CR or PR, whichever is recorded first, is met until death or the first date by which progressive disease is documented. Subjects who are progression free and alive at the time of clinical cut-off or have unknown status will be censored at the last tumor assessment. Subjects with no baseline disease assessment will be censored on cycle 1, day 1. Non-responders will be excluded from the analysis for DOR. Kaplan-Meier methodology will be used to estimate event-free curves, median, and 95%CI.

EFS will be measured from the date of cycle 1, day 1 to the date of first documented progression, transformation to diffuse large B-cell lymphoma, initiation of new anti-lymphoma treatment, or death. Kaplan-Meier methodology will be used to estimate event-free curves, median, and 95%CI.

OS will be measured from the date of cycle 1, day 1 to the date of death regardless of cause. For subjects who have not died, subjects will be censored at the time of last contact. Kaplan-Meier methodology will be used to estimate event-free curves, median, and 95%CI.

Safety Analysis

Analysis of safety data will be conducted on the safety population. Safety summaries will include tabulations in the form of tables and listings. The frequency (number and percentage) of treatment-emergent AEs will be reported. Additional AE summaries will include AE frequency by AE severity and by relationship to study drug.

Clinically significant abnormal laboratory values will be summarized.

Handling of Missing Data

Subjects lost to follow up will be included in the statistical analyses up to the point of their last evaluation or contact.

Data for subjects without disease progression or death will be censored at the date of the last tumor assessment and before the date of initiation of alternative anticancer therapy. Subjects with no post-baseline assessment will be censored on cycle 1, day 1.

Determination of Sample Size

The primary endpoint is PFS. It is expected that the experimental regimen will achieve better efficacy compared to the standard of care for this population. It was reported that the standard of care of lenalidomide and rituximab in this patient population had a two-year PFS rate of 86.5%(95%CI: 77% 97.2%). We will enroll a total of 90 patients with an accrual rate of 4 patients per month. All patients will be followed for at least 3 years or until death. The final analysis will be performed when the last patient is followed for 3 years. When the sample size is 90, a two-sided 95%CI for the PFS rate at 2 years will extend 0.087 from the observed rate for an expected rate of 77%(nQuery Advisor 7.0). According to our previous experience, we will be able to obtain biomarker data from about 30%of patients enrolled. We will explore the correlation between the biomarkers and clinical outcomes.

Trial Monitoring

Due to the fast accrual planned for the study and long median PFS time expected for the experimental regimen, a formal futility monitoring rule is not feasible.
Because of the limited number of patients who have received the combination treatment, for patient safety we will monitor the prohibitive toxicity, defined as frequent discontinuation (>2 discontinuations) of treatment during cycles 1 and 2. The prohibitive toxicity rate of 15%or higher will be considered unacceptable. The prior probability of the rate is assumed to follow a Beta (0.3, 1.7) distribution with two patients worth of information. We will monitor patients by a cohort size of 10. At any time after at least 10 patients have completed toxicity evaluations, the trial will be stopped if the following statement is true

$$\Pr[\text{prohibitive toxicity rate} > 15\% \mid \text{data}] > 0.95,$$

which means that the trial will be stopped for toxicity if the posterior probability of the rate being greater than 15%is greater 95%

Patients will be monitored by a cohort size of 10 according to the following stopping boundaries for prohibitive toxicity at cycles 1 and 2:

Number of patients evaluated	Stop if ≥ prohibitive toxicities observed
10	4-10
20	7-20
30	9-30
40	11-40
50	13-50
60	15-60
70	16-70
80	18-80
90	Always stop with this many patients

Operating characteristics for the stopping rules
For prohibitive toxicity monitoring

True Prohibitive Toxicity Rate	Probability Stop Early	Average sample size
0.05	0.0011	89.92
0.10	0.0166	88.78
0.15	0.1226	83.13
0.20	0.4483	67.77
0.25	0.8052	47.27
0.30	0.9639	31.40

Toxicity and response summaries will be submitted to the IND Office Medical Affairs & Safety after the first 10 evaluable participants are treated in the study and every 10 evaluable participants thereafter.

To ensure patient safety, we will also utilize an additional monitoring rule for treatment-related death. Any treatment-related death occurring at any time will result in pause in accrual pending complete evaluation and discussion between the Principal Investigator and the FDA.
Any second malignancy other than non-melanoma skin cancer that occurs anytime during the study will result in pause in accrual pending complete evaluation and discussion between the Principal Investigator and the FDA.

The above stopping boundaries and operating characteristics are calculated using MultcLean (v.2.1.0) design software downloaded from
http://biostatistics.mdanderson.org/SoftwareDownload.

Reporting of Adverse Events

Assessment of Safety

Timely, accurate, and complete reporting and analysis of safety information is the responsibility of the PI and will be conducted in accordance with Institution policies.

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

Adverse Events

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

This includes the following:

AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with follicular 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.

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 time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.
- 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 sponsors guidelines, and Institutional Review Board policy

Methods and Timing for Assessing and Recording Safety Variables

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

Adverse Event Reporting Period

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

Assessment of Adverse Events

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

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

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

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

Procedures for Eliciting, Recording, and Reporting Adverse Events

Eliciting Adverse Events

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

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

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

Specific Instructions for Recording Adverse Events

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

Diagnosis versus Signs and Symptoms

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

Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 10.2.1), 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".

Preexisting Medical Conditions

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

Hospitalizations for Medical or Surgical Procedures

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

Hospitalizations for the following reasons do not require reporting:

Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions

Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or

Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v4.0.

Pregnancy

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 obinutuzumab or lenalidomide, or within 18 months of the subject's last dose of obinutuzumab and 3 months of the last dose lenalidomide, are considered immediately reportable events. Obinutuzumab or lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Genentech, Inc. and Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

IF THE OUTCOME OF THE PREGNANCY WAS ABNORMAL (E.G., 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 OTHERAPPROPRIATE METHOD, WITHIN 24 HOURS OF THE INVESTIGATOR'S KNOWLEDGE OF THE EVENT USING THE SAE REPORT FORM, OR APPROVED EQUIVALENT FORM.

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

method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

Male Subjects

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

If the female partner of a male study subject becomes pregnant while the study subject is receiving obinutuzumab or within 6 months of the last dose of obinutuzumab, a report should be completed and expeditiously submitted to Genentech.

Post-Study Adverse Events

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

Adverse Events of Special Interest (AESIs)

The following AEs are considered of special interest and must be reported to Sponsor expeditiously (see Section 10.3.2.9 for reporting instructions) **irrespective of regulatory seriousness criteria:**

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 and based on the following observations: - Treatment-emergent ALT or AST > 3 x baseline value in combination with total bilirubin > 2 x ULN (of which > 35% is direct bilirubin) - Treatment-emergent ALT or AST > 3 x baseline value in combination with clinical jaundice

Suspected transmission of an infectious agent by the study treatment, 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 study treatment is suspected

The obinutuzumab Events of Special Interest are:

Tumor Lysis Syndrome (serious and non-serious events)

Second malignancies

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.

MedWatch 3500A Reporting Guidelines

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 and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A 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

- **Reporting to Regulatory Authorities, Ethics Committees and Investigators**

MD Anderson Cancer Center as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the Regulatory Authorities (FDA) where it has filed a clinical trial approval, in compliance with local regulations.

MD Anderson Cancer Center 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.

Additional Reporting Requirements for IND Holders (if applicable):

For Investigator-Initiated 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 or lenalidomide. An unexpected adverse event is one that is not already described in the obinutuzumab or lenalidomide 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 or lenalidomide. An unexpected adverse event is one that is not already described in the obinutuzumab or lenalidomide 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., summary letter).

FDA fax number for IND Safety Reports:

Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to

Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-4630
Email: usds_aereporting-d@gene.com

And MD Anderson Cancer Center will be responsible for the distribution of safety information to Site IRB.

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

Expedited Reporting by Investigator to Celgene Study Close-Out

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events of being related to lenalidomide based on the Investigator Brochure. In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.SAEs are defined above, Section 10.1.2. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/ 1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (RV-CL-FL-PI-005632) 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.

Investigator Communications with Celgene:

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

Maintenance of safety information

Safety information will be maintained in RedCap/ CORe. At a minimum, at the end of the treatment phase (="last patient off treatment") as well as the end of the follow-up phase (="last patient out") of the Study, the Principal Investigator shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent review of the safety data may be necessary, e.g. to fulfill a regulatory request, and as

such the data shall be made available within a reasonable timeframe at Genentech and/ or Celgene's request. The data must also be available at the request of the FDA and the IRB.

Study Close-Out

Any study report submitted to the FDA by the Sponsor- Investigator 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 (GA101) Protocols
Email: ga101-gsur@gene.com

Study administration

Regulatory and Ethical Compliance

This clinical study was designed and will be implemented in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practices, with the ethical principles laid down in the Declaration of Helsinki, and in compliance with our IRB guidelines.

The Investigator or his/ her authorized representative will be provided a copy of the IRB letter that grants formal approval and a copy of the IRB approved lCF before entering subjects in this study.

Informed Consent

The ICF will document the study- specific information the Investigator or his/ her designee provides to the subject and the subject's agreement to participate.
The Investigator or designee (designee must be listed on the Delegation of Authority log), must explain in terms understandable to the subject the purpose and nature of the study, study procedures, anticipated benefits, potential risks, possible AEs, and any discomfort participation in the study may entail. Each subject must provide a signed and dated ICF before any study- related (nonstandard of care) activities are performed. The original and any amended signed and dated ICFs must remain in the subject's file. A copy of each signed consent form must be given to the subject.

Quality Control and Quality Assurance

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki and in accordance with FDA regulations and the guidelines of Good Clinical Practices.

Protected Subject Health Information Authorization

Information on maintaining subject confidentiality in accordance with our local and national subject privacy regulations must be part of the informed consent process. A HIPPA consent form will be used. The investigator or designee must explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with the Principal Investigator and his/ her designees, regulatory agencies, and the IRB. The Investigator will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. If a subject withdraws permission to use protected health information, it is the Investigator's responsibility to obtain the withdrawal request in writing from the subject and to ensure no further data will be collected from the subject. Any data collected before withdrawal will be used in the analysis of the study results.

Record Retention

The Investigator/ study staff must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Essential documentation includes, but is not limited to, the package insert signed protocols and amendments, IRB approval letters, signed ICFs (including subject confidentiality information), drug dispensing and accountability records, signed (electronically), dated and completed CRFs, and documentation of CRF corrections, SAE forms transmitted to Genentech and/ or Celgene, or designee, and notification of SAEs and related reports, source documentation, and all relevant correspondence and other documents pertaining to the conduct of the study.

Investigational Drug Accountability

Obinutuzumab and lenalidomide must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the Investigator or other site personnel supply obinutuzumab or lenalidomide to other Investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol without prior authorization from Genentech/ Celgene.

Accountability records for obinutuzumab and lenalidomide must be maintained and readily available for inspection by representatives of Genentech or Celgene and are open to inspections by regulatory authorities at any time.

Investigator Responsibilities

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

Genentech Drug Safety Fax: (650) 225- 4682 OR (650) 225- 5288

Celgene Corporation
Attn: Medical Affairs Operations
Connell Corporate Park
400 Connell Drive Suite 700
Berkeley Heights, NJ 07922

The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above (Section 10.1.2) are present. The investigator is responsible for reporting adverse events to Genentech and Celgene as described.

The investigator will forward a copy of the Final Study Report to Genentech upon completion of the Study.

Publication of Study Results

The results of this study may be used for papers, abstracts, posters, or other material presented at scientific meetings or published in professional journals or as part of an academic thesis by an Investigator. In all cases, to avoid disclosures that could jeopardize proprietary rights and to ensure accuracy of the data, Genentech and Celgene reserve the right to preview all manuscripts and abstracts related to this study, allowing the Investigator sufficient time to make appropriate comments before submission for publication. The Investigators shall be listed as lead authors on manuscripts and reports of study results. The Principal Investigator will forward a copy of the Publication to Genentech upon completion of the Study.

Study Completion

The study is expected to be completed approximately 2 years after the last subject's last study drug dose.

Any study report submitted to the FDA by the Principal Investigator 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 (GA101) Protocols
Email: ga101-gsur@gene.com
Fax: 866-706-3927

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Appendix 1 Study Flowchart

	Screening Phase	Treatment phase							End of Treatment	Follow up Phase
Treatment Cycle/ Title	Screening Visit				To be repeated up to 18 cycles			Cycles 20-30	End of Treatment Visit	Follow up visits[b]
		1[a]	2[a]	3	4	5	6			
Scheduling Window[c] (Days)	-28 to -1	± 2	± 2	± 2	± 2	± 2	± 2	± 7	± 14	q 24 weeks x 3 visits, and then annually (± 4 weeks)
Clinical/Administrative Assessments										
Informed Consent[d]	X									
Inclusion/ Exclusion Criteria	X	X								
Demographics and Medical History	X									
Record FLIPI score and GELF tumor burden	X									
Concomitant Medication Review[e]	X	Day 1, 8, 15	X	X	X	X	X	X	X	
Drug accountability			X	X	X	X	X			
Obinutuzumab Administration[f]		Day 1, 8, 15	X	X	X	X	X	X		
Lenalidomide prescription[g]		X	X	X	X	X	X			
Review Adverse Events[h]		Day 1, 8, 15	X	X	X	X	X	X	X[h]	X[h]
Physical Examination	X	Day 1, 8, 15	X	X	X	X	X	X	X	X
Vital Signs and Weight[i]	X	Day 1, 8, 15	X	X	X	X	X	X	X	X
ECOG Performance Status	X	Day 1, 8, 15	X	X	X	X	X	X	X	X
ECG	X									
Laboratory Assessment										
Pregnancy Test – Serum b-HCG[j]	X									
PT/ INR and aPTT[k]	X									
HIV 1 and 2 antibody	X									
HBsAg, anti-Hep Bc, Hep C Ab[l]	X									
CBC with Differential	X	Day 1, 8, 15	X	X	X	X	X	X	X	X

Comprehensive Serum Chemistry Panel	X	Day 1, 8, 15	X	X	X	X	X	X	X	X
Creatinine clearance (modified Cockcroft-Gault)	X	Day 1, 8, 15	X	X	X	X	X			
TSH	X								X	
Bone marrow biopsy and aspirate[m]	X									
Optional research Biopsy (core needle or FNA)[n]	X	Day 8							X	
Optional research blood sample[o]	X	Day 8			Day 1				X	
Radiologic Assessment										
Response Assessment: CT/PET/or MRI[p]	X				X			X	X	X

a. For each Cycle, assessment is assumed to be on Day 1 unless otherwise specified.
b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status as per the follow-up schedule until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first. Survival assessments will continue up to 3 years after the last study drug.
c. Treatment cycles are 28 days; however the treatment cycle interval may be increased due to toxicity according to the dose modification guidelines provided in Section 5.4. If the interval is increased, all procedures except for response assessment should be performed based on the new dosing schedule
d. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 28 days prior to the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.
e. Record all medications taken within 28 days of screening visit. Concomitant medications – Enter new medications started through the treatment phase as well as up to 30 days after the last study drug dose. Record all medications taken for SAEs as defined in Section 10.1.2.
f. Obinutuzumab administration will occur on day 1, 8, and 15 of Cycle 1; Day 1 of cycles 2-6; Day 1 of cycles 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, and 30. Hypersensitivity reaction should be managed according to institution policy and as outlined in Section 6.4.
g. Patients with creatinine clearance (CrCl) >60 mL/min as determined by modified Crockcroft-Gault will receive 6 cycles of lenalidomide, 20mg daily on days 1-21 of a 28 day cycle (± 2days). Patients with a CR after 6 cycles will then receive 10mg of lenalidomide daily on days 1-21 every 28 days (± 2days) for a total of 18 cycles. Patients with a PR after 6 cycles will continue 20mg of lenalidomide on days 1-21 every 28 days (± 2days) for 3 to 6 more cycles until they achieve a CR at which time they will receive 10mg lenalidomide on days 1-21 every 28 days (± 2days) for the remainder of 18 cycles. Patients with a PR after 12 cycles will then receive 10mg of lenalidomide on days 1-21 every 28 days (± 2days) for the remainder of 18 cycles. Patients that fail to achieve at least a PR after 6 cycles with discontinue study drug. For subjects with earlier evidence of nonresponse that warrants change in therapy in the opinion of the treating physician, will discontinue study drug.
h. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.03. All AEs, will also be evaluated for seriousness and handled as discussed in Section 10.1. Unresolved abnormal labs that are drug related AEs should be followed weekly until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range. AEs will be monitored until 30 days after last study drug dose.
i. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at Screening visit 1 only.
j. For women of child-bearing potential, a serum pregnancy test should be performed10-14 days and 24 hours prior to the initial prescription of lenalidomide. . Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.

k. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. For subjects requiring anticoagulation during the study, appropriate coagulation tests should be done when clinically indicated to monitor anticoagulation.
l. These screening tests need to be finalized prior to the first dose of obinutuzumab. HCV RNA will be performed if Hep C Ab is positive.
m. All subjects will have bone marrow biopsy/aspirate performed at baseline (within 90 days of cycle 1, day 1). Subsequent bone marrow assessments will only be performed in subjects who have bone marrow involvement at baseline to confirm disease response (CR).
n. In consenting patients, a fresh tumor biopsy can be collected. If this is not possible, archival tumor tissue (paraffin embedded) when available should be collected at Screening for biomarker analyses. On C1D8 (± 2 days) an optional research biopsy should be performed. At the time of confirmed PD, if a tumor biopsy is planned as part of routine clinical practice, for consenting patients, a fresh tumor sample should be collected and processed.
o. Biomarker blood samples will be collected and processed. During screening or within 28 days of the first infusion of obinutuzumab, on cycle 1, day 8 (± 2 days), cycle 4, Day 1 (± 2 days), and at the time of documented PD (±14 days), blood biomarker collection should be performed.
p. Disease response assessment is based upon Cheson 2014 lymphoma response criteria and Cheson 2007 revised response criteria. "Diagnostic quality" PET-CT with oral contrast/or water and IV contrast should be performed at Screening unless there is a contraindication. If CT scans have already been completed, a PET can be performed at Screening. PET/CT or CT and PET should be repeated to confirm complete remission and/or at treatment discontinuation. For lymphomas that are not FDG-avid, PET does not need to be repeated in subsequent assessments. CTs of the neck, chest, abdomen, and pelvis with IV contrast will otherwise be conducted at baseline for those who do not undergo diagnostic quality PET-CT, at approximately Cycle 4, Day 1 (± 7 days), Cycle 7, Day 1 (± 7 days), Cycle 10, Day 1 (± 7 days), Cycle 14, Day 1 (± 7 days), Cycle 20, Day 1 (± 7 days), Cycle 26, Day 1 (± 7 days), and at the completion of treatment. During the follow-up phase, response assessment will occur every 24 weeks (±4 weeks) x 3 assessments, and then annually (±4 weeks) until study completion, PD, withdrawal of consent, death, or lost to follow up, whichever comes first. When a contraindication prevents CT, an MRI of the chest, abdomen/pelvis can be substituted. In subjects who discontinue study therapy without confirmed disease progression, a radiological assessment should be performed at the time of treatment discontinuation (i.e. date of discontinuation ± 2 weeks). If previous scan was obtained within 4 weeks prior to the date of discontinuation, then a repeat scan at treatment discontinuation isn't mandatory.

Appendix 2 Calculation of Creatinine Clearance Using the Cockcroft-Gault Formula

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

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

Reference:

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

Appendix 3 FLIPI Score

FLIPI (Solal Celigny, 2004)

Score 1 point for each of the following risk factors:

- Hemoglobin, g/dL < 12 g/L
- Number of nodal areas >4 (The spleen is considered as an extranodal site and not a nodal area)
- Age, years > 60
- LDH level > normal
- Ann Arbor Stage III/IV

RISK GROUPS	Number of Factors
Low	0-1
Intermediate	2
High	3-5

Appendix 4 Determination of Tumor Burden

Normal lactate dehydrogenase
Largest nodal or extranodal mass < 7 cm
No more than 3 nodal sites with a diameter > 3 cm
Less than 5×10^9/L circulating tumor cells
Hemoglobin > 10 g/dL, absolute neutrophil count > 1.5×10^9/L, platelets > 100×10^9/L
No significant serous effusions
No risk of organ compression or compromise
Spleen ≤ 16 cm by CT scan

If patients meet all the above criteria and are without B symptoms (drenching night sweats, fever that is non-infectious, weight loss > 10% of body weight, fatigue, or

pruritus), they are considered low tumor burden by the Groupe D'Etude des Lymphomes Folliculares (GELF) criteria. (Khal. ASH Education 2012) If they do not meet all of the above criteria, they are considered high tumor burden.

Appendix 5 Response Assessment

Cheson Lugano Criteria 2014

Table 3. Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDI
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDI > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDI or SDI from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Table 3. Revised Criteria for Response Assessment (continued)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDI, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDI and perpendicular diameter; SDI, shortest axis perpendicular to the LDI; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Cheson Revised Response Criteria 2007

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Appendix 6 Safety Reporting Fax Cover Sheet

Genentech
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Genentech Supported Research
AE/ SAE FAX No: (650) 225-4682
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Page 1 of __

Genentech Study Number	

Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	
Initial Report Date	_____/ _____/ _____ dd / mmm / yyyy
Follow-up Report Date	_____/ _____/ _____ dd / mmm / yyyy
Patient Initials (Please enter a dash if the patient has no middle name)	___- ___-___

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

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

Appendix 7 FDA MedWatch 3500 Form

This form is included in the study start-up zip file to be sent to sites via email.

Appendix 8 Current NCI Common Terminology Criteria for Adverse Events (CTCAE)

Please use the following link to the NCI CTCAE website:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm