PROTOCOL

TITLE: A Phase I/II Study of Lenalidomide and Obinutuzumab with CHOP for Diffuse Large B Cell Lymphoma

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TEST PRODUCTS: Obinutuzumab (*Gazyva™,* GA101)
Lenalidomide (*Revlimid*)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ABC	activated B cell
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody dependent cellular phagocytosis
AE	adverse event
anti-HBc	antibody to hepatitis B core antigen
aNHL	aggressive Non-Hodgkin lymphoma
aPTT	activated partial thromboplastin time
BCR	B-cell receptor
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
COO	cell of origin
CR	complete response or complete remission
Cru	unconfirmed complete response
CSR	Clinical Study Report
D	day
DFS	disease-free survival
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
EC	Ethics Committee
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
F	phenylalanine
FACS	fluorescent-activated cell sorter
FcγR	leukocyte receptors for the Fc portion of IgG
FDA	Food and Drug Administration
^{18}F-FDG	^{18}F-fleurodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FISH	fluorescence in situ hybridization

Abbreviation	Definition
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
IgH	Immunoglobulin heavy chain
IHC	immunohistochemistry
IND	Investigational New Drug
IMC	Internal Monitoring Committee
IRR	infusion-related reaction
IV	intravenous
IL	interleukin
iNHL	Indolent non-Hodgkins lymphoma
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
MM	multiple myeloma
MRD	minimal residual disease
MTD	maximum tolerated dose
MRI	magnetic resonance imaging
MUGA	multigated acquisition scan
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

Abbreviation	Definition
NGS	next generation sequencing
NHL	non-Hodgkin's lymphoma
NONMEM	Non-Linear Mixed Effect Model
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
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
SNPs	single nucldeotide polymorphisms
SOC	Scientific Oversight Committee
TCR	T-cell receptor
TLS	tumor lysis syndrome
ULN	upper limit of normal
U.S.	United States
V	valine
WHO	World Health Organization

1. INTRODUCTION

Although this protocol contains sufficient information regarding the medications utilized in this clinical trial, for additional information please refer to the Investigator's Brochures for lenalidomide and obinutuzumab, Appendix A and B, for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profiles.

1.1 DIFFUSE LARGE B-CELL LYMPHOMA

Diffuse large B-cell Lymphoma (DLBCL) is a distinct histological type within mature B-cell non-Hodgkin lymphoma (NHL) that is characterized by large tumor cells and aggressive clinical behavior. This type accounts for approximately 31% of all newly diagnosed malignant lymphomas.(1)

CHOP chemotherapy in combination with the anti-CD20 monoclonal antibody rituximab on a 21-day schedule is a standard of care in newly diagnosed cases in most countries worldwide.(2-4) In the GELA study of R-CHOP versus CHOP front line therapy in elderly subjects, following R-CHOP treatment the 5-year event-free survival (EFS) was 47%, the 5-year progression free survival (PFS) was 54%, and the 5-year overall survival (OS) was 58%.(5) While approximately 50% to 60% of patients are cured, for those patients who are refractory or who progress following R-CHOP, treatment options are limited and outlook is poor; most die within the next two years. Since roughly 40% to 50% of patients are not cured on initial therapy, evaluating other front line treatment options is warranted. Other attempts to improve cure rate, including R-ACVBD, CHOEP, dose dense regimens (R-CHOP14), and high dose regimens (DA-EPOCH), have not replaced R-CHOP21 as a standard of care.(4)

1.2 PET/CT SCANS IN LYMPHOMA

^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) scans are used in NHL to evaluate residual masses detected on CT after completion of chemotherapy, with the negative predictive values for outcome of 80% to 100%.(6, 7) Results from a FDG PET scan after one cycle of chemotherapy were essentially equivalent to results from a FDG PET scan obtained at the completion of chemotherapy in predicting PFS in NHL and HD.(8)

Moskowitz et al evaluated the predictive value of an FDG PET in patients with high risk untreated DLBCL after 3 cycles of conventional chemotherapy.(9) Of the 38 patients with a positive interim FDG PET, only 5 (13%) had biopsy-confirmed persistent disease. Interestingly, the patients with positive interim FDG PET and negative biopsy had no significant difference in long-term outcomes from patients with negative interim FDG PET (p=0.27). As a result of this important trial, the positive predictive value of an interim FDG PET is considered low enough that a biopsy for confirmation is mandatory prior to altering the treatment plan. Essentially, interim FDG PET scans have an excellent negative predictive value, however the positive predictive value is not clinically viable.

1.3 NON-IMAGING BASED DISEASE MONITORING

A novel technology (LymphoSIGHT, Sequenta) has been shown to allow a detection of a tumor-specific clonotype (DoC) in blood and to correlate with therapeutic response and identification of relapse prior to imaging findings.(10-12) This novel technology amplifies the immunoglobulin (Ig) gene segments from tumor biopsy DNA, and subsequent quantification of the same clonotype in blood. Genomic DNA from tumor is isolated using standard kits from Qiagen, and is subsequently amplified using locus-specific primer sets for all known alleles of germine line immunoglobulin heavy chain (IgH) and T-cell receptor (TCR) sequences.(10) The tumor-specific sequences identified at diagnosis are then used as a target to assess the presence of tumor-specific clonotype in follow-up samples. For quantitation, multiple sequencing reads (~10X coverage) are generated for each rearranged B cell in the reaction.

To determine the absolute measure of the tumor-specific clonotype present in the follow-up sample, a known quantity of reference IgH sequence is added into the reaction and the associated sequencing reads are counted. The resulting number of reference IgH reads per sequence are then applied to the tumor-specific clonotype reads to obtain an absolute measure of the total tumor-specific clonotype in the reaction.

The tumor-specific clonotype reads and the absolute number of total leukoctyes in the reaction metrics can be combined to calculate a final tumor-specific clonotype measurement, which is the number of tumor-specific clonotype reads divided by the total leukocytes in the sample.

1.4 BIOLOGICAL AND CLINICAL SIGNIFICANCE OF DLBCL TYPING

As initially described by Staudt and colleagues, DLBCL is composed primarily of two biologically distinct disease subtypes.(13) The authors successfully classified DLBCL by gene expression profiling (GEP) into the germinal center B-cell (GCB) and the activated B cell (ABC) types, derived from their putative cells of origin (COO). Subsequently, an additional type was noted by GEP called type III,(14) which has since been renamed as unclassifiable type. Although GEP is fully capable of discerning all three types, GCB, ABC, and unclassifiable; immunohistochemistry (IHC) is capable of discerning only two, GCB and non-GCB, via the algorithm described by Hans.(15) The less precise, though widely utilized, IHC method groups ABC and unclassifiable together as the non-GCB type. The Lymphoma/Leukemia Molecular Profiling Project reported approximately 60% GCB and 40% non-GCB (including ABC and unclassifiable) in 240 newly diagnosed DLBCL subject biopsy samples examined by GEP.(14, 16, 17)

The different DLBCL types have been reported to have distinct clinical outcomes with CHOP(14) and R-CHOP(17) therapy, further supporting that these are distinct clinical and molecular subtypes. With frontline CHOP therapy, the 5-year OS rates for the GCB,

unclassifiable, and ABC types were 60%, 39%, and 35%, respectively.(14) With frontline R-CHOP therapy, the 3-year EFS for GCB and non-GCB subtypes was 67% and 52% respectively, and the 3-year OS was 85% and 69%, respectively.(17) With RCHOP therapy for predominantly higher risk patients (International Prognostic Index, IPI 0/1 = 21%, IPI 2/3 = 63%, and IPI 4/5 = 15%) the median PFS for the ABC type was only 1.5 years.(18, 19) In the relapsed setting, the prognosis for the COO subtype appears to be approximately equal,(20, 21) which may reflect the selection of GCB subjects with adverse biology not cured initially by R-CHOP.

1.4.1 GCB versus ABC Gene Expression Profiling Assay Used in This Protocol

The COO as characterized by GEP and performed on fresh tissue biopsy samples is considered the gold standard for disease subtyping. However, defining COO is not performed currently in routine clinical practice and is often not a practical method for subject selection in clinical trials due to the fresh biopsy sample requirement, technological expertise, and bioinformatics required to perform and interpret the assay.

This protocol will utilize a validated GEP based assay performed on NanoString's nCounter® Analysis System with formalin-fixed paraffin-embedded (FFPE) biopsy material to identify eligible subjects with the required ABC type. The NanoString 20-gene assay, referred to as Lymph2Cx, was validated against the original COO model defined by Lenz(18) using an independent cohort of 68 FFPE biopsies. In the validation cohort the assay was highly accurate, as only one case with definitive COO was incorrectly assigned by NanoString; and robust, with >95% concordance of COO determination between two independent laboratories.(22)

1.5 BIOMARKERS IN DLBCL

1.5.1 Biomarkers in DLBCL Pathogenesis

In recent years a number of chromosomal rearrangements, acquired mutations, or aberrant expression of genes) have been identified in DLBCL. Many are associated with a particular DLBCL COO subtype or yield prognostic information. As an example, BCL2 is a commonly translocated or mutated gene in the GCB subtype, and EZH2 is also mutated in the GCB subtype.(23, 24) Activation of NF-κB is critical for the ABC subtype survival, and mutation of MYD88 is more common in the ABC type).(25, 26) Coexpression of MYC/BCL2 as defined by FISH or IHC is associated with a very aggressive clinical course in both subtypes, although it has been reported to be more common in the ABC type.(27-30) Additionally, mutations in MYC, CDKN2A, SOCS1, MYD88, CARD11, TP53, and other genes have demonstrated prognostic information in patients with DLBCL receiving front line treatment. (31-34) Single nucleotide polymorphisms (SNPs) are also reported to be associated with prognosis in DLBCL patients. (35, 36)

1.5.2 Minimal Residual Disease and Clonal Heterogeneity

In order to be able to adapt treatment intensity, extend duration of response, and prolong PFS, more sensitive clinical assessment methods are necessary to better define treatment outcomes at the molecular level. Recently, investigators from the National Cancer Institute evaluated samples from untreated DLBCL patients treated with DA-EPOCH +/- rituximab to assess for minimal residual disease (MRD) using a next generation sequencing (NGS) based test with DNA present in the tumor biopsy and serum.(10) IgH variable, diversity, and joining segments as well as immunoglobulin light chain gene segments from genomic DNA were sequenced, and analysis of these data demonstrated that NGS MRD measurement detected relapse of DLBCL a median of 7.4 months before the disease was detected via CT scan.(37)

This study will evaluate the ability of NGS sequencing to assess MRD status compared to CT scan in a larger sample size to help determine quality of treatment and detection of relapse. The MRD and clonality assessments will be conducted according to the laboratory manual.

1.5.3 Mechanistic Biomarkers

Research on the mechanism of action of lenalidomide, pomalidomide, and thalidomide suggest that in tumor cells and T cells, cereblon, a component of E3 ubiquitin ligase complexes, is a critical target for binding by these compounds.(38-40) These and other studies showed that the loss of cereblon or a binding partner, such as DDB1, decreases or eliminates the antitumor and immunomodulatory activity of lenalidomide and pomalidomide. A number of recent studies have reported a correlation between pre-treatment levels of cereblon measured by GEP or by IHC methods and clinical outcomes in subjects treated with regimens containing lenalidomide, pomalidomide or thalidomide. In addition, multiple groups have described Aiolos (IKZF3) and Ikaros (IKZF1) as two direct substrates of the CRL4 CRBN E3 ligase complex. These proteins act as transcriptional repressors in T-cells and are also drivers of proliferation in multiple myeloma (MM) cells.(41)

This study will explore the functions of Aiolos and Ikaros by examining their expression levels in DLBCL patient samples and evaluate for correlation with clinical outcomes, as well as genetic mutations that could have functional consequences. Validated assays for both GEP and IHC methods will be used to measure baseline and treatment levels of cereblon, Aiolos and Ikaros to investigate whether there is any potential correlation between their expression level and clinical outcome. Additional biomarkers may be included in the analysis based on accumulated evidence for their inclusion.

Mechanistic biomarker measurements for cereblon and other potential biomarkers, including substrates of the CRL4-CRBN complex, gene expression, DNA mutational analysis, and metabolic factors, will be performed as appropriate. The mechanistic biomarker assessments will be conducted according to the laboratory manual.

1.6 LENALIDOMIDE

REVLIMID® (lenalidomide), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. Lenalidomide is indicated for the treatment of patients with transfusion-dependent anemia due to low- or Intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Revlimid® is also approved in combination with dexamethasone for the treatment of patients with multiple myeloma that have received at least one prior therapy.

Lenalidomide, an oral agent, is a thalidomide derivative that belongs to a new class of agents known as immunomodulatory drugs (IMiDs). Lenalidomide has clinical activity in non-Hodgkin's lymphoma (NHL) and has been shown to possess several immunomodulatory properties. 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.

The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2H-isoindol-2-yl) piperidine-2, 6-dione and it has the following chemical structure:

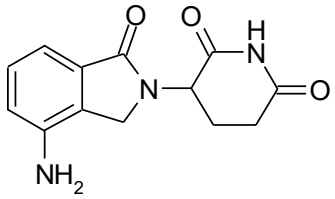


Figure 1 Chemical Structure of Lenalidomide

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

1.6.1 Preclinical Data on Lenalidomide in DLBCL

There is biological plausibility and also preclinical data that provide strong support for why lenalidomide should be expected to significantly enhance the efficacy of the current standard of care R-CHOP in the treatment of the ABC type of DLBCL.

In DLBCL cell line models, lenalidomide preferentially suppresses the proliferation of ABC cells in vitro and delays tumor growth in a human tumor xenograft model, with minimal effect on GCB cells.(42) The synthetically lethal effect was associated with down-regulation of interferon regulatory factor 4 (IRF4, also known as MUM1), a hallmark of ABC cells.(43) IRF4 inhibition by lenalidomide induced down-regulation of B-cell receptor (BCR)-dependent NF-κB, and this effect was reported to require co-expression of cereblon, a molecular target of lenalidomide. It has also been reported that NF-κB mediates resistance to chemotherapy and that decreased NF-κB expression may restore sensitivity to chemotherapy and targeted agents.(44, 45) The ability of lenalidomide to kill ABC DLBCL cell lines by augmenting autocrine interferon beta (IFN-ß) production is dependent on oncogenic MYD88 mutations.(42) In a cereblon-dependent fashion, lenalidomide downregulated IRF4 and SPIB transcription factors which repress IFN-ß production.

In addition to affecting lymphoma cells directly, lenalidomide exerts potent immunomodulatory activity and thus modulates immune responses. Preclinical studies have shown an enhancement of antibody dependent cell mediated cytotoxicity and antitumor effects in vivo when lenalidomide was combined with rituximab.(46-48) In a murine NHL model, lenalidomide induced a significant increase in the recruitment of NK cells to tumor sites, resulting in enhanced antitumor activity of rituximab.(49) When combined with rituximab, lenalidomide improved survival in a mouse NHL model and the antitumor activity was shown to be NK cell-mediated.(50)

Lenalidomide reverses immunosuppression of T cells by tumor cells of MM, chronic lymphocytic leukemia (CLL), and follicular lymphoma (FL).(51-53) Impaired T-cell immunological synapse formation has been reported in CLL, FL and DLBCL patients and is thought to be a mechanism of cancer immune evasion. Lenalidomide increases expression of T cell co-stimulatory molecules, T cell activating cytokines, and the number of cytotoxic T cells in MM patient samples. In indolent lymphomas including FL, we found that R-lenalidomide activated many different immune cell subsets, including T and natural killer cells, and enhanced tumor infiltration by CD8+ T cells.(54, 55) Lenalidomide treatment of the T-cells and the tumor cells collected from these patients repaired the immune synapse defects by enhancement of the F-actin synapse. In vitro studies have shown that lenalidomide induced actin cytoskeleton reorganization and polarization of NHL cells as early as 30 minutes, a process termed “capping,” which is considered an important subcellular component of the immune synapse formation.(56)

Additionally it has been shown that the combined use of lenalidomide and rituximab enhances NK cell-mediated immune synapse formation and the resultant cytotoxicity, versus using each agent alone.(56) Lenalidomide induces CD20-localization within the “cap,” and the addition of

rituximab can enhance immune synapse formation. The capping of CD20 is accompanied by redistribution of other proteins that become part of the immune synapse complex. Therefore, the capping process induced by lenalidomide appears integral to immune synapse formation and may coordinately enhance the clustering of both the CD20 antigen and the attached rituximab, potentially further enhancing its activity, which would support the clinical combination of these agents. Additional agents which target CD20, including obinutuzumab, should have a similar mechanism of potential synergy.

1.6.2 Lenalidomide Clinical Pharmacology:

Mechanism of Action:

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

Metabolism and Excretion

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

1.6.3 Lenalidomide Pharmacokinetics and Drug Metabolism:

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 area under the concentrated time curve (AUC) but does reduce the maximal plasma concentration (Cmax) by 36%. The pharmacokinetic (PK) disposition of lenalidomide is linear. Cmax and AUC increase proportionately with increases in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Pharmacokinetic analyses were performed on 15 multiple myeloma patients treated in the phase I studies. Absorption was found to be rapid on both Day 1 and Day 28 with time to maximum blood levels ranging from 0.7 to 2.0 hours at all dose levels (5mg, 10mg, 25mg, and 50mg). No plasma accumulation was observed with multiple daily dosing. Plasma

lenalidomide declined in a monophasic manner with elimination half-life ranging from 2.8 to 6.1 hours on both Day 1 and 28 at all 4 doses. Peak and overall plasma concentrations were dose proportional over the dosing range of 5mg to 50mg (5). Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

Multiple dosing at the recommended dose-regimen does not result in drug accumulation. Pharmacokinetic sampling in 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.

Distribution:
In vitro (14C)-lenalidomide binding to plasma proteins is approximately 30%.

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

1.6.4 Clinical Efficacy Data on Lenalidomide in DLBCL

1.6.4.1 Relapsed / Refractory DLBCL

Single agent lenalidomide activity in relapsed or refractory DLBCL subjects has been noted in two Celgene-sponsored single arm clinical trials in aggressive NHL (aNHL): study CC-5013-NHL-002 and study CC-5013-NHL-003.(57, 58) Data from both studies were combined for a revised analysis of 134 DLBCL subjects as study design was nearly identical and subject baseline characteristics were similar. Results showed an overall response rate (ORR) of 26.1% (35/134), a median PFS of 2.7 months, and a median response duration of 6.0 months.(59) In these clinical trials, COO typing was not conducted.

Hernandez-Ilizaliturri et al reported in a retrospective analysis of 40 relapsed/refractory aNHL subjects (34 DLBCL, 6 composite/transformed DLBCL) treated with single agent lenalidomide at Roswell Park Cancer Institute, Mayo Clinic, University of Bologna, and Hackensack University that there was a preferential clinical activity of lenalidomide in patients with the non-GCB subtype DLBCL.(47) The tumor response rate was an impressive 52.9% (5 CR, 4 PR) in the non-GCB subtype although with the caveat of a small sample size (n=17) compared with only 8.7% (1 CR, 1 PR) in the GCB subtype (n=23). The median PFS for lenalidomide was 6.2 months for the non-GCB and 1.7 months for the GCB subtype (p=0.004). Importantly, there were no significant differences in the age, disease stage at time of treatment, international

prognostic index (IPI) scores, or number of prior therapies between the COO groups.

These observations led to the CC-5013-DLC-001 phase II/III randomized clinical trial of single agent lenalidomide versus investigator's choice in subjects with relapsed/refractory DLBCL in GCB and non-GCB subtypes. In this trial, subjects with relapsed DLBCL underwent COO typing during the screening phase, which was used to assign subjects to two different cohorts defined by the subtype. The subjects were subsequently randomized to receive lenalidomide or single agent of investigator choice, and the ongoing as of December 2014. At the time of the planned final analysis (N=102 intention to treat patients (ITT) who were randomized, received at least one dose of therapy; 54 non-GCB, 48 GCB), the CC-5013-DLC-001 study showed a statistically significant improvement of median PFS for lenalidomide versus investigator's choice treatment in the non-GCB subtype as assessed by the imaging and response assessment core (IRAC, control 7.1 weeks versus lenalidomide 15.2 weeks; p = 0.021, HR [95% CI] = 0.50 [0.27, 0.92]). In addition, there was a favorable trend in ORR as assessed by IRAC (control 11.5% versus lenalidomide 28.6%, p=0.179)). There was also a favorable trend in median OS in the non-GCB subtype (control 20.4 weeks versus lenalidomide 32.3 weeks; p = 0.253, HR [95% CI] = 0.70 [0.38, 1.30]). Potentially influencing the OS data, 16/26 (61.5%) of non-GCB subjects in the control arm crossed over to lenalidomide upon radiological evidence of disease progression on the comparator treatment.

The CC-5013-DLC-001 study also included exploratory objectives related to gene expression profiling. If medically feasible, subjects were required to provide a fresh frozen lymph node or tumor biopsy at study enrollment; biopsies for 65 subjects were provided. Samples were then typed as ABC, GCB, or unclassifiable using Affymetrix U133 Plus 2.0 GeneChip microarrays. At the time of planned final analysis (N= 65 ITT who were randomized, received at least one dose of therapy, 27 ABC type, 8 unclassifiable type, 30 GCB type) the study showed a favorable trend in median PFS for lenalidomide versus investigator's choice treatment in the ABC type as assessed by IRAC (control 6.3 weeks versus lenalidomide 82.0 weeks; p = 0.105, HR [95% CI] = 0.44 [0.15 – 1.23]). There was also a favorable trend in median OS in the ABC type (control 18.6 weeks versus lenalidomide 108.4 weeks; p = 0.144, HR [95% CI] = 0.47 [0.17, 1.33]).

Taken together, these data of lenalidomide single agent in subjects with relapsed DLBCL suggest that lenalidomide has preferential activity in non-GCB and ABC types of DLBCL. Further evidence supporting this preferential activity in the non-GCB subtype is observed in preclinical models (Section 1.4).

1.6.4.2 Front Line DLBCL

The chemo-immunotherapeutic regimen of R-CHOP is a standard of care worldwide for the

treatment of patients with newly diagnosed DLBCL.(4) Two academic clinical research groups have developed the combination regimen of lenalidomide + rituximab + CHOP (R2-CHOP) in patients with newly diagnosed DLBCL: the Mayo Clinic Cancer Center in the US and the Italian cooperative group, Fondazione Italiana Linfomi (FIL).

1.6.4.2.1 Mayo Clinic R2-CHOP Data

Protocol MC078E is an investigator initiated Phase 1/2 study of R2-CHOP in subjects with newly diagnosed, previously untreated DLBCL and follicular grade IIIA/B B-cell lymphoma, sponsored by the Mayo Clinic.

The objective of the Phase 1 cohort of this study was to establish the maximum tolerated dose (MTD) of lenalidomide that could be combined with R-CHOP. A total of 24 subjects with newly diagnosed, untreated CD20-positive DLBCL or follicular grade III NHL were enrolled. Twenty of these 24 subjects had DLBCL. Subjects received oral lenalidomide on Days 1-10 with standard dose R-CHOP every 21 days. The lenalidomide dose levels tested were 15, 20, and 25 mg. The median age was 65 (35-82) years and 54% were over 60 years. Three subjects received 15 mg, 3 received 20 mg, and 18 received 25 mg of lenalidomide. No dose-limiting toxicity (DLT) was found, and 25 mg on Days 1-10 was the recommended dose for the Phase 2 portion of this study. The incidence of Grade 4 neutropenia and thrombocytopenia was 67% and 21%, respectively. Febrile neutropenia was rare (4%) and there were no deaths due to toxicity. The ORR was 100% with a CR rate of 77%. It was concluded that lenalidomide at the dose of 25 mg/day administered on Days 1 to 10 of 21-day cycle can be safely combined with R-CHOP in the initial chemotherapy of aggressive B-cell lymphoma.(60)

Table 1. Patient Characteristics from Nowakowski et al

Characteristics	R2CHOP (n = 64) No.	%	Contemporary Cohort of R-CHOP (n = 87) No.	%	*P*
Age, years					.0132*
Median	65.0		61.0		
Range	22.0-87.0		41.0-86.0		
Sex					.5337†
Female	24	37.5	37	42.5	
Male	40	62.5	50	57.5	
IPI					.0508†
Low	7	10.9	18	20.7	
Intermediate-low	24	37.5	16	18.4	
Intermediate-high	24	37.5	38	43.7	
High	9	14.1	15	17.2	
Ann Arbor stage					.0467†
2	7	10.9	20	23.0	
3	19	29.7	14	16.1	
4	38	59.4	53	60.9	
ECOG PS					.36350‡
0	30	46.9	32	36.8	
1	28	43.8	41	47.1	
2	6	9.4	11	12.6	
3	0	0.0	3	3.4	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance score; IPI, International Prognostic Index, R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R2CHOP, lenalidomide added to R-CHOP.
*Kruskal-Wallis test.
† χ^2 test.
‡ Fisher's exact test.

Based on these phase 1 results, the phase 2 cohort of the study was conducted to assess the efficacy of this combination. Response was evaluated using PET/CT by standard criteria.(6) The final results were recently reported with a total of sixty four subjects with DLBCL accrued to the Phase 2 cohort with median follow up of 23.5 months.(61) All subjects received R-CHOP21 for 6 cycles plus lenalidomide 25 mg (R2-CHOP) on Days 1 – 10 of each cycle. Although not prospectively planned, subjects were retrospectively subtyped by IHC using the Hans algorithm (Hans, 2004). In the 60 evaluable patients, the overall response rate was 98%, with 80% achieving a complete response. Furthermore, 87 consecutive subjects with DLBCL and similar clinical characteristics participating in the Mayo Clinic Lymphoma Database and treated with standard R-CHOP alone served as a contemporaneously matched control. Table

1 below describes the baseline characteristics of the DLBCL subjects treated with R2-CHOP in the Mayo Clinic phase 2 trial and the 87 subjects treated with R-CHOP as matched control.(61) Subjects treated with R2-CHOP had fewer subjects with low IPI score and were also older as compared to the R-CHOP cohort.

Safety data of the R2-CHOP regimen showed the most common Grade 3 and 4 toxicities with R2-CHOP were neutropenia (12% Grade 3, 74% Grade 4), thrombocytopenia (30% Grade 3, 16% Grade 4), anemia (20% Grade 3, 0% Grade 4), febrile neutropenia (12% Grade 3, 0% Grade 4), pneumonia (2% Grade 3, 0% Grade 4), sepsis (0% Grade 3, 2% Grade 4), venous thrombosis (0% Grade 3, 2% Grade 4), fatigue (2% Grade 3, 0% Grade 4) and dehydration (2% Grade 3, 0% Grade 4). Overall, R2-CHOP is considered well tolerated and has promising efficacy.(61)

It is noted that an unplanned COO subtype cohort analysis, as defined by IHC testing, found that combination of lenalidomide with RCHOP appears to have improved outcomes, especially in the non-GCB subtype in comparison with the historical control patients. The 2-year PFS in the RCHOP control group was only 52% (95% CI: 43% – 64%), and the median follow up for patients still alive was 41.2 months (range: 11.6 – 78.3 months). By COO subtype, the historical RCHOP therapy achieved a 2-year PFS of 28% (95% CI: 15% – 51%) for the non-GCB subtype, and 64% (95% CI: 53% - 78%) for the GCB subtype (log-rank p<0.001). In the patients treated with lenalidomide and RCHOP (R2CHOP), there was no difference in 2-year PFS between non-GCB (60%, 95% CI: 41% - 81%) and GCB (59%, 95% CI: 44% - 80%). In the RCHOP group, the 2-year OS in the non-GCB was 46%, as compared with 78% in the GCB group. In the R2CHOP group, the 2-year OS was improved to 83% in the non-GCB group, as compared to 75% in the non-GCB group. The implication of this evaluation of a prospective clinical trial and historical control is that the PFS and OS for non-GCB DLBCL patients is significantly improved with the addition of lenalidomide to RCHOP. An additional finding is that the outcome for patients with GCB DLBCL did not appear to have worsened outcomes with the addition of lenalidomide to standard immunochemotherapy.

1.6.4.2.2 FIL R2-CHOP Data

The Italian cooperative group FIL conducted a prospectively designed multicenter phase 1/2 study to evaluate the toxicity and efficacy of lenalidomide plus R-CHOP21 in untreated elderly DLBCL subjects, the REAL07 trial.(62)

The objective of the Phase 1 cohort of the REAL07 trial was to determine the maximum tolerated dose of this combination. Four lenalidomide doses (5, 10, 15, and 20 mg/day on Days 1-14) using the continual reassessment method were planned in combination with each course of R-CHOP for a total of 6 courses. Seven subject cohorts (n=3 each) were treated (total n=21) at 10, 20, 15, 15, 15, 10, and 10 mg of lenalidomide. Dose-limiting toxicities

occurred in seven subjects during the first three treatment courses. The third dose-level of lenalidomide (15 mg/day) was selected as the maximum tolerated dose, with an estimated DLT probability of 0.345 (95% credibility interval 0.164-0.553). Grade 3-4 hematologic adverse events were: neutropenia in 28% of the courses, thrombocytopenia in 9%, and anemia in 3%. Non-hematologic toxicities were moderate: grade 4 increase of creatinine phosphokinase (n=1), grade 3 cardiac (n=2), grade 3 neurologic (n=3), and grade 3 gastrointestinal (n=1). In this phase 1 study, 90% of subjects achieved an overall response with 81% achieving complete remission. It was concluded that this combination is tolerable in elderly DLBCL subjects, and lenalidomide given at 15 mg on Days 1-14 of each cycle in combination with standard R-CHOP21 was the recommended dosing schedule for Phase 2 study.(63, 64) Nine subjects were treated at this dosing schedule in the Phase 1 cohort.

Phase 2 of the REAL07 trial was a study to investigate the efficacy of R2-CHOP in CD20+ elderly DLBCL or FL grade IIIB subjects. Key inclusion criteria included age 60-80, Ann Arbor stage II-IV, and IPI > 2. The primary endpoints were ORR and CR rate after 6 courses of R2-CHOP by using Cheson, 2007 criteria and included PET negativity as a requirement for CR. The secondary endpoints were 2-year OS, 2-year PFS, and relationship between response and histopathological features. Subjects were treated with lenalidomide given at 15 mg on Days 1-14 of each cycle in combination with standard R-CHOP21 for 6 cycles. Subjects were retrospectively subtyped by IHC using the Hans algorithm, although this analysis was not prospectively planned.(15)

Forty-nine subjects were enrolled. The phase 2 cohort data analyses included these 40 subjects plus 9 subjects from the phase 1 cohort treated at the recommended phase 2 dose/schedule (total N=49). The most significant common hematological toxicities recorded in 277 cycles of treatment were neutropenia (9% grade 3, 22% grade 4), leukocytopenia (15% grade 3, 13% grade 4), febrile neutropenia (3% grade 3, 1%, grade 4), thrombocytopenia (5% grade 3, 7% grade 4), and anemia (4% grade 3, < 0.5% grade 4) The most significant common hematological toxicities recorded in 277 cycles of treatment were neutropenia (9% grade 3, 22% grade 4), leukocytopenia (15% grade 3, 13% grade 4), febrile neutropenia (3% grade 3, 1%, grade 4), thrombocytopenia (5% grade 3, 7% grade 4), and anemia (4% grade 3, < 0.5% grade 4).

The overall results for all 49 subjects showed a CR rate of 86%, ORR 92%, 2-year PFS 80%, and 2-year OS 92%. Among these 49 subjects, GCB vs. non-GCB typing assignment was achieved in 34 subjects (17 subjects with GCB, and 17 subjects with non-GCB) by Hans criteria.(15) The CR rate in subjects with non-GCB subtype appears to be essentially equivalent to that of the in GCB subtype subjects (88% vs. 81%). In addition, as was observed in the Mayo Clinic study, among the subjects treated with R2-CHOP regimen, the PFS and OS curves of the subjects with the non-GCB subtype appear to be about the same as or better

than the GCB subtype subjects. The 2-year PFS of patients with COO subtyping available was not different from those who did not have tissue available for subtyping. Among the patients with non-GCB DLBCL, the 2-year PFS was 81% (95% CI: 51-93) compared with 71% (95% CI: 51-93) for the patients with GCB DLBCL, with a hazard ratio of 0.78 (95% CI: 0.21 - 2.9, p=0.705). The 2-year OS was 94% (95% CI: 63 – 99) in non-GCB DLBCL, and 88% (95% CI: 59 – 97) in GCB DLBCL, with a hazard ratio of 0.51 (95% CI: 0.05 – 5.63, p=0.58). Together, these data suggest that adding lenalidomide to standard therapy improved treatment outcome in non-GCB subjects who have a poor prognosis and typically have a worse outcome to treatment.

1.6.5 Clinical Efficacy Data Conclusion

In summary, the R2-CHOP efficacy data from the Mayo Clinic MC078E study and the FIL REAL07 study compare favorably to historical R-CHOP21 data with a better CR rate at the end of induction therapy and better PFS. Furthermore, promising efficacy results were also demonstrated in the non-GCB subtype, which generally has a poorer outcome when treated with R-CHOP alone. Clinically meaningful improvements as demonstrated by higher CR rate and longer PFS in non-GCB DLBCL subjects are considered significant in this difficult to treat sub-population (Table 2).(61, 62) This data is not direct comparison, but supports the hypothesis that lenalidomide is able to overcome the adverse outcomes associated with non-GCB DLBCL.

Table 2. Pooled outcomes from Mayo and FIL R2CHOP studies and Mayo RCHOP control

		Non-GCB	GCB
FIL			
	2y PFS	81%	71%
	2y OS	94%	88%
Mayo R2CHOP			
	2y PFS	60%	59%
	2y OS	83%	75%
Mayo RCHOP			
	2y PFS	28%	64%
	2y OS	46%	78%

The combination of lenalidomide and RCHOP is tolerable, without unexpected toxicities. The Grade 3 and 4 toxicities are primarily hematological, and manageable with supportive care.

1.7 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(65, 66): 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®).

1.7.1 Obinutuzumab Preclinical Data

Non-clinical in vitro studies show that obinutuzumab mediates superior induction of direct cell death and effector cell-mediated ADCC and ADCP on a panel of NHL cell lines as compared to the Type I CD20 antibodies rituximab and ofatumumab. Its potency to mediate CDC is significantly reduced as compared to these two antibodies. In ex vivo autologous whole blood B-cell depletion studies with blood from healthy volunteers as well as CLL patients, obinutuzumab mediated superior B-cell depletion when compared with rituximab.

These properties of obinutuzumab translated into superior anti-tumor efficacy in direct comparison to rituximab against a number of aggressive SC and disseminated NHL xenograft models. Obinutuzumab induced complete tumor remission and long term survival (cures) and increased the overall survival in disseminated NHL xenograft models. The efficacious and optimal dose range of obinutuzumab in xenograft models was in the range of 10-30 mg/kg, corresponding to trough levels of 300-600 µg/mL. In addition, obinutuzumab showed efficacy in combination with classical chemotherapeutic agents, such as chlorambucil, fludarabine and bendamustine. Importantly, the combination of obinutuzumab with chemotherapeutic agents was superior to the combination of these agents with rituximab. Treatment with obinutuzumab also resulted in potent and superior depletion of B-cells in the peripheral blood and in lymphoid tissues of hCD20 transgenic mice and cynomolgus monkeys. Vaccination studies in cynomolgus monkeys and human CD20 transgenic mice showed that the enhanced efficacy in terms of B-cell depletion of obinutuzumab translated into suppression of de novo antibody responses, but left the protective humoral memory responses intact.

The data generated to date imply that obinutuzumab represents a novel therapeutic CD20 antibody with outstanding efficacy compared to classical Type I and non-ADCC enhanced

CD20 antibodies, such as rituximab and ofatumumab. Based on these non-clinical data it can be anticipated that the combination of the recognition of a Type II epitope together with improved ADCC and ADCP potency exclusive to obinutuzumab may translate into superior clinical efficacy.

1.7.2 Obinutuzumab Clinical Pharmacology

The clinical pharmacology properties of obinutuzumab have been characterized in a number of clinical studies, in patients with CLL or NHL. These studies include Phase 1 and 2 monotherapy studies (BO20999 and BO21003), a Phase Ib combination study (BO21000) and a Phase 3 combination study (BO21004). A serum sampling scheme for the quantitation of obinutuzumab was undertaken in these studies to enable population PK analysis.

Population PK modeling was undertaken on all available serum concentration data from studies BO20999, BO21003, BO21000 and BO21004/CLL11 to provide a robust description of the PK behavior of obinutuzumab. This demonstrated that a two compartment PK model comprising both a linear clearance pathway and a non-linear time varying clearance pathway adequately described serum obinutuzumab concentration data. The initial clearance of obinutuzumab was 2.85 times higher than the steady state clearance which is consistent with a decrease in the time varying clearance component, which is high at the start of treatment and which declines with repeated cycles of obinutuzumab treatment. The time varying clearance pathway is consistent with target mediated drug disposition, such that at the start of treatment when there is a large quantity of CD20 positive cells, this binds obinutuzumab. With repeated dosing of obinutuzumab this saturates the pool of CD20 positive cells, hence reducing this component in clearance. The linear clearance pathway is consistent with catabolism of IgG antibodies, and is therefore independent of CD20 positive cells. This analysis further supports the need to minimize the time varying clearance component quickly, and has lead to the proposed dose and regimen of 1000 mg in both induction and extended treatment. In the Phase II part of study BO21003, which investigated the 1000 mg obinutuzumab dose taken into Phase III, the PK of obinutuzumab was assessed in patients with indolent non-Hodgkin's lymphoma (iNHL) who received weekly administrations of 1000 mg of obinutuzumab during the induction phase (4 administrations; Cycle 1 – Cycle 4) followed by an extended maintenance treatment phase of 1000 mg obinutuzumab every 2 months until disease progression. The mean obinutuzumab serum concentration increased markedly over the 4 treatment cycles. Following the final (i.e., fourth) administration of the induction treatment, obinutuzumab serum levels decreased. Overall, mean C_{trough} serum levels of obinutuzumab observed during the maintenance regimen were similar across the 12 maintenance cycles.

In study BO21004/CLL11, a pivotal Phase III study in CLL patients, mean serum obinutuzumab concentrations increased from Cycle 1 to Cycle 2 following administration of obinutuzumab on Day 1/2 (45 patients in Stage 1a received the first 1000 mg dose over 2

days: 100 and 900 mg on Days 1 and 2, respectively), Day 8 and Day 15 of Cycle 1. From Cycle 3 until Cycle 6, pre- and post-infusion serum concentrations remained constant during the course of treatment. Having the first 1000 mg administered over 2 days did not impair the rapid minimization of the time varying clearance component indicative of depletion of CD20+ tumor cells.

In Phase Ib study BO21000, the PK of obinutuzumab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or fludarabine and cyclophosphamide (FC) is being investigated in patients with relapsed/refractory FL. Based on preliminary PK data, for both combinations, obinutuzumab serum concentrations increased with increases in dose. In this same study, the effect of obinutuzumab on the PK of bendamustine was investigated in first-line NHL patients. The 2 cohorts (obinutuzumab + bendamustine and obinutuzumab + CHOP) showed similar PK profiles (serum obinutuzumab serum concentrations versus time), similar increases in systemic exposure (Cmax and AUC7 days) from Cycle 1 (Day 1 and Day 8) to end of treatment cycle, total clearance, and volume of distribution (Vc). The effect of obinutuzumab on the PK of bendamustine is also being investigated in an ongoing Phase III study in rituximab-refractory iNHL patients. Based on preliminary data, there were no differences in bendamustine clearance when given with obinutuzumab compared to bendamustine alone following single administration. Similarly, no changes in half-life were observed for bendamustine when given in combination with obinutuzumab compared to bendamustine alone.

Consistent with the mechanism of action of obinutuzumab, extensive B-cell depletion was observed both in patients with NHL and CLL. In most patients receiving obinutuzumab monotherapy, there was no notable increase in complement levels during or following an infusion. Changes in the levels of IL-6 and IL-8 were observed, i.e., increases during the course of the first infusion followed by a decrease to pre-infusion levels 7 days later.

1.7.3 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 PK 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.

1.7.4 Clinical Experience with Obinutuzumab

For the most up-to-date information on obinutuzumab, please refer to the current version of the Investigator's Brochure.

Table 3 shows the end-of-treatment response in patients with relapsed or relapsed/refractory NHL treated with obinutuzumab as monotherapy or in combination chemotherapy.

1.7.4.1 Obinutuzumab Monotherapy

In the monotherapy setting, the proportion of patients who had a CR or PR at the end of treatment ranged from 28% to 58%. Although this was a population with treatment-refractory or relapsed disease, some patients in studies BO20999 and JO21900 achieved a CR by the end-of-treatment assessment. The Phase I of study BO20999 recruited 21 NHL patients; lymphoma subtypes were follicular (n=13), mantle cell (n=4), diffuse large B-cell (n=1), small lymphocytic (n=1), lymphoplasmacytic lymphoma (n=1) and Waldenström's macroglobulinaemia (n=1). In the Phase I part of the study, 7 patients (33%) had a response at the end of treatment. In the Phase II part, 11 patients (28%) with aNHL and 15 patients (38%) with iNHL had a response at the end of treatment. In Phase II, end-of-treatment response for iNHL was 17% (3 PR) for patients receiving 400/400 mg (n=18) obinutuzumab and 55% (2 CR, 10 PR) in the 1600/800 mg cohort (n=22). The Phase I part of study BO21003 included 17 patients: 10 with FL, 3 with DLBCL, 2 with lymphocytic lymphoma, and one each with mantle cell lymphoma (MCL) and marginal zone lymphoma. At the end of the (induction) treatment period, no patients had CR, 5 patients (29%) had PR, 2 patients had progressive disease (PD), and 1 patient had no data.

1.7.4.2 Obinutuzumab Combination Therapy

In the Phase Ib chemotherapy combination study, BO21000, 53/56 relapsed/refractory patients (95%) had a response (CR+PR) at the end of treatment; one had PD, one had stable disease (SD) and one had no response assessment due to early withdrawal. In patients with previously untreated B-cell FL, 76/81 patients (94%) responded at the end of treatment; one each had SD

and PD, and 3 patients had no response assessment as they withdrew prior to the first response assessment. The proportion of patients with a CR was higher in this chemotherapy combination study than for the monotherapy studies (relapsed/refractory setting: 39% [11/28 patients] in the obinutuzumab + CHOP arm and 50% [14/28 patients] in the obinutuzumab + FC arm; first-line setting: 39% [16/41 patients] in the obinutuzumab + bendamustine arm and 35% [14/40 patients] in the obinutuzumab + CHOP arm).

Table 3 Summary of Response in Patients with NHL Treated with Obinutuzumab

	Number of Patients (%) with Response					
	(CR + PR)	**CR**	**PR**	**SD**	**PD**	**No Data**
Monotherapy						
BO20999 Phase I N=21 (relapsed/refractory NHL)	7 (33)	4 (19)	3 (14)	5 (24)	8 (38)	1 (5)
BO20999 Phase II N=40 (relapsed/refractory aNHL)	11 (28)	3 (8)	8 (29)	4 (10)	24 (60)	1 (3)
BO20999 Phase II N=40 (relapsed/refractory iNHL)	15 (38)	2 (5)	13 (33)	12 (30)	13 (33)	-
BO21003 Phase I N=17 (relapsed/refractory NHL)	5 (29)	-	5 (29)	9 (53)	2 (12)	1 (6)
BO21003 Phase II* N=87 (relapsed/refractory iNHL)	39 (45)	10 (11)	29 (33)	37 (47)	8 (9)	4 (5)
JO21900 Phase I N=12 (relapsed/refractory NHL)	7 (58)	2 (17)	5 (42)	5 (42)	-	-
Combination Therapy						
BO21000 (relapsed/refractory FL)						
Obinutuzumab + CHOP: N=28	27 (96)	11 (39)	16(57)	1 (4)	-	-
Obinutuzumab + FC: N=28	26 (93)	14 (50)	12 (43)	-	1 (4)	1 (4)
BO21000 (first line FL)						
Obinutuzumab + Bendamustine: N=41	38 (93)	16 (39)	22 (54)	1 (2)	1 (2)	1 (2)
Obinutuzumab + CHOP: N=40	38 (95)	14 (35)	24 (60)	-	-	2 (5)

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.
Table shows the primary efficacy analysis at the end of treatment period (BO20999, JO21900)/ end of induction treatment period (BO21003, BO21000)
*: analysis includes all patients, both follicular and non-follicular lymphoma, bur primary efficacy endpoint was only based on FL patients

To date, more than 470 patients have been enrolled into one of the six ongoing or completed

studies with obinutuzumab for patients with CD20-positive B-cell malignancies. Obinutuzumab monotherapy has been well tolerated, with a preliminary safety profile similar to that of rituximab in NHL patients (i.e., mainly Grade 1 and 2 toxicities, with more frequent IRRs occurring in patients around the time of the first infusion, and decreasing with subsequent infusions). Obinutuzumab has been administered to patients at doses ranging between 50 and 2000 mg, reaching cumulative doses per treatment regimen of up to 17,200 mg. Responses have been observed in all cohorts, with B-cell depletion being observed already at the lowest cohort. No dose-limiting toxicities have been observed. A high intra-individual and inter-individual degree of antibody clearance has been observed.

1.7.5 Rationale for Use of Flat Dosing of Obinutuzumab

Similar to most current monoclonal antibodies, a flat dose (not adapted to body weight or body surface area [BSA]) has been chosen for obinutuzumab combination trials. The rationale for use of flat dosing was based on the fact that antibody clearance is mostly determined by target volume and target access, i.e., tumor burden and accessibility to normal or malignant tumor cells in various compartments, such as blood, bone marrow, and lymphatic organs, rather than body weight or surface area. In contrast, the dose of the first monoclonal antibody licensed for the treatment of B-cell malignancies was calculated on the basis of BSA.

In the 1990s, determination of the dose for monoclonal antibodies followed an approach typical for cytotoxic drugs, for which an upper dose-limiting toxicity is usually determined. The toxicity is generally a function of the capacity to eliminate the drug by organs such as liver and spleen, limiting and narrowing the therapeutic window, and thereby requiring an adaptation of the dose using body weight or BSA. In effect, most monoclonal antibodies, including those targeting CD20, reveal a wide therapeutic window without the need to adjust dosing by BSA or body weight. However, because quantifying the target and adjusting individual dosing according to target has been notoriously difficult, the currently accepted approach for most monoclonal antibodies, including nearly all of those targeting CD20 in various stages of development, is flat dosing

1.7.6 Rationale for Administration of Additional Doses of Obinutuzumab on Days 1 and 8

In the Phase II part of Study BO20999, the first two doses of obinutuzumab in the HD cohort were set at 1600 mg. Although well tolerated by patients, the dosing scheme resulted in administration times of up to and exceeding 5 hours. With the goal in mind to maintain the loading dose concept, and to provide a significant amount of antibody early on during the treatment course, it was decided to split obinutuzumab administration and to change the schedule and dose during the first 2 weeks of any future studies from 1600 mg on Days 1 and 8 to 1000 mg on Days 1, 8, and 15, providing comparably fast rising PK exposure and early target saturation, while avoiding the practical challenges of delivering 1600 mg of drug in a single day together with chemotherapy. The dose for subsequent cycles is also set at 1000

mg. This dose and schedule result in an obinutuzumab exposure of 3000 mg during the first 2 weeks for a cumulative exposure of 10,000 mg and is therefore very close to the regimen that has delivered the best results thus far for obinutuzumab in both indolent and aggressive lymphoma. There is no indication that the additional obinutuzumab doses on Days 8 and 15 in the first cycle would negatively affect the safety of patients.

1.7.7 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, infusion-related reactions (IRR) were 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 DLT, 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 (aNHL] and 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 tumor lysis syndrome (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.

In the Phase III Study BO21004 (CLL11), comparison of obinutuzumab + chlorambucil to chlorambucil alone showed that the most common AEs (all grades, Grades 3 – 4), respectively, were IRRs (69% vs. 0, 21% vs. 0), neutropenia (40% vs. 18%, 34% vs. 16%), thrombocytopenia (15% vs. 7%, 11% vs. 3%), anemia (12% vs. 10%, 4% vs. 5%), leukopenia (7% vs. 0, 5% vs. 0), pyrexia (10% vs. 7%, < 1 vs. 0), and cough (10% vs. 7%, 0 vs. < 1%).
The incidence of IRRs was 69% with the first infusion of obinutuzumab. The incidence of Grade 3 or 4 IRRs was 21%, with 8% of patients discontinuing therapy. The incidence of reactions with subsequent infusions was 3%, with the second 1000-mg dose and <1% thereafter. No Grade 3 or 4 IRRs were reported beyond the first 1000-–mg infusion. Of the first 53 patients receiving obinutuzumab in the trial, 47 (89%) experienced an IRR. After this

occurrence, study protocol modifications were made to require pre-medication with a corticosteroid, antihistamine, and acetaminophen. The first dose was also divided into two infusions (100 mg on Day 1 and 900 mg on Day 2). Of the 45 patients for whom these mitigation measures were implemented, 21 patients (47%) experienced a reaction with the first 1000-mg dose and <2% thereafter.

The incidence of neutropenia reported as an AE was 40% in the obinutuzumab-treated arm and 18% in the chlorambucil-alone arm, with the incidence of serious adverse events (SAEs) being 1% and 0%, respectively. Cases of late-onset neutropenia (occurring 28 days after completion of treatment or later) were 16% in the obinutuzumab-treated arm and 12% in the chlorambucil-alone arm.
The incidence of infections was similar between arms. Thirty-eight percent of patients in the obinutuzumab-–treated arm experienced an infection, 9% were Grade 3 – 4, and none were fatal.

The incidence of thrombocytopenia reported as an AE was 15% in the obinutuzumab-treated arm and 7% in the chlorambucil-alone arm. Five percent of patients in the obinutuzumab-treated arm experienced acute thrombocytopenia (occurring within 24 hours after the obinutuzumab infusion).

The incidence of Grade 3 or 4 TLS was 2% in the obinutuzumab-treated arm vs. 0% in the chlorambucil-alone arm.

AEs related to musculoskeletal disorders, including pain (System Organ Class), have been reported with obinutuzumab with higher incidence than with the comparator (17% vs. 13%, respectively).(67)

1.7.8 Risks Associated with Obinutuzumab Therapy

1.7.8.1 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.

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.

1.7.8.2 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.

1.7.8.3 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.

1.7.8.4 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.

1.7.8.5 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.

1.7.8.6 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.

1.7.8.7 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.

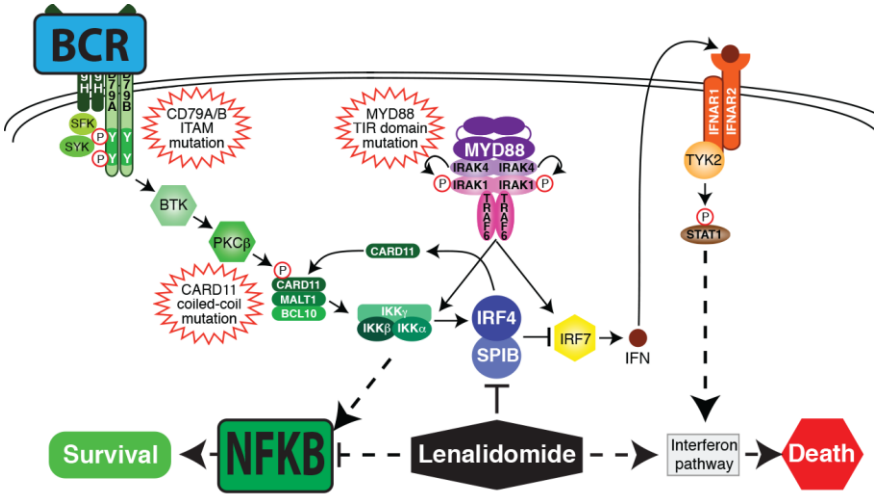
1.8 STUDY RATIONALE

Diffuse large B-cell lymphoma (DLBCL), the most common lymphoid malignancy with ~30,000 new cases in the US annually, is uniformly treated with a combination (CHOP) which remains essentially unchanged over the past 30+ years.(1) DLBCL biology now includes the definition of two distinct subtypes with unique gene expression programs,(2-4) genomic abnormalities,(5) microRNA profiles,(6-8) signaling pathways,(9-12) and response to targeted therapies.(13,14) These substantial advances in understanding DLBCL biology do not yet influence the frontline therapy of DLBCL patients, which achieves 5-year overall survival rates in activated B-cell (ABC) and germinal center B-cell subtypes (GCB) DLBCL of ~50% and ~70%, respectively. The ABC subtype requires constitutive activity of the targetable B-cell receptor and NF-κB pathways for survival. Recent work has demonstrated the subtype-selective activity of lenalidomide in ABC DLBCL comes from inhibition of the expression of the survival-critical transcription factor IRF4 (Figure 2). When lenalidomide reduces IRF4 expression, a synthetically lethal interferon response occurs in ABC DLBCL cell lines.

Figure 2. The BCR pathway and target for lenalidomide

The clinical activity of lenalidomide in DLBCL has been shown to be significant, as a single agent (ABC DLBCL ORR 52%, 14, 16) or in combination with R-CHOP. (ORR 92%, CR 86%, equivalent in ABC and GCB DLBCL, 17-19). Equally impressive is that both lenalidomide was able to be dose escalated to its maximal studied level without significant toxicity when combined with R-CHOP. Based on the promising efficacy and toxicity data, lenalidomide is being evaluated in two randomized trials in combination with R-CHOP, and may file for an FDA indication/registration.

Obinutuzumab (G) is a novel, glycoengineered type II anti-CD20 monoclonal antibody with



Lenalidomide and Obinutuzumab with CHOP for Diffuse Large B Cell Lymphoma

increased direct cell death and antibody dependent cell-mediated cytotoxicity when compared with rituximab. Obinutuzumab has shown promising single agent activity in relapsed DLBCL (ORR: 24 – 37% in a Phase I study, 20). Obinutuzumab has also been combined successfully with chemotherapy including CHOP in indolent lymphomas (21) and aggressive lymphomas (22). A randomized trial comparing rituximab and obinutuzumab with CHOP has recently completed accrual, with highly anticipated results expected in 2015 (23).

The ***hypothesis*** of this clinical trial is that the combination of lenalidomide + obinutuzumab with CHOP will be tolerable and result in an ORR at least even to lenalidomide + rituximab with CHOP. Based upon the above data, we propose to conduct a Phase Ib/II trial to evaluate the combination of lenalidomide, obinutuzumab, and CHOP in patients with DLBCL

2. OBJECTIVES

2.1 PRIMARY

The primary objective of the phase Ib portion of the trial will be to determine the maximum tolerated dose of lenalidomide + obinutuzumab with CHOP.

The primary objectives of the Phase II portion of the trial will be to determine the efficacy (complete and overall response rate).

2.2 SECONDARY

The secondary objectives of the Phase Ib portion will include the efficacy (overall and complete response rate) and tolerability of lenalidomide + obinutuzumab with CHOP.

The secondary objectives of the Phase II portion will include determination of the survival outcomes (progression free and overall survival), and safety.

Exploratory objectives will include the comprehensive genomic profiling of patient tumor and blood samples to attempt correlation with response, evaluation of immune cell subsets in peripheral blood at diagnosis and end of therapy to attempt correlation with response, and use of novel technology to evaluate for circulating tumor DNA of the lymphoma immunoglobulin heavy chain to attempt correlation with response.

3. STUDY DESIGN

This will be a single arm, single institution, open-label phase Ib/II clinical trial of lenalidomide, obinutuzumab, and CHOP to evaluate the safety and efficacy in subjects with previously untreated CD20+ DLBCL. This study is divided into Screening (3.2), Treatment (3.3) and Follow-up Periods (3.4). Details of the study treatments are described in Section 5.

3.1 DESCRIPTION OF THE STUDY

During Phase Ib, patients will receive previously demonstrated tolerable doses of lenalidomide with planned fixed dosing of obinutuzumab and CHOP to determine if the toxicity data from R2CHOP remains relevant. In the unlikely event that obinutuzumab and lenalidomide are found to result in unexpected toxicity, we may explore lower dosing levels of obinutuzumab. Patients will be evaluated in a standard 3+3 design.

During Phase II, patients will receive lenalidomide + obinutuzumab with CHOP for a total of 6 cycles.

It is anticipated that a total of 59 patients will be enrolled in the Phase Ib/Phase II trial. The study will be conducted in compliance with Good Clinical Practice (GCP).

3.2 SCREENING PERIOD

Screening for eligibility determination may begin after the subject signs the informed consent form. All screening assessments must be completed within 28 days prior to enrollment. The only exceptions to the 28-day time period are for the lymph node / tumor biopsy and the bone marrow biopsy / optional aspirate, which may occur up to 6 weeks prior to Cycle 1 Day 1.

During the Screening Period, subjects will undergo safety and other assessments to determine eligibility for the study as shown in Section 7.1.
Key aspects of screening include MD Anderson Pathology assessment of disease diagnosis, CD20+ status; local assessment of bone marrow involvement by lymphoma; documentation of measurable disease by CT scan; collection of a PET scan; and verification of adequate liver, renal, cardiac, and bone marrow function.

3.3 TREATMENT PERIOD

The Treatment Period begins with Cycle 1 Day 1 dosing of the chemotherapy drugs as described in Section 5. Subjects will receive protocol-specified treatments for 6 cycles. Treatment will continue to completion, or until the outcome of the mid-therapy PET scan between Weeks 7 – 9 (after Cycle 3 but before Cycle 4) indicates a treatment change; disease progression; unacceptable toxicity; death; or withdrawal of consent, whichever occurs first.

In order to manage toxicity and allow subjects to complete 6 cycles of treatment, dose delay

and modification rules will be followed (Section 5.1 and 6). Key aspects of ongoing safety monitoring include physical exam, AE assessment, and hematology / chemistry laboratory testing prior to the initiation of every cycle, and at additional time points as shown in the Section 7.

Key aspects of ongoing efficacy assessment include physical exam; CT scans at screening, once between 3 – 4 weeks after completing Cycle 6, and in follow-up at specified time points; and PET scans at Screening, between Weeks 7 – 9 (after Cycle 3 but before Cycle 4), and once 3 – 4 weeks after start of Cycle 6.

The treatment will be defined in Section 5, but in brief the starting dosage level in the phase I trial will be:

Dose level 1 (cycle is q21 days)
Lenalidomide 15mg po daily 1 – 14
Obinutuzumab 1000mg IV day 1, 8, 15 C1, day1 C2-6
Cyclophosphamide 750mg/m2 IV on day 1
Doxorubicin 50mg/m2 IV on day 1
Vincristine 1.4mg/m2 (max 2mg) IV on day 1
Prednisone 100mg po daily on days 1-5

3.4 FOLLOW-UP PERIOD

The Follow-up Period begins upon study treatment discontinuation for all subjects. This includes subjects who complete the full course of treatment, who discontinue treatment due to progression or toxicity, as well as those who discontinue before progression to pursue a new anti-lymphoma / salvage therapy (chemotherapy, SCT, radiotherapy, etc.).

3.5 RATIONALE FOR STUDY DESIGN

The CHOP regimen is well established as efficacious in our target population, as it has remained the standard therapy for nearly 40 years. The dosing for lenalidomide is based on the previous lenalidomide + RCHOP trials.(60, 62, 68). The dosing for obinutuzumab will be based on the Gather Study (NCT01414855)(69): 1000mg IV on day 1, 8, and 15 of cycle 1, then on day 1 of cycles 2 – 6.

The rationale for conducting a phase Ib trial portion is to confirm that there is no adverse increase in toxicity from the previous Obinutuzumab-CHOP and Rituximab-Lenalidomide-CHOP trials. Based on the large number of patients treated on these similar trials, it is anticipated that the Phase Ib portion will be limited in size.

Although there has been compelling data that lenalidomide may have increased activity in the ABC subtype of DLBCL, we will allow all patients with newly diagnosed DLBCL to enroll in this

study. There is no suggestion that adding lenalidomide worsens outcomes in the GCB DLBCL subtype, and the combination of Obinutuzumab with lenalidomide-CHOP has not previously been explored.

3.6 OUTCOME MEASURES

Outcome measurements will be detailed in Section 7. In brief, CT scans will be obtained at screening, once between 3 – 4 weeks after start of Cycle 6, and in follow-up at specified time points; and PET scans at Screening, between Weeks 7 – 9 (after Cycle 3 but before Cycle 4), and once 3 – 4 weeks after start of Cycle 6.

3.6.1 Primary Efficacy Outcome Measure

Phase Ib: Maximum Tolerated Dose as defined in Section 5.1
Phase II: CR and ORR rate after 6 courses as defined in Section 8

3.6.2 Secondary Efficacy Outcome Measures

Phase Ib: ORR and CR rate and tolerability after 6 courses as defined in Section 8
Phase II: Survival outcomes (progression free and overall survival), and safety after 6 courses as defined in Section 8

4. STUDY POPULATION

Untreated CD20+ Diffuse Large B Cell Lymphoma, including both non-GCB/ABC and GCB patients.

4.1 ELIGILITY CRITERIA

4.1.1 Inclusion Criteria

Patients must meet all of the following criteria for study entry:

- 4.1.1.1 Confirmed treatment-naïve de novo CD20+ DLBCL, regardless of cell of origin, with Stage II-IV disease, or Stage I disease if 6 cycles of chemotherapy are planned.
- 4.1.1.2 Measurable disease on cross section imaging that is at least 1.5 cm in the longest diameter and measurable in two perpendicular dimensions
- 4.1.1.3 Appropriate candidate for systemic immune-chemotherapy such as the standard RCHOP21 6 cycles as determined by the treating physician
- 4.1.1.4 Age ≥18
- 4.1.1.5 Adequate organ function (normal cardiac ejection fraction of >45%, serum bilirubin <1.5 mg/dl, AST or ALT $\leq 5 \times$ ULN, and creatinine clearance > 30 mL/min (Calculated according to Cockcroft–Gault formula) unless due to lymphoma with documentation of normal function prior to onset of lymphoma. In the case of Gilberts Syndrome, or documented liver or pancreatic involvement by lymphoma, the requirement for total bilirubin is ≤ 5.0 mg/dl
- 4.1.1.6 ANC >1000/mm3, hemoglobin >8.0, and platelets >100,000/mm3. If bone marrow is involved with lymphoma and normal marrow function prior to onset of lymphoma is documented: ANC of >750, any hemoglobin, and platelets of >50,000/mm3.
- 4.1.1.7 Performance status <3 (unless previous performance status was 0 or 1 and deterioration is due to lymphoma which treating MD expects to reverse with therapy)
- 4.1.1.8 Consent to potential need for transfusion of blood products
- 4.1.1.9 Able to give informed consent
- 4.1.1.10 Ability and willingness to comply with the requirements of the study protocol

4.2 EXCLUSION CRITERIA

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

4.2.1.1 Prior history of low grade lymphoma with transformation to DLBCL. If a patient has a composite diagnosis of DLBCL and low grade without a prior history of lymphoma, they will not be considered ineligible.

4.2.1.2 Pregnant or lactating females

4.2.1.3 Symptomatic CNS lymphoma involvement

4.2.1.4 Significant comorbidity (cirrhosis, severe coronary artery disease, significant psychiatric illness, or other that may compromise the ability to safely administer the therapy at the discretion of the primary investigator)

4.2.1.5 HBV: Patients with positive serology for Hepatitis B defined as positivity for HBsAg or anti-HBc. Patients who are positive for anti-HBc may be considered for inclusion in the study on a case-by-case basis if they are hepatitis B viral DNA negative and are willing to undergo ongoing HBV DNA testing by real-time PCR. Patients with positive serology may be referred to a hepatologist or gastroenterologist for appropriate monitoring and management.

4.2.1.6 Hepatitis C (HCV): Patients with positive hepatitis C serology unless HCV RNA is confirmed negative and *may* be considered for inclusion in the study on a case-by-case basis.

4.2.1.7 Known HIV or HTLV infection

4.2.1.8 Previous malignancy with diagnosis or suspicion of recurrence within the past 2 years, not including non-melanoma skin cancers or in situ malignancies.

4.2.1.9 History of severe allergic or anaphylactic reactions to monoclonal antibody therapy

4.2.1.10 Known hypersensitivity to any of the study drugs

4.2.1.11 Known active bacterial, viral, fungal, mycobacterial, or other infection (excluding fungal infections of nail beds) or any major episode of infection requiring treatment with IV antibiotics or hospitalization (related to the completion of the course of antibiotics) within 4 weeks before the start of Cycle 1

4.2.1.12 Major surgery (within 4 weeks prior to the start of Cycle 1), other than for diagnosis

4.2.1.13 Fertile men or women of childbearing potential unless 1) surgically sterile or 2) using an adequate measure of contraception such as oral contraceptives, intrauterine device, or barrier method of contraception in conjunction with spermicidal jelly.

4.2.1.14 Vaccination with a live vaccine a minimum of 28 days prior to the start of treatment
4.2.1.15 Peripheral neuropathy ≥ Grade 2
4.2.1.16 Subjects who are unwilling to take VTE prophylaxis

5. TREATMENT PLAN

This will be a single arm, single institution, open-label phase Ib/II clinical trial of lenalidomide, obinutuzumab, and CHOP to evaluate the safety and efficacy in subjects with previously untreated CD20+ DLBCL.

5.1 PHASE IB

In the Phase Ib portion of the trial, the standard 3+3 design will be employed. Three patients will be enrolled in the Dose Level 1 cohort with dosing as:

Dose level 1 (cycle is q21 days)
Lenalidomide 15mg po daily 1 – 14
Obinutuzumab 1000mg IV day 1, 8, 15 C1, day1 C2-6
Cyclophosphamide 750mg/m2 IV on day 1
Doxorubicin 50mg/m2 IV on day 1
Vincristine 1.4mg/m2 (max 2mg) IV on day 1
Prednisone 100mg po daily on days 1-5

Drug dosing should occur at the above schedule unless it is not feasible due to patient travel delays, holiday schedule, or other unforeseen circumstance. In that event, the schedule may be modified for a therapeutic cycle to be between 20 and 23 days (range of -1 day - +2 days). For obinutuzumab cycle 1 dosing, the day 8 and day 15 dosing can administered +/-1 day if necessary for similar to above issues.

If zero of the initial 3 patients experiences a dose limiting toxicity (DLT, as defined below), an additional three patients will be treated at this dose level. If 0 or 1 DLT is observed out of the total 6 patients treated at Dose Level 1, then Dose Level 1 will be selected for the Phase II portion of the trial and no further patients will be accrued to the phase Ib portion of the trial.

The DLT evaluation period will be cycle 1. DLT will be defined as grade ≥ 3 non-hematologic toxicity per NCI CTCAE 4.0 unmanageable with aggressive supportive care or toxicity resulting in a delay of over 7 days of cycle 2. The incidence of neutropenic fever will be carefully monitored, but will not be considered a DLT as neutropenic fever is known to occur with R-CHOP.

If 1 out of the initial 3 patients develops a DLT, an additional 3 patients will be treated at the same dose level. If no more DLTs develop at this dose (i.e., 1 out of a total of 6 patients develops a DLT), Dose Level 1 will be selected for the Phase II portion of the trial and no further patients will be accrued to the phase Ib portion of the trial.

At any given dose, if greater than 1 out of 3 patients or 1 out of 6 patients experience DLT, the dose level exceeds the MTD and 3 more patients will be treated at the next lower dose if there are less than 6 patients already treated at that dose.

Lower dose levels are defined as:

Dose level 0
Lenalidomide 10mg po daily 1 – 14
Obinutuzumab 1000mg IV day 1, 8, 15 C1, day1 C2-6
CHOP standard dosing

Dose level -1
Lenalidomide 10mg po daily 1 – 10
Obinutuzumab 1000mg IV day 1, 8, 15 C1, day1 C2-6
CHOP standard dosing

Dose level -2
Lenalidomide 5mg po daily 1 – 10
Obinutuzumab 1000mg IV day 1, 8, 15 C1, day1 C2-6
CHOP standard dosing

Following the above scheme, MTD is defined as the highest dose level in which 6 patients have been treated with less than 2 instances of DLT. Given the history of good tolerance of lenalidomide with RCHOP (including 2 planned/ongoing Phase III trials comparing RCHOP vs R2CHOP), and Obinutuzumab with CHOP, it is anticipated that a maximum of 15 will be enrolled in the phase Ib portion of the trial. The MTD identified in the Phase Ib portion of the trial will be selected as the recommended phase II dosing (RP2D) for further evaluation in the Phase II portion of the trial

The 6 patients treated at the MTD in the phase Ib component of the trial will be included in the efficacy analysis of patients treated in the Phase II trial.

5.2 PHASE II

In the Phase II portion of the trial, patients will be treated at the RP2D determined in the Phase Ib potiion for 6 cycles of therapy. The trial plans to enroll 50 patients at the RP2D.

A Bayesian toxicity monitoring rule will be used to ensure patient safety. The patient enrollment will be stopped at any time when excessive toxicity is observed. If the trial is halted prior to planned completion due to increased incidence of DLTs, the principle investigator would evaluate the etiology of DLTs.

If there is a minor modification that is estimated to likely correct the etiology of DLTs (e.g., addition of a specific prophylactic antibiotic as mandatory for all patients), the trial will resume at the previously determined MTD, with the same monitoring strategy as detailed above.

If the etiology of the increased DLTs in unknown or not correctable with a minor modification, the trial will resume at the next lower dosing level from the Phase Ib portion of the trial if deemed appropriate by the principle investigator. If the increased DLTs are significant and unavoidable, the principle investigator may elect to end the trial before full enrollment is completed.

6. CLINICAL TRIAL MEDICATIONS

6.1.1 Obinutuzumab

6.1.1.1 Formulation

Obinutuzumab is provided as a single-use vial. Each vial contains a sterile liquid formulation in a 50-mL pharmaceutical-grade glass vial containing a nominal dose of 1000 mg of obinutuzumab (G3 material). The formulated drug product consists of 25 mg/mL drug substance formulated in histidine/histidine-HCl, trehalose, and poloxamer 188. The vial contains 41 mL (with 2.5% overfill).

6.1.1.2 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, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C 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. Do not use an additional in line filter because of potential adsorption.

6.1.1.3 Preparation

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

To prepare a 1000-mg dose: The final drug concentration of a 1000-mg dose

should be 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 it 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.

Administration sets with polyvinyl chloride, polyurethane, or polyethylene as product contact surface and IV bags with polyolefin, polypropylene, polyvinyl chloride, or polyethylene as product contact surface are compatible and may be used. Use of a port or peripherally inserted central catheter line is acceptable.

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

6.1.1.4 Dosage and Administration

Obinutuzumab administered by IV infusion for up to 6 cycles (21-day cycles):

- On Cycle 1, Days 1, 8 and 15, 1000 mg of obinutuzumab will be administered.
- On Cycles 2 – 6, Day 1, 1000 mg of obinutuzumab will be administered (see Table ~~Table~~ 4)

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Obinutuzumab must be administered in a clinical setting (inpatient or outpatient). Full emergency resuscitation facilities should be immediately available, and patients should be under close supervision by the investigator or designated infusion team at all times. Obinutuzumab should be given as a slow IV infusion through a dedicated line. IV infusion pumps (such as Braun Infusomat Space) should be used to control the infusion rate of obinutuzumab. Do not administer as an IV push or bolus. After the end of the first infusion, the IV line should remain in place for at least 2 hours in order to be able to administer IV drugs if necessary. If no AEs occur after 2 hours, the IV line may be removed. For subsequent infusions, the IV line should remain in place for at least 1 hour from the end of infusion; if no AEs occur after 1 hour, the IV line may be removed. The rate of infusion and time of IV removal should be documented in the medical record.

Table 4 Obinutuzumab Dosing Schedule

Cycle and Day of Administration		Dose of Obinutuzumab	Rate of Infusion (in the Absence of Infusion Reactions/ Hypersensitivity during Previous Infusions)
Cycle 1	Day 1	1000 mg	• Administer at 50 mg/hour over 4 hours. If no infusion reaction occurs, increase the infusion rate in 50-mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. • If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional protocol. Resume the infusion at a 50% reduction in rate (the rate being used at the time that the hypersensitivity or infusion-related reaction occurred) if the reaction has resolved.
	Day 8	1000 mg	• If the patient tolerated the prior infusion well (defined as an absence of Grade 2 reactions during a final infusion rate of ≥ 100 mg/hr), begin the infusion at a rate of 100 mg/hr. • If a patient experienced an infusion reaction during the prior infusion, start at the same rate as the first infusion (50 mg/hr) and follow directions as noted. • If no infusion reaction occurs, increase the infusion rate in 100-mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. • If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional protocol. Resume the infusion at a 50% reduction in rate (the rate being used at the time that the hypersensitivity or infusion-related reaction occurred) if the reaction has resolved.
	Day 15	1000 mg	
Cycles 2–6	Day 1	1000 mg	

6.1.1.5 Premedication Requirements

Infusion-Related Reactions

Since some patients may develop hypersensitivity or other IRRs to

obinutuzumab, pre-medication is recommended to reduce the risk of infusion reactions as outlined below:

- Cycle 1, Day 1, all patients require pre-medication with:
  - IV glucocorticoid: dexamethasone (20 mg) or methylprednisolone (80 mg) administered at least one hour prior to obinutuzumab infusion. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.
  - An oral acetaminophen (1000 mg) and an antihistamine such as diphenhydramine (50 mg) administered at least 30 minutes before starting each obinutuzumab infusion.
- Cycle 1, Days 8 and 15 and Cycles 2-6, Day 1:
  - All patients require pre-medication with oral acetaminophen (1000 mg) administered at least 30 minutes before starting each obinutuzumab infusion.
  - Patients who experience an IRR (Grade 1 or more) with the previous infusion will require pre-medication with an antihistamine such as diphenhydramine (50 mg) administered at least 30 minutes before starting each subsequent obinutuzumab infusion.
  - Patients who experience a Grade 3 IRR with the previous infusion or who have lymphocyte counts of $\geq 25 \times 10^9$/L prior to the next treatment will require pre medication with IV glucocorticoid: dexamethasone (20 mg) or methylprednisolone (80 mg) administered at least one hour prior to obinutuzumab infusion. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.

Hypotension may be expected to occur during obinutuzumab infusions. Withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their hypertensive medication.
For TLS prophylaxis, see Section 6.1.1.8.

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

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

Upon resolution of symptoms, continue infusion and, if patient does not experience any infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose.

6.1.1.6 Toxicity Management

If a patient experiences an IRR of any grade during infusion, adjust the infusion as follows:

- Grade 4 (life-threatening): Stop infusion immediately and permanently discontinue obinutuzumab therapy.
- Grade 3 (severe): Interrupt infusion and manage symptoms. Upon resolution of symptoms, consider restarting obinutuzumab infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred) and, if the patient does not experience any further infusion-reaction symptoms, the infusion rate escalation may resume at the increments and intervals appropriate for the treatment cycle dose. Permanently discontinue treatment if a patient experiences a Grade 3 infusion-related symptom at re-challenge.
- Grade 1 – 2 (mild to moderate): Reduce the infusion rate or interrupt infusion and treat symptoms. Upon resolution of symptoms, continue or resume infusion and, if the patient does not experience any further infusion-reaction symptoms, infusion rate escalation may resume at the increments and intervals appropriate for the treatment cycle dose.

6.1.1.7 Hepatitis B Virus Reactivation

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

For the subset of patients who are Hepatitis B viral DNA negative and anti-HBc positive and have undetectable Hepatitis B viral DNA levels at screening, Hepatitis B viral DNA levels must be followed approximately every 4 weeks. Guidelines for the management of hepatitis B reactivation are outlined in Table ~~Table~~ 5.

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Table 5 Management of Hepatitis B Reactivation

Hepatitis B Viral DNA Level by Real-Time PCR	Guideline
> 100 IU/mL	• Hold obinutuzumab • Begin anti-viral medication and treat for at least 1 year after the last dose of obinutuzumab. • Immediately refer the patient to a gastroenterologist or hepatologist for management. • Resume obinutuzumab once Hepatitis B viral DNA levels decrease to undetectable levels.
> 100 IU/mL while on anti-viral medication	Discontinue obinutuzumab.
29–100 IU/mL	Retest within 2 weeks. If still hepatitis B viral DNA positive: • Hold obinutuzumab • Begin anti-viral medication and treat for at least 1 year after the last dose of obinutuzumab. • Immediately refer the patient to a gastroenterologist or hepatologist for management • Resume obinutuzumab once Hepatitis B viral DNA levels decrease to undetectable levels

6.1.1.8 Management of Infusion-Related Reactions and Anaphylaxis

Please refer to Section 6.2.1 for information relating to concomitant medications. Medications (including subcutaneous epinephrine, corticosteroids, and intravenous diphenhydramine) and resuscitation equipment should be available for immediate use.

Life-Threatening Infusion-Related Reactions and Anaphylaxis

In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or IgE-mediated anaphylactic reaction, obinutuzumab should be discontinued and no additional obinutuzumab should be administered (see 10.3). Patients who experience any of these reactions should receive aggressive treatment of symptoms and will be discontinued from study treatment.

Tumor Lysis Syndrome

For patients with evidence of TLS, obinutuzumab should be discontinued and the patient treated as clinically indicated. Following the complete resolution of

TLS complications, obinutuzumab may be re administered at the full dose during the next infusion in conjunction with prophylactic therapy.

6.1.2 Lenalidomide

6.1.2.1 Formulation

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

6.1.2.2 Storage

Lenalidomide will be packaged in bottles, and each bottle will contain 14 capsules. The label for lenalidomide will include sponsor name, address and telephone number, the protocol number, lenalidomide name, dosage form and strength (where applicable), amount of lenalidomide per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

6.1.2.3 Dosing and administration

Lenalidomide is initiated on Day 1 of Cycle 1 at a dose of 15 mg (oral administration) PO once daily for 14 days in each 21-day cycle. Lenalidomide should be taken at approximately the same time each day. There is no requirement for taking lenalidomide with or without food, or with or without certain types of foods or liquids.

A rest period of at least 6 days following the 14 days of dosing is required. A rest period may be extended for toxicity as needed (Table 6).

If a subject misses a dose of lenalidomide and it is within 12 hours of their normal dosing time, the subject should be instructed to make up the missed dose, and to then take their next dose according to their regular schedule. Lenalidomide concentration is low at 12 hours post dose, therefore making up a missed dose and then resuming regular dosing with a greater than or equal to (≥) 12 hour interval between the two doses will not cause considerable drug accumulation.

Dose modifications are per Table 6. The dose may also be reduced for reasons in

addition to those listed in Table 6 per investigator discretion. If a dose is reduced, re-escalation is not permitted.

6.1.2.4 Drug Dispensing Requirements

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. Patients will be enrolled in the REMS program after they have provided informed consent for the trial. 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.

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

6.1.2.5 Toxicity Management

As the DLT evaluation period is cycle 1, the below events will be monitored but will not be considered DLT unless they occur within cycle 1. The dose modifications for lenalidomide mentioned below are identical to ongoing trials evaluating the combination of lenalidomide or placebo with RCHOP, and thus will be considered acceptable as long as below modifications are able to mitigate non-DLT issues delineated below.

Table 6

NCI CTCAE Toxicity Grade v 4.0	Action Required
Neutropenia* Sustained (≥ 7 days) Grade 3 OR ≥Grade 3 associated with fever (temperature ≥ 38.5°C) OR Grade 4 *unless secondary to lymphoma bone marrow involvement per investigator assessment	□ Withhold dose □ Monitor CBC at least every seven days □ If neutropenia has resolved to ≤ Grade 2 on first occurrence, restart at the same dose level □ If neutropenia has resolved to ≤ Grade 2 on subsequent occurrences, restart at the next lower dose level
Thrombocytopenia* ≥Grade 3 (platelet count <50,000 /mm³ *unless secondary to lymphoma bone marrow involvement per investigator assessment	□ Withhold dose □ Monitor CBC at least every seven days □ If thrombocytopenia resolves to ≤ Grade 2 on first occurrence, restart at the same dose level □ If thrombocytopenia resolves to ≤ Grade 2 on subsequent occurrences, restart at next lower dose level
Rash Grade 2 or 3 non-desquamating (blistering)	□ Determine causative investigational product and if attributable to lenalidomide then: - Hold dose; administer antihistamines or short course of ≤

---------- Desquamating (blistering) ≥ Grade 3 OR Non-desquamating Grade 4	20 mg prednisone (or equivalent) - When toxicity resolves to ≤ Grade 1, restart at the same dose level ---------- □ Determine causative investigational product and if attributable to lenalidomide then: - Discontinue lenalidomide
Allergic reaction or hypersensitivity Grade 2 ---------- Grade 3–4	□ Determine causative investigational product and if attributable to lenalidomide then: - Withhold dose. Follow at least every seven days - When the toxicity resolves to ≤ Grade 1, restart lenalidomide at next lower dose level ---------- - Discontinue lenalidomide
Constipation Grade 1–2 ---------- ≥ Grade 3	□ Initiate bowel regimen and maintain dose level ---------- □ Withhold dose. Follow at least every seven days □ When the toxicity resolves to ≤ Grade 2, restart at same dose level
Venous thrombosis/embolism ≥ Grade 3	□ Withhold dose and start therapeutic anticoagulation; restart at investigator's discretion (maintain dose level)
Tumor Lysis Syndrome (TLS) Grading is per Cairo-Bishop, and not per NCI CTCAE, for TLS only Laboratory TLS or Grade 1 TLS ---------- Grade 2 – 4	□ Continue lenalidomide (maintain dose), or at the investigator's discretion, continue lenalidomide and reduce dose by one level □ Provide vigorous IV hydration and appropriate medical management, until electrolyte abnormalities are corrected. Rasburicase therapy is allowable. □ Hospitalization will be at investigator's discretion ---------- □ Withhold dose □ When symptoms resolve to Grade 0, restart at same dose level □ If lenalidomide is resumed prior to the start of the subsequent cycle, a chemistry test should be performed every other day for the first week following re-initiation of lenalidomide
Abnormal Liver Function: AST or ALT > 3 x ULN	□ Withhold lenalidomide dose; re-test at least weekly until AST or ALT < 2.5 x ULN or return to baseline □ If the event is considered related to lenalidomide, restart lenalidomide at next lower dose level □ If the event is considered NOT related to lenalidomide, restart the same dose of lenalidomide
Abnormal Liver Function: Bilirubin > 3 x ULN	□ Withhold lenalidomide dose; re-test at least weekly until bilirubin < 1.5x ULN □ If the event is considered related to lenalidomide, restart lenalidomide at next lower dose level □ If the event is considered NOT related to lenalidomide, restart the same dose of lenalidomide

Other lenalidomide related non-hematologic AEs ≥ Grade 3	□ Withhold dose □ When the AE resolves to ≤ Grade 2, restart at the same or next lower dose level per the investigator's discretion

6.1.3 CHOP Chemotherapy

The CHOP regimen will be administered over a 21-day cycle. Treatment will continue until the CHOP regimen has completed 6 cycles, or until unacceptable toxicity, inadequate response to treatment is determined, disease progression, or withdrawal of consent, whichever occurs first.

CHOP is a standard chemotherapy which has been employed routinely worldwide over the past 39 years. The dosing and schedule will be as per standard practice:

Cyclophosphamide 750mg/m2 IV on day 1
Doxorubicin 50mg/m2 IV on day 1
Vincristine 1.4mg/m2 (max 2mg) IV on day 1
Prednisone 100mg po daily on days 1-5

6.1.4 Pre-medications:

6.1.4.1 Supportive Care

Anti-emetics are required to be administered prior to each dosage of CHOP chemotherapy and may be administered with additional pre-medications given prior to obinutuzumab. However, the dosage and medication choice will not be mandated and will be at the discretion of the treating physician, but there will be suggested dosing on the order sets. Subsequent anti-emetics after start of a chemotherapy cycle will be given to as needed per the discretion of the treating physician.

6.1.5 Pre-phase Treatment

For subjects with bulky disease, systemic symptoms, compressive disease, elevated bilirubin due to lymphoma, or rapidly progressing adenopathies, pre-phase treatment with 1 mg/kg/day prednisone, or equivalent, for a maximum of 7 days is permitted prior to beginning the Treatment Period, at the discretion of the investigator.

In the case of pre-phase corticosteroid treatment, there is no protocol specified definition of bulky disease. A washout period is not required; prophase treatment may be given, immediately followed by the prednisone as part of CHOP, and then a corticosteroid taper is allowed if the treating physician feels indicated. However, the Screening PET, CT, lymph node biopsy, and bone marrow biopsy (and if applicable, also the bone marrow aspirate) should be completed before initiating corticosteroids.

Pre-phase treatment with vincristine or any other chemotherapy is prohibited.

6.1.6 Consolidation Treatment (Pre-Specified)

The investigator may prospectively choose to give local radiotherapy after study chemotherapy for the treatment of a particular site of bulky disease or a large mass. In the case of consolidation treatment, bulky disease is defined as ≥ 7.0 cm. However, the decision to treat and the location to be treated must be determined during the Screening Period. In this case, the consolidation radiotherapy will not count as a treatment event for the EFS endpoint.

If the investigator should decide at anytime after Cycle 1 Day 1 to give consolidation treatment, or to switch treatment to a different lesion, receipt of consolidation treatment will count as an EFS event.

6.2 CONCOMITANT AND EXCLUDED THERAPIES

6.2.1 Concomitant Therapy

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 14 days preceding the study entry evaluation and the early study treatment termination visit/study treatment completion visit. All concomitant medications should be reported to the investigator and recorded on the appropriate electronic Case Report Form (eCRF).

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. Effective contraception is required while receiving obinutuzumab and/or lenalidomide. For women, effective contraception is required to continue for ≥ 12 months after the last dose of obinutuzumab and/or lenalidomide. For men, effective contraception is required to continue for ≥ 3 months after the last dose of obinutuzumab and/or lenalidomide.

6.2.1.1 Prophylaxis for Tumor Lysis Syndrome

All patients with peripheral blood lymphocyte counts of $\geq 25 \times 10^9$/L or bulky lymphadenopathy must receive prophylaxis for TLS prior to the initiation of study treatment. This includes appropriate hydration consisting of a fluid intake of approximately 3 L/day starting 1 day prior to the first dose of obinutuzumab and administration of allopurinol (300 mg/day orally) or a suitable alternative treatment starting prior to the first infusion of obinutuzumab (Cycle 1, Day 1). All patients should then be carefully monitored during the initial weeks of treatment. Patients still considered at risk for TLS because of persistently high tumor burden (i.e., peripheral blood lymphocyte counts $\geq 25 \times 10^9$/L) before the second and subsequent infusions of obinutuzumab should continue TLS prophylaxis with allopurinol and adequate hydration until the risk is abated, as determined by the investigator.

6.2.1.2 Venous Thrombosis:

Based upon prior trial data, it will be required for all patients to receive either aspirin (81 – 325 mg PO daily) or another prophylaxis agent while on lenalidomide. Exceptions will be made if a patient has a previous history of significant bleeding or other condition which makes anticoagulation unsafe in the determination of the principle investigator.

The choice of VTE prophylaxis agent relies upon the investigator's discretion and should be tailored to the subject's individual risk/benefit profile by taking into account the individual thrombotic risk, bleeding risk, and the quality of compliance with the VTE prophylaxis.

The use of clopidogrel or ticolpidine alone is not recommended as VTE prophylaxis in this trial.

VTE prophylaxis may need to be held during therapy due the potential of thrombocytopenia associated with either CHOP, lenalidomide, or obinutuzumab. For guidelines regarding VTE management related to thrombocytopenia, refer to Table 7.

Table 7

NCI CTCAE Toxicity Grade v 4.0	Action Required
Thrombocytopenia* ≥Grade 3 (platelet count <50,000/mm³	□ Withhold anticoagulation □ Monitor CBC at least every seven days □ If thrombocytopenia resolves to < Grade 3 (>50,000/mm³), restart anticoagulation unless other contraindication

6.2.1.3 Administration of Granulocyte Colony-Stimulating Factor

Neutropenia prophylaxis with either granulocyte-colony stimulating factor (G-CSF) is required. However, the selection of a particular drug, for example filgrastim, pegfilgrastim, or other is per treating physician discretion.

6.2.1.4 Infections Prophylaxis

Pneumocystis jirovecii pneumonia prophylaxis is required. However, the drug, dose and schedule selection are per treating physician discretion.

Additional antibiotic, antiviral, and antifungal prophylaxis is not required. However, treating physicians will be allowed to administer antibiotic, antiviral, and antifungal prophylactic medications if they desire. The use of live viral vaccines is contraindicated.

6.2.1.5 CNS Lymphoma Prophylaxis

Subjects at risk for CNS involvement may receive CNS lymphoma prophylaxis treatment. At risk for CNS involvement is defined as high LDH with ≥2

extranodal disease sites, testicular, vertebral body, bone marrow, paranasal sinus, renal, or adrenal involvement, or at the discretion of the treating physician. The following may be considered by the investigator: 4 – 8 doses of intrathecal methotrexate and/or cytarabine administered during the systemic treatment. CNS prophylaxis with IV drugs is not permitted.

7. STUDY EVALUATIONS

7.1 SCREENING EVALUATIONS

- A history and physical examination, including determination of height, weight and performance status should be performed within 28 days prior to enrollment
- The following laboratory studies should be performed within 28 days prior to enrollment:
    - CBC with differential, Serum chemistries – sodium (Na), potassium (K), chloride (Cl), glucose, bicarbonate (CO_2), blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), magnesium (Mg), phosphorus, total protein, albumin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, uric acid, lactate dehydrogenase (LDH), β-2 microglobulin, and urine analysis.
- Females undergo pregnancy testing within 28 days prior to enrollment.
- Quantitative immunoglobulins (IgG, IgA, and IgM) within 28 days prior to enrollment.
- HIV, Hepatitis C viral antibody, Hepatitis B surface antigen, Hepatitis B core antibody within 28 days prior to enrollment.
- The following staging studies should be performed within 28 days prior to enrollment:
    - CT scans of neck, chest, abdomen, and pelvis;
    - PET/CT Scan
    - Chest X-ray – PA and lateral;
    - An echocardiogram or MUGA scan

7.2 PRE-TREATMENT EVALUATIONS

The below testing may use the same data as Section 7.1 as long the test was performed within the below time windows

- A history and physical examination, including determination of vital signs, height, weight and performance status should be performed within 3 working/business days prior to the start of therapy
- The following laboratory studies should be performed within 3 working/business days prior to the start of therapy:
    - CBC with differential, Serum chemistries – sodium (Na), potassium (K), chloride (Cl), glucose, bicarbonate (CO_2), blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), magnesium (Mg), phosphorus, total protein, albumin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, uric acid, and lactate dehydrogenase (LDH)
- Females must follow pregnancy testing requirements as outlined in the Revlimid REMS™ program.
- For correlative studies, 30 ml of blood sample [one purple top tube (10 ml) and 2 heparin containing green top tubes (20 ml)] will be collected within 14 working/business days prior to the first dose of therapy. 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 2.2206, at M. D. Anderson Cancer Center (MDACC). Blood from red top and green top tubes will be processed for isolation of serum and peripheral blood mononuclear cells (PBMC), respectively using standard laboratory protocols.

- For correlative studies, an optional core needle biopsy and fine needle aspiration may be requested from an accessible FDG avid lymph nodes. 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 2.2206, at M. D. Anderson Cancer Center (MDACC).
- Unilateral Bone marrow biopsy and aspirate
- Standard of care testing not required by the protocol will include lumbar puncture for flow cytometry, glucose, protein, cell count and cytology if deemed necessary by the treating physician as part of initial disease workup.

7.3 EVALUATIONS DURING THERAPY

- A lymphoma therapy focused history and physical examination, including vital signs, height, weight and performance status assessment, should be performed within 3 working/business days prior to the start of each therapeutic cycle
- The following laboratory studies should be performed within 3 working/business days prior to the start of each therapeutic cycle:
    - CBC with differential, Serum chemistries – sodium (Na), potassium (K), chloride (Cl), glucose, bicarbonate (CO_2), blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), magnesium (Mg), phosphorus, total protein, albumin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, uric acid, lactate dehydrogenase (LDH). Serum β-HCG in women of child-bearing potential.
- The following staging studies should be performed at the conclusion of cycle 3 and before the start of cycle 4 of therapy:
    - FDG PET/CT scan. Interim imaging can be CT scans when PET/CT scans cannot be obtained.
- The following laboratory studies should be performed once weekly after the completion of therapy during the first treatment cycle, and in additional cycles at the treating physician's discretion:
    - CBC with differential. Additional laboratory studies can be obtained at the discretion of the treating physician.
- For correlative studies, 30 ml of blood sample [one purple top tube (10 ml) and 2 heparin containing green top tubes (20 ml)] will be collected 21 days (+/- 72 hours) after the first cycle of therapy, prior to start of cycle 2. An additional purple top tube (10ml) will be obtained prior to the start of each additional cycle of therapy. 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 2.2206, at M. D. Anderson Cancer Center (MDACC). Blood from red top and green top tubes will be processed for isolation of serum and peripheral blood mononuclear cells (PBMC), respectively using standard laboratory protocols. The isolation of serum from red top tubes may also be performed at the CTRC Laboratory at MDACC using standard laboratory protocols.

7.4 EVALUATIONS PERFORMED AFTER COMPLETION OF THERAPY

- A history and physical examination should be performed within 3 - 4 weeks after the start of Cycle 6
- The following laboratory studies should be performed within 3 - 4 weeks after the start of Cycle 6:
    - CBC with differential, Serum chemistries – sodium (Na), potassium (K), chloride (Cl), glucose, bicarbonate (CO_2), blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), magnesium (Mg), phosphorus, total protein, albumin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, uric acid, lactate dehydrogenase (LDH).
- The following staging studies should be performed within 3 – 4 weeks after the start of Cycle 6 (scan at end of therapy, EOT) :
    - PET/CT scan
    - Combined PET/CT and CT with IV contrast is acceptable, if applicable
    - Unilateral Bone marrow biopsy and aspirate (only if positive at the pre-treatment bone marrow obtain in 6.1.6 was positive for lymphoma)
    - Core needle biopsy of lymph nodes with suspicion of residual lymphoma (only if biopsy site is accessible by interventional radiology)
- A lymphoma specific history and physical examination should be performed every 3 months (+/- 4 weeks) during the first year after the EOT scan
- The following laboratory studies should be performed every 3 months (+/- 4 weeks) during the first year after the EOT scan:
    - CBC with differential, Serum chemistries – sodium (Na), potassium (K), chloride (Cl), glucose, bicarbonate (CO_2), blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), magnesium (Mg), phosphorus, total protein, albumin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, uric acid, lactate dehydrogenase (LDH).
- The following staging studies should be performed every 3 months (+/- 4 weeks) during the first year after the EOT scan:
    - PET/CT Scan or CT Scan with IV/oral contrast (CT is preferred if EOT PET/CT showed no FDG avid or suspicious lesions)
- A history and physical examination should be performed every 4 months (+/- 9 weeks) during the second year after the EOT scan
- The following laboratory studies should be performed every 4 months (+/- 9 weeks)

during the second year after the EOT scan:

- CBC with differential, Serum chemistries – sodium (Na), potassium (K), chloride (Cl), glucose, bicarbonate (CO_2), blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), magnesium (Mg), phosphorus, total protein, albumin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, uric acid, lactate dehydrogenase (LDH).

- The following staging studies should be performed every 4 months (+/- 9 weeks) during the second year after the EOT scan:
  - PET/CT Scan or CT Scan with IV/oral contrast (CT is preferred if EOT PET/CT showed no FDG avid or suspicious lesions)
- Beyond the second year after EOT scan: restaging imaging, laboratory studies, and history and physical examination schedule will be determined by the treating physician.
- For correlative studies, 30 ml of blood sample [one purple top tube (10 ml) and 2 heparin containing green top tubes (20 ml)] will be collected within 3-4 weeks after the last cycle of therapy. An additional purple top tube (10ml) will be obtained at future visits at the discretion of the principle investigator if there is suspicion for relapse or other new disease related complaint. 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 2.2206, at MDACC. Blood from red top and green top tubes will be processed for isolation of serum and peripheral blood mononuclear cells (PBMC), respectively using standard laboratory protocols. The isolation of serum from red top tubes may also be performed at the CTRC Laboratory at MDACC using standard laboratory protocols.

8. EVALUATION OF RESPONSE

Response assessment testing will be detailed in Section 7. In brief, CT scans will be obtained at screening, once between 3 – 4 weeks after start of Cycle 6, and in follow-up at specified time points. FDG PET/CT scans will be obtained at screening, between Weeks 7 – 9 (after Cycle 3 but before Cycle 4), and once 3 – 4 weeks after start of Cycle 6. Obtaining FDG PET concurrently with CT scans will be allowable as long as the CT imaging is sufficient for response assessment.

The primary endpoint of the phase II trial and patients treated at the MTD in the phase Ib trial will be the response rate, complete and overall, at the EOT scan, as defined by the Lugano Criteria and will be assessed by a dedicated Radiology collaborator.(70) For full details, please see the reference.

Table 8

Response	PET-CT Based Response	CT-Based Responses
CR	Complete metabolic response Score 1, 2, or 3 with or without a residual mass on 5 point scale 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	Complete Radiographic Response Target Nodes/nodal masses must regress to <= 1.5cm in longest dimension No extralymphatic sites of disease
PR	Partial Metabolic Response Score 4 or 5 with reduced uptake compared with baseline and residual masses of any size At interim, these findings suggest responding disease As end of treatment, these findings indicate residual disease	Partial Remission (all of the following): >=50% decrease in sum of the product of diameters of up to 6 target measureable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5mm as default value When no longer visible on CT, assign 0 x 0 mm For a node 5 mm x 5mm, but smaller than normal, use actual measurement
SD	No metabolic response Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	Stable disease < 50% decrease in sum of the product of diameters of up to 6 target measureable nodes and extranodal sites, no criteria for disease progression are met
PD	Progressive metabolic disease Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	Progressive disease requires at least one of the following: 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 (e.g, a 15-cm spleen must increase to >=16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline

The complete response rate is calculated as the proportion of subjects who have achieved CR prior to any treatment change. The overall response rate is defined as the proportion of subjects who have achieved either CR or PR prior to any treatment change. Of note, patients who had an initial positive bone marrow biopsy during testing in Section 7.1 will need to have a bone marrow biopsy repeated after therapy to confirm response.

The secondary endpoint of the phase II and patients treated at the MTD in the phase Ib trial will be the survival outcomes (progression free and overall survival), and safety after 6 courses.

Progression free survival is defined as the time from study entry to objective disease progression or death from any cause, whichever occurs first. Objective disease progression will be evaluated utilizing the Lugano criteria.(70) Subjects who did not experience disease progression and who did not die before the clinical data cut-off date will be censored at the time of the last visit with adequate response assessment.

Overall survival is defined as the time between study entry and death from any cause. Subjects who complete the study and are still alive at the time of the clinical data cutoff date will be censored at the last visit date or the last contact date, whichever is later. Subjects who were lost to follow-up prior to the clinical data cut-off date will also be censored at the time of the last contact.

Safety is defined as a description of the significant toxicities encountered by patients, as defined in section 10.

9. STATISTICAL CONSIDERATIONS

9.1 DETERMINATION OF SAMPLE SIZE

The maximum sample size for this phase Ib/II study is 59 with 15 for the phase Ib portion and additional 44 for the phase II portion. The 6 patients treated at the MTD in the phase Ib portion will be included in the analysis for the phase II portion to reach the sample size of 50 (6+44). The phase II trial will determine the complete response rate after completion of therapy at the recommended phase 2 dosing levels. The obinutuzumab-CHOP trial (Gather) found an ORR of 83%, and CR rate of 55%. It is hypothesized that the combination of lenalidomide, obinutuzumab and CHOP should result in a CR rate of >75%. With a sample size of 45, the study will have a power of 0.8 to detect the difference between the null hypothesis response rate of 0.55 and the alternative hypothesis response rate of 0.75 assuming a two-sided type I error rate of 0.05. We would plan to enroll 50 patients in the phase II portion and MTD cohort of the of the Phase Ib portion of the trial to account for potential dropout or other issues impacting our final numbers for efficacy evaluation.

9.2 PLANNED EFFICACY EVALUATIONS

The planned efficacy evaluations will be defined by each portion of the trial:

9.2.1 Phase Ib:

The primary endpoint of the phase Ib trial is not efficacy, but determination of the MTD. The patients treated at the MTD in the phase Ib component of the trial will be included in the efficacy analysis of patients treated in the Phase II trial.

The MTD determination is defined in Section 5.1

9.2.2 Phase II:

The efficacy evaluation in patients treated at the MTD in phase Ib and in phase II portions of the trial will occur by evaluation of the end of treatment and subsequent follow up PET/CT scans, as defined in Sections 7.4 and 8.

9.3 METHOD OF ANALYSIS

9.3.1 Clinical Outcomes Analysis:

Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize categorical variables. Logistic regression will be utilized to assess the effect of patient prognostic factors on the response rate and the toxicity rate. The distribution of time-to-event endpoints including overall survival and progression free survival will be estimated using the method of Kaplan and Meier. Comparison of time-to-event endpoints by important subgroups will be made using the log-rank test. Cox proportional hazard regression may be employed for multivariate analysis on time-to-event outcomes.

Toxicity data will be summarized by frequency tables for all patients. For the efficacy

endpoints, intend-to-treat analysis will be applied to the eligible patients. For the toxicity endpoint, per-treated analysis will be performed to include any patient who received the treatment regardless of the eligibility or the duration or dose of the treatment received.

9.3.1.1 Phase Ib:

The primary objectives of phase 1b are to determine the MTD of lenalidomide, obinutuzumab, and CHOP. The secondary objectives are to determine the efficacy (complete and overall response rate) and tolerability. Dose de-escalation will be guided by standard 3+3 design. The first cohort of 3 patients will be treated at Dose Level 1 and evaluated for DLT (definition in section 5.1) at the end of the first cycle (21 days per cycle). The algorithm is as follows: (1) As this trial has a high expectation of dosing safety, dosing will start at the anticipated MTD level (i.e., Dose Level 1). At Dose Level 1, if 0 or 1 out of 3 patients experiences DLT, an additional 3 patients will be treated in this cohort. (2) If no more DLTs develop at this dose (i.e., < 2 out of a total of 6 patients develops a DLT), Dose Level 1 will be the MTD and used in the Phase II portion of the trial. (3) At any given dose, if greater than 1 out of 3 patients or 1 out of 6 patients experience DLT, the dose level exceeds the MTD and 3 patients will be treated at the next lower dose. (4) If 0 or 1 out of 3 patients experiences DLT, an additional 3 patients will be treated at this dose level. (5) If no more DLTs develop at this dose level, then the current dose level will be the MTD and used in the Phase II portion of the trial. Following the above scheme, MTD is defined as the highest dose level in which 6 patients have been treated with less than 2 instances of DLT. MTD will be used in the Phase II portion of the trial.

Given the prior tolerance of R2CHOP and Obinutuzumab-CHOP, it is anticipated that eligible number of patients are required for the phase 1b part will be a maximum of 15 patients, and possibly only six patients.

9.3.1.2 Phase II

Once the MTD is determined, a planned 50 patients will be treated at the RP2D (6 patients will be from the phase Ib who are treated at the MTD).

To ensure treatment efficacy and patient safety, end of therapy complete response rate and DLT at 1 cycle during the Phase II portion of the trial will be monitored simultaneously using the Bayesian approach of Thall, Simon, Estey(71) as extended by Thall and Sung(72). The stopping boundaries will be calculated based on conjugate beta-binomial distribution. The trial will be stopped early if

$$\Pr(\text{CR rate} < 0.55 \mid \text{data}) > 0.95$$

or

$$\Pr(\text{DLT rate} > 0.30 \mid \text{data}) > 0.95$$

That is, the trial will be stopped early if there is more than a 95% probability that the CR rate is lower than 55% or if there is more than a 95% probability that the DLT rate is higher than 30%. We assume that CR and DLT follow a prior distribution of beta (0.55, 0.45) and beta (0.3, 0.7),

respectively.

The above futility and toxicity monitoring rules will be implemented by a cohort size of 10, starting from the 10th patient in Phase 2 have been enrolled. The corresponding stopping boundaries are listed in Table 9.1. For example, the patient enrollment will be stopped if more than 5 DLTs or less than 3 complete responses are observed among the first 10 patients. The patient enrollment will be halted for interim toxicity look if the number of non-DLT required for continuing the trial to next stage has not been achieved, but will not be halted for interim efficacy look.

Table 9.1: The stopping boundaries of Phase II trial

Number of patients evaluated	Stop the trial if there are this many responses observed	Stop the trial if there are this many toxicities observed
10	0-2	6-10
20	0-7	10-20
30	0-11	13-30
40	0-16	17-40
50	Always stop with this many patients	Always stop with this many patients

Table 9.2: The operating characteristics are summarized in the following table (based on simulations from 10,000 trials).

True CR Rate	True Toxicity Rate	Prob(stop the trial early)	Average number of patients treated
0.40	0.10	0.652	32.1
	0.30	0.686	30.5
	0.50	0.947	18.9
0.55	0.10	0.096	47.2
	0.30	0.185	44.4
	0.50	0.862	23.0
0.70	0.10	0.003	49.9
	0.30	0.102	46.8
	0.50	0.848	23.7

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

9.3.2 Analysis Plan:

Data analysis will be performed using SAS or R, as appropriate. The overall and complete response rates, DLT rate, and OS/PFS rate at 1 year will be summarized by relative frequency and 95% confidence interval. Patients who received at least one dose of the treatment drug will be evaluable for toxicity outcomes. Toxicities will be summarized by dose levels, by grade and by their relationship to the treatment. The intent-to-treat patients will be used for the primary efficacy analysis; patients who are lost-to-follow up in the first 3 cycles will be treated as failures. The distribution of time-to-event endpoints including OS and PFS will be estimated by the method of Kaplan and Meier Analysis. Comparison of time-to-event endpoints by important subgroups will be made using the log-rank test. Cox proportional hazard regression will be employed for multivariate analysis on time-to-event outcomes.

9.3.3 Correlative Assay Analysis:

The following correlative studies will be performed in Dr. Neelapu, Dr. Davis, or an MD Anderson Core laboratory using the blood, serum, and biopsy samples.

9.3.3.1 To determine whether obinutuzumab, lenalidomide, and CHOP enhance the frequency and function of tumor-specific T-cells in the peripheral blood, the phenotype and function of T cells will be assessed as follows:

Phenotypic studies for T cells. PBMC (1 x 10^5 per tube) will be analyzed by multiparametric flow cytometry on 6-color, 8 parameter FACS Canto (BD Pharmingen) after staining with a panel of antibodies in 2 separate tubes. Tube 1: PBMC will be stained with CD3, CD4, CD8, CD45RO, CD69, and PD-1 to determine the percentage of total T cells, CD4+ T cells, CD8+ T cells, effector/memory (CD45RO+) T cells within each subset, activation status (CD69+) of T cells within each subset, and PD-1 expression within each subset. Tube 2: PBMC will be stained with CD3, CD4, CD8, CD45RO, CD62L, CD27, CD127 and CCR7 to determine the percentage of effector memory T cells (CD45RO+CD27-CCR7-, CD62L-CD127+) and central memory T cells (CD45RO+CD27+CCR7+, CD62L+CD127+) within CD4+ and CD8+ T-cell subsets. The absolute number of each of these T-cell subsets in the peripheral blood of the patients will be calculated using the following formula: (absolute number of lymphocytes per μl of blood on the CBC analysis) x (% of T-cell subset in lymphocyte gate).

9.3.3.2 *Statistical considerations for 9.3.3.1.* The percentage of various T-cell subsets will be collected at each of the planned time points. Spaghetti plots will be used to show the biomarker measurements change overtime. Longitudinal analysis including mixed effects model for time-dependent variables will be performed. The percentage change for the biomarkers from baseline to the various time points will be calculated. The correlations among the percentage changes for different biomarkers will be assessed by scatter plots and Spearman's correlation coefficient. The association between the percentage change and patient's clinical outcome such as complete and overall response will be evaluated. Wilcoxon rank sum test will be used to test the difference in percentage change of biomarker between the response group and the non-response group. The percentage change will also be dichotomized into two categories (high vs. low) based on a cutoff point which will be determined after examination of the data. Fisher's exact test will be used to assess the associations between the dichotomized variables for percentage change and clinical response.

To evaluate changes in T-cell subsets by phenotypic studies before and after obinutuzumab, lenalidomide, and CHOP treatment at the different time points, we will perform a two-sided paired t-test or Wilcoxon signed rank test for the experiments proposed under 9.3.3.1.

9.3.3.3 To evaluate the mutational and gene expression data from RNA-Seq of tumor biopsy material, the following analyses will be performed. The baseline biopsy will be evaluated with RNA sequencing (RNA-Seq)(73), in comparison with germline DNA, to determine gene expression, translocations, and mutations including those known to correlate with ibrutinib resistance (e.g., *BTK, PLCγ2, MYD88*, *CARD11, CD79A/B*).(18, 74-77) To attempt correlation of GEP data with clinical responses to obinutuzumab, lenalidomide, and CHOP by comparing baseline aggregate expression data between responders and non-responders, a regression analysis will be performed. Data from RNA-Seq will be processed using published methods, including standard quality assessments and R software packages.(73, 78, 79) Gene expression will be compared against the continuous variable of tumor regression percentage and/or changes in LymphoSIGHT values, and analyzed using Gene Set Enrichment Analysis (GSEA)(80) to evaluate for processes in the tumor cells and microenvironment which are associated with response to R-CHOP, but have an unknown

relevance to obinutuzumab, lenalidomide, and CHOP.(18) We will also perform RNA-Seq on biopsies of residual disease, and potentially perform focused deep sequencing of DNA from residual tumor, PBMC (germline), and initial biopsy. Based upon findings in 9.3.3.1 and from RNA-Seq of biopsy material, we may elect to perform gene expression profiling or RNA-Seq on PBMC, was employed in our previous rituximab and lenalidomide trials.

9.3.3.4 Analysis of LymphoSIGHT data

Minimum Residual Disease (MRD) will be determined by NGS method as MRD negative or MRD positive at each MRD assessment time point. MRD status of subjects will be assessed by an NGS-based method and compared with results from imaging based assessments. Correlation of MRD status from both types of assessment with clinical outcomes will be analyzed. In order to evaluate how well the MRD assay predicts clinical outcome, its sensitivity and specificity in predicting disease progression will be calculated.

The sensitivity and specificity of MRD in predicting disease progression is described in the table below.

Post-baseline MRD Assays	Clinical Outcome	
	Subjects who progressed/relapsed during the study	Subjects who did not progress/relapse during the study
At least one assay with MRD positive	True Positive	False Positive
All assays with MRD negative	False Negative	True Negative
	↓ Sensitivity	↓ Specificity

$$Sensitivity = \frac{True\ Positive}{True\ Positive + False\ Negative}$$

$$Specificity = \frac{True\ Negative}{True\ Negative + False\ Positive}$$

In subjects who achieve CR, the MRD test results will also be evaluated to assess time to achieve MRD status, duration of MRD status, and their correlation to clinical progression.

The sensitivity and specificity of MRD in predicting clinical outcomes such as PFS and OS will be similarly analyzed.

10. REPORTING OF ADVERSE EVENTS

10.1 ASSESSMENT OF SAFETY

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

10.1.1 Adverse Events

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

This includes the following:

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

10.1.2 Serious Adverse Events

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

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

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

treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the 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 for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

10.2 METHODS 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), Celgene, and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

10.2.1 Adverse Event Reporting Period

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

10.2.2 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 obinutuzumab, lenalidomide, or CHOP (see following guidance), and actions taken.

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

Yes

There is a plausible temporal relationship between the onset of the AE and administration of obinutuzumab, lenalidomide, or CHOP, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a

known pattern of response to the [study drug}; and/or the AE abates or resolves upon discontinuation of the [study drug} or dose reduction and, if applicable, reappears upon re-challenge.

No

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

Expected AEs are those AEs that are listed or characterized in the Package Inserts or current Investigator Brochures.

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

10.2.2.1 Second Primary Malignancies

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm the subject is in. This includes any second primary malignancy, regardless of causal relationship to obinutuzumab, lenalidomide, or CHOP, occurring at any time for the duration of the study, from the time of signing the informed consent document (ICD) for at least 5 years from the date the last subject is entered into the study. Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF (i.e., AE and SPM CRF) and subject's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (e.g., any confirmatory histology or cytology results, X-rays, CT scans, etc.).

10.2.2.2 Pregnancies

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

and/or lenalidomide, or the partner of a male patient becomes pregnant while receiving therapy or within three months of completing therapy, a report should be completed and expeditiously submitted to Genentech and Celgene, Inc.

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

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

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

10.3 PROCEDURES FOR RECORDING, AND REPORTING SERIOUS ADVERSE EVENTS

- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

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

Reporting to FDA:

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

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

10.3.1 Specific Instructions for Recording Adverse Events

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

10.3.1.1 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.

10.3.1.2 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".

10.3.1.3 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").

10.3.1.4 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.

10.3.1.5 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.

10.3.1.6 Safety Reconciliation

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

10.3.1.7 Adverse Events of Special Interest (AESIs)

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

The following AEs are considered of special interest and must be reported to the Sponsor expeditiously (see Section 10.3.1.8 for reporting instructions) irrespective of regulatory seriousness criteria:

- Tumor Lysis Syndrome (TLS - all grades)

10.3.1.8 Serious Adverse Event Reporting

Investigators must report all SAEs to Genentech and Celgene within the timelines described below. The completed MedWatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:
(650) 225 4682

OR
(650) 225 5288
Email: us_drug.safety@gene.com

Celgene Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

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

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

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

Additional reporting requirements to Genentech include the following:

- Any reports of pregnancy following the start of administration with the obinutuzumab and within the follow-up period (for female patients within one year after the last dose of obinutuzumab or the partner of a male patient within three months of completing therapy) will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.
- All non-serious *obinutuzumab* AEs originating from the study will be forwarded Genentech *quarterly.*

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

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using 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 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.

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

MedWatch 3500A Reporting Guidelines

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

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the AE 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 AE description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and AE was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the medical science lisason assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at:
http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm

10.3.2 Additional Reporting Requirements for IND

For investigator-sponsored IND studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the 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 AE that is unexpected and assessed by the investigator to be possibly related to the use of obinutuzumab. An unexpected AE is one that is not already described in the Obinutuzumab Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of obinutuzumab. An unexpected AE is one that is not already described in the Obinutuzumab investigator brochure.

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

Written IND safety reports with analysis of similar events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

Contact Information for IND Safety Reports

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 the following:

Genentech Drug Safety Fax: (650) 225 4682 or (650) 225 5288
Site's IRB: [(713)794-4589 Contact info/fax]

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

Tel: (888) 835-2555
Fax: (650) 225-4682 OR (650) 225-5288

10.4 STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech and Celgene. 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 and Celgene. 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

11. RETENTION OF RECORDS

U.S. FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply. It is the policy of MD Anderson to maintain records from clinical research indefinitely. A storage location memo will be provided to the MD Anderson IND office at the time of protocol close out.

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

Appendix 1 Study Flowchart

	During Screening	Obtain ≤ 28 days of cycle 1	Obtain ≤ 3 d of cycle 1 - 6 start	Obtain at the end of cycle 3 and prior to start of cycle 4	Obtain within 3 to 4 weeks after start of cycle 6 (End of Therapy)	Obtain every 3 months during year 1 and every 4 months during year 2 after End of Therapy testing
Informed Consent		X				
Lymphoma-relevant History and Physical		X	X		X	X
Performance status Assessment		X	X			
Vital Signs			X			
Routine Clinical Laboratory Assessment[1]		X	X		X	X
Quantitative Immunoglobulins		X				
HIV, HCV, HBV testing		X				
DLBCL Confirmation Biopsy	X[2]					
FDG PET/CT	X[2]	X[2]		X	X	X[5]
CT with IV contrast of neck – pelvis[3]	X[2]	X[2]			X	X[5]
Chest X-ray	X[2]	X[2]				
Echo or MUGA	X[2]	X[2]				
Correlative Blood Draw		X	X[6]		X	X[4]
Bone Marrow Biopsy		X			X[4]	
Lumbar Puncture		X[4]				

1: Routine clinical laboratory assessment will include: CBC with differential, Serum chemistries – sodium (Na), potassium (K), chloride (Cl), glucose, bicarbonate (CO_2), blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), magnesium (Mg), phosphorus, total protein, albumin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, uric acid, and lactate dehydrogenase (LDH), and other testing at the discretion of the treating physician.

2: These tests are standard of care tests required of all patients treated by the M.D. Anderson Department of Lymphoma for newly diagnosed DLBCL. As these tests are not protocol specific, they may be obtained at the discretion of the treating physician during the screening period (i.e., they will be allowed for protocol analysis if they are obtain as routine standard of care testing prior to the patient undergoing screening for the protocol). DLBCL Confirmation (lymph node biopsy and bone marrow) will be within 42 days of Day 1.

3: CT with IV contrast may be obtained simultaneously with FDG PET/CT scans as per MD Anderson Diagnostic Imaging protocols.

4: This test is not required by the protocol and will be obtained at the discretion of the treating physician if deemed necessary for initial disease workup.

5. At follow up time points, either FDG PET/CT or CT with IV and oral contrast are acceptable

6. Per Section 7.3 An additional purple top tube (10ml) will be obtained prior to the start of each additional cycle of therapy

N.B.: All time points mentioned in the Study Flowchart are detailed in Section 7, and are included in this table format for easy visualization. The time points in section 7 include +/- time windows to account for scheduling issues/delays. Any discrepancies between Section 7 and the Study Flowchart will be resolved in favor of Section 7.

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 Safety Reporting Fax Cover Sheet

Genentech
A Member of the Roche Group

GENENTECH SUPPORTED RESEARCH

AE/SAE FAX No: (650) 225-4682
Alternate Fax No: (650) 225-5288

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 4 FDA MedWatch 3500 Form

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

Appendix 5 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

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