IRB 20-0986: A Multicenter, Single-Arm, Phase I/II Dose Finding and Efficacy Study of Venetoclax, CC-486, and Obinutuzumab in Minimally-Pretreated Follicular Lymphoma

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This study is being conducted by institutional members of the Personalized Cancer Care Consortium (PCCC).

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STUDY SUMMARY

TITLE	A Multicenter, Single-Arm, Phase I/II Dose Finding and Efficacy study of Venetoclax, CC-486, and Obinutuzumab in Minimally-Pretreated Follicular Lymphoma
COLLABORATOR PROTOCOL NUMBER:	Celgene S13676 / Genentech #ML41369
FUNDING	Celgene Corporation, a Bristol-Myers Squibb subsidiary Address: 86 Morris Avenue Summit, NJ 07901 Telephone: (908) 673-9000 Genentech Incorporated, a Roche subsidiary Address: 1 DNA Way South San Francisco, CA 94080 Telephone: (650) 225-1000
TYPE OF RESEARCH:	Interventional (clinical trial) with correlative biomarker studies
PRIMARY OBJECTIVES	● Determine the RP2D of combined venetoclax/CC-486 in patients with minimally pre-treated follicular lymphoma via a dose-escalation protocol. ● Determine the safety and tolerability of combined venetoclax, CC-486, and obinutuzumab in human subjects by rates of adverse events and discontinuation. ● Determine the complete response (CR) rate in the expansion cohort by positron emission tomography (PET) scan.
SECONDARY OBJECTIVES	● Determine median overall survival (OS) and median progression-free survival (PFS) of patients in the expansion cohort. ● Determine effect of three cycles of combined oral therapy alone (venetoclax + CC-486) in expansion cohort through a window design (assessed by PET scan). ● Determine CR rate at 30 months after initiation of therapy (CR30), assessed with PET scan.
EXPLORATORY OBJECTIVES	● Assess biomarkers and markers of advanced disease by gene sequencing of pre-treatment biopsy material tumor ● Measurement of minimal residual disease (MRD) via circulating tumor DNA ● Pharmacodynamic assessment of the effect of oral azacitidine on circulating cell-free DNA methylation
STUDY CENTER(S)	*University of Chicago Personalized Cancer Care Consortium*

NUMBER OF SUBJECTS	44-50, with approximately 50% of planned enrollment at University of Chicago Medicine main campus and the remainder distributed among participating sites.
DIAGNOSIS AND MAIN INCLUSION CRITERIA	Adult patients with grade 1-3a follicular lymphoma with an indication for treatment due to symptoms or clinical criteria, have measurable disease with documented progression, and who are treatment-naive or previously treated with two or fewer therapeutic courses consisting of a total of 16 or fewer doses of anti-CD20 antibody therapy.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	The treatment duration is up to 12 months. Screening: up to 7 days. Treatment: 12 consecutive cycles of 28 days each. Follow-up: final imaging study at 30 months post treatment initiation. After the end of treatment, each subject will be followed for the occurrence of adverse events per Section 8.2 of the protocol. Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status per Section 8.2 until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. The total duration of the study is expected to be 55 months inclusive of treatment and follow up.
INVESTIGATIONAL PRODUCT	A three-drug combination of venetoclax (Venclexta ®), CC-486 (oral azacitidine), and obinutuzumab (Gazyva ®)
DOSE, ROUTE, REGIMEN	**Venetoclax**: 400-800mg by mouth once daily on days 1-28 of a 28 day cycle. **CC-486**: 100-200mg by mouth once daily on days 1-14. **Obinutuzumab**: 1000mg intravenous administration on day 1, 8, and 15 of the first cycle, followed by day 1 only.
DURATION OF ADMINISTRATION	Venetoclax: twelve 28-day cycles. CC-486: twelve 28-day cycles. Obinutuzumab: nine 28-day cycles. Obinutuzumab will start in cycle 1 in the dose finding arm and on cycle 4 of the expansion cohort.
STATISTICAL METHODOLOGY	Dose finding: 3+3 design with 3 dose levels and 2 optional dose de-escalation levels.

	Expansion cohort: Simon 2-stage design with 80% power and a type I error rate (α) of 10% to detect a difference in the primary study outcome: ≥ 50% 6-month complete metabolic response (CR) rate indicating an effective combination, versus ≤ 30% 6-month CR rate indicating an ineffective combination.

LIST OF ABBREVIATIONS

ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
AML	Acute Myeloid Leukemia
amu	Atomic Mass Unit
BMI	Body Mass Index
BSA	Body Surface Area
BSD	Biological Sciences Division
CBC	Complete Blood Count
CC-486	Investigational name for oral azacitidine (Celgene Corp.)
CCTO	Cancer Clinical Trials Office
CD20	Cluster of Differentiation 20 (B-lymphocyte antigen)
CLL	Chronic Lymphocytic Leukemia
CR	Complete metabolic Remission
CRF	Case Report Form
CRA	Clinical Research Associate
CRAC	Clinical Research Advisory Committee
CTRC	Clinical Trials Review Committee
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DNMT	Deoxyribonucleic acid methyltransferase
DOA	Delegation of Authority
DSMB	Data and Safety Monitoring Board
ECI	Event of Clinical Interest
FDA	United States Food and Drug Administration
FL	Follicular Lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GELF	Groupe d'Etude des Lymphomes Folliculaires
HBcAb	Hepatitis B core Antigen
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
IB	Investigators' Brochure
IDS	Investigational Drug Services
IRB	Institutional Review Board
IV	Intravenous
JC Virus	John Cunningham Virus
MTD	Maximal Tolerated Dose

NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NHL	Non-Hodgkin Lymphoma
OCR	Office of Clinical Research
ORR	Overall Best Response Rate
OS	Overall Survival
OTC	Over the Counter
PD	Progression of Disease
PFS	Progression-Free Survival
PHI	Protected Health Information
PI	Principal Investigator
PML	Progressive Multifocal Leukoencephalopathy
PO	Per Os, Oral
PR	Partial Response
REDCap	Research Electronic Data Capture software
RGU-CHO	N-formylguanylribosylurea
RGU	Guanlyribosylurea
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 Dose
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAM	Scientific Accrual and Monitoring Committee
SC	Subcutaneous
SD	Stable Disease
SLL	Small Lymphocytic Lymphoma
TGI	Tumor Growth Inhibition
TLS	Tumor Lysis Syndrome
UCCCC	University of Chicago Comprehensive Cancer Center
UP	Unanticipated Problem

1 INTRODUCTION

1.1 BACKGROUND AND RATIONALE

1.1.1 Background: Current Understanding of Follicular Lymphoma

Follicular lymphoma (FL) is an incurable, indolent B-cell lymphoma. It is the most common indolent lymphoma, and second-most common subtype of non-Hodgkin lymphoma overall (Bosman et al. 2017). The majority of patients live with their disease over a period of years to decades, and experience repeated relapses requiring therapy, creating a major public health burden (Monga et al. 2019). Cumulative therapy-related toxicity and disease progression can result in diminished functional status or shortened survival over time. 1-2% of patients with FL per year will experience histologic transformation to an aggressive lymphoma subtype (Link et al. 2013). If a patient has received anthracycline-based chemotherapy prior to transformation, anthracycline-sparing salvage chemotherapy may be required at the time of transformation (Godfrey, Leukam, and Smith 2018). The threat of transformation and disease progression hangs over patients; emotional and psychological distress accompany both periods of therapy and active surveillance (Poe, Hayslip, and Studts 2012).

Not all patients with known FL require immediate treatment. The decision to treat is based on the presence of symptoms attributable to FL or by clinical criteria put forth by the Groupe d'Etude des Lymphomes Folliculaires (GELF) (Brice et al. 1997). Patients who do not meet the threshold for immediate therapy are typically managed with active surveillance without any anti-cancer treatment. A short course of treatment with an anti-CD20 monoclonal antibody is an alternative to observation alone in patients not meeting treatment criteria for intensive treatment (National Comprehensive Cancer Network 2017), though this strategy does not confer a survival benefit (Ardeshna et al. 2014). Once a need for systemic therapy is established by symptoms or clinical criteria, the current standard-of-care options include 1) one of several combinations of chemotherapy and anti-CD20 immunotherapy or 2) lenalidomide and anti-CD20 immunotherapy. The goal of this treatment is to induce remission for a time and to improve symptoms. Neither is thought to be curative. The limited options for chemotherapy-sparing options result in broad population exposure to chemotoxicity without the benefit of a cure.

In order to develop chemotherapy-sparing therapy options, preclinical studies have identified a number of recurrent genomic alterations in FL as potential therapeutic targets. Among the candidate targets, the pro-survival protein Bcl-2 would appear to be the most promising: FL is defined by near-universal chromosomal rearrangements of *BCL2* and the immunoglobulin heavy chain loci leading to Bcl-2 overexpression (Burkhard et al. 2015). However, monotherapy trials of venetoclax (BH3 mimetic peptide) targeting Bcl-2 have found only modest efficacy (Davids et al. 2017). A potential explanation for the limited observed efficacy is that *BCL2* rearrangement is a very early event in the disease, often preceding any clinical manifestation (Mamessier, Broussais-Guillaumot, et al. 2014). At the time of clinically meaningful disease, additional mutations are typically found, most commonly in epigenetic regulatory factors (Okosun et al. 2014; Korfi et al. 2017). Increasing understanding of FL biology and pathogenesis over the past several years has resulted in a consensus model of FL common progenitor cells which likely live in the marrow, shuttle in and out of lymph node germinal centers (Burkhard et al. 2015; Mamessier, Song, et al. 2014). In germinal centers, the early malignant cells undergo repeated antigenic stimulation and hypermutation, resulting in

increasingly deleterious mutations and activation of additional survival pathways through epigenetic modification (Basso and Dalla-Favera 2015). Late in the course of some patients' disease, certain subclones develop oncogenic mutations in proliferative pathways associated with histologic transformation to aggressive lymphoma (Scherer et al. 2016; Loeffler et al. 2015). Based on these preclinical models, we hypothesize that targeting epigenetic reprogramming of malignant cells along with the Bcl-2 survival signal in early stages of the disease course, before additional oncogenic mutations accumulate in aggressive clones, may restore the anti-cancer effect of Bcl-2 inhibition in this disease.

Given universal CD20 expression, therapies incorporating anti-CD20 therapy have shown a survival benefit in FL compared to therapies without it (Marcus et al. 2005; Hiddemann et al. 2005), and this is now standard of care. Obinutuzumab is a second-generation anti-CD20 therapy which has been shown to confer a benefit compared to first generation therapy rituximab in patients previously treated with rituximab (Marcus et al. 2017; Bruce D. Cheson et al. 2018). Since patients in this trial may have been treated with rituximab, obinutuzumab will be incorporated into the treatment regimen to maintain the known benefit of CD20-directed therapy.

Herein, we propose a dose-finding safety and tolerability trial of venetoclax, oral azacitidine (CC-486), and obinutuzumab in minimally pretreated follicular lymphoma patients with progression of disease after prior therapies. We define minimally pretreated as patients who are treatment-naïve or have received fewer than two prior lines of anti-CD20 monotherapy consisting of a total of 16 or fewer doses. If a safe and tolerable recommended Phase 2 dose is found (RP2D), an expansion cohort targeting complete metabolic remission rate (CR) at 6 months will be pursued to evaluate efficacy.

NOTE: There are multiple regimens approved by the FDA for patients with previously untreated or relapsed follicular lymphoma. This proposed regimen is investigational and has not been proven to provide benefit over the available therapies. Current options for management of follicular lymphoma are available at www.NCCN.org.

1.1.2 Investigational Agents

1.1.2.1 Venetoclax

a) Physical Properties

Venetoclax is a small-molecule BH3 protein mimetic with the chemical name 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide). The molecular formula for venetoclax is $C_{45}H_{50}ClN_7O_7S$ and its molecular weight is 868.4 amu. It is formulated for oral administration and is supplied as a tablet.

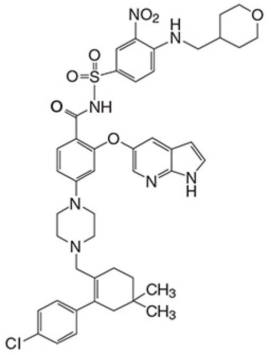

Figure 1: Molecular structure of venetoclax.

b) Mechanism of Action and Approved Indications

Venetoclax (Venclexta®) is a Bcl-2-selective inhibitor, which binds with high affinity to Bcl-2 and with lower affinity to Bcl-XL and Bcl-w. Inhibition by venetoclax efficiently disrupts Bcl-2 signaling in cells and rapidly induces multiple hallmarks of apoptotic cell death in Bcl-2-dependent human tumor cell lines (Souers et al. 2013). Venetoclax was first approved in the United States (U.S.) on 11 April 2016 for the treatment of patients with chronic lymphocytic leukemia (CLL) with del (17p). On 08 June 2018, the FDA approved the combination therapy of venetoclax and rituximab and the venetoclax expanded monotherapy. This approval confirmed the clinical benefit of venetoclax in the relapsing/refractory (R/R) CLL population with or without del (17p).

On May 15, 2019, the FDA approved venetoclax in combination with obinutuzumab in previously untreated patients with CLL or SLL. In addition, venetoclax is approved in combination with azacitidine or decitabine or low-dose cytarabine (LDAC) for the treatment of newly-diagnosed AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. This indication is approved under accelerated approval based on response rates.

In the EU, venetoclax in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least 1 prior therapy. Monotherapy is indicated for the treatment of CLL in the presence of 17p del or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or in the absence of 17p del or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

c) Pharmacologic Data

The pharmacokinetic behavior of venetoclax was evaluated in CD1 mice, Sprague-Dawley rats, cynomolgus monkeys, and beagle dogs. The pharmacokinetics were characterized by plasma elimination half-lives which ranged from 2.2 hours in monkey to 12.0 hours in dog. Volumes of distribution at steady state (Vss) were low to moderate in all species, with values increasing from 0.30 L/kg in dog to 1.1 L/kg in rat. Plasma clearance values were low in all species, decreasing from a high of 0.27 L/hr*kg in monkey to a low of 0.02 L/hr*kg in dog (AbbVie internal report). The apparent permeability of venetoclax was in the low to moderate range: 0.4 – 0.9 × 10–6 cm/sec in MDCK cells and 1.9 – 2.3 × 10–6 cm/sec in

Caco-2 cells (AbbVie internal report). In bile duct-cannulated Sprague-Dawley male rats given a 5 mg/kg single oral dose of [3H]venetoclax, only about 14.7% of the dose was absorbed, as indicated by the sum of radioactivity recovered in bile and urine (AbbVie internal report).

Venetoclax is highly protein-bound, independent of concentration, with fraction unbound (fu) values < 0.01 in mouse, rat, dog, and human; M27 is also highly protein bound in mouse, rat, dog, monkey, and human with fu < 0.01. Blood-to-plasma concentration ratios show venetoclax and M27 do not partition preferentially into the cellular compartment in any of the species studied (AbbVie internal report). Following oral administration in mouse, rat, dog, and human, venetoclax and its metabolites were cleared primarily via biliary excretion and fecal elimination, with minimal renal clearance.

Venetoclax and M27 are predominantly metabolized by CYP3A4 in vitro, thus CYP3A4 inhibitors or inducers are expected to cause changes in venetoclax and M27 exposures (AbbVie internal report). Clinical studies have supported the in vitro observations for venetoclax as a sensitive substrate of CYP3A4: > 5-fold increase in AUC when co-dosed with ketoconazole, and 71% decrease in AUC when co-dosed with rifampin (AbbVie internal reports). At the 400 mg QD dose venetoclax and M27 are not predicted to be perpetrators of the major CYP enzymes, but venetoclax may weakly inhibit UGT1A1.

Administration of venetoclax with a low-fat meal increased venetoclax exposure by approximately 3.4-fold, and administration with a high-fat meal increased venetoclax exposure by 5.1- to 5.3-fold compared to fasting conditions (AbbVie internal reports). Previous studies of venetoclax have recommended taking each dose with a meal.

1.1.2.2 CC-486

a) Physical Properties

Azacitidine (Vidaza®) has a chemical name of 4-amino-1-β-D-ribofuranosyl-s-triazin- 2(1H)-one, and is an analog of the naturally occurring pyrimidine nucleoside, cytidine. It differs from cytidine in having nitrogen in the 5-position of the heterocyclic ring (see Figure 2). The drug has been formulated for oral administration (CC-486) and is supplied as a tablet or a capsule. The molecular formula for azacitidine is $C_8H_{12}N_4O_5$, and its molecular weight is 244 amu.

b) Mechanism of Action and Approved Indications

Azacitidine is a DNA methyltransferase inhibitor which reverts hypermethylation-induced gene silencing of tumor suppressor and other cancer-related genes, stopping the growth of cancer cells in in vitro models (Stresemann and Lyko 2008). Azacitidine is currently approved by the FDA for use in combination with venetoclax for the treatment of Acute Myeloid Leukemia (AML) and as monotherapy for the treatment of Myelodysplastic Syndrome (MDS).

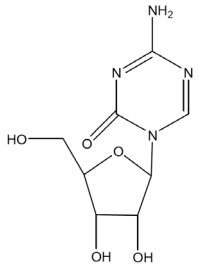

Figure 2: Molecular structure of azacitidine.

c) Pharmacologic Data

Azacitidine is rapidly absorbed in mouse, rat and dog following SC or oral (PO) administration (Celgene internal report). Compared with exposure following IV administration, the SC bioavailability was greater than 70% in rat and dog. Following oral administration, it was estimated that greater than 60% of the dose was absorbed and the PO bioavailability was relatively good (22% to 47%) in mouse, rat and dog. Following PO (50 mg/kg) or IV (10 mg/kg) administration of 14C-azacitidine to mice, radioactivity was widely distributed throughout all organs and tissues (Celgene internal reports). Following a single dose administration to male rats, azacitidine penetrates into rat brain, with brain/plasma exposure ratios of 2.3 and 0.9 for oral (10 mg/kg) and IV (3 mg/kg) dose, respectively (Celgene internal report). Cerebrospinal fluid/plasma exposure (area under the plasma concentration-time curve from time 0 to time) ratio was 1.3 following the IV dose.

The protein binding of azacitidine in human serum was low (< 10% bound) (Celgene internal report). The distribution ratios of radioactivity into human blood cells were approximately 30% to 34% in vitro. The human serum protein binding and the distribution into human blood cells were independent of 14C-azacitidine concentration and were not impacted by the cytidine deaminase inhibitor tetrahydrouridine. Partitioning of azacitidine-related radioactivity into blood cells was also observed following IV or SC administration of 14C-azacitidine to male rats (Celgene internal report).

Catabolism of azacitidine is by spontaneous hydrolysis in neutral, alkaline, and acidic solutions and by deamination (Daher, Harris, and Diasio 1990). Spontaneous hydrolysis of azacitidine results in equilibration with N-formylguanylribosylurea (RGU-CHO) culminating in the irreversible formation of guanlyribosylurea (RGU) (Beisler 1978). The metabolism of azacitidine was examined following PO and IV administration of radiolabeled azacitidine to mice (Celgene internal report). Up to 10 metabolites were observed in plasma, urine, and/or feces samples. While there were some quantitative differences between the PO and IV metabolic profiles, there were no qualitative differences. In plasma, the same metabolites were present in both genders and following both administration routes; the main circulating metabolites were RGU (M10) and an uncharacterized metabolite (M1). Urine was the major excretion route of radioactivity in mice and rats following PO, SC or IV dose of 14C-azacitidine (Celgene internal report). In rats, excretion of radioactivity was rapid (> 73% within 24 hours) and complete (> 95% in 168 hours). Approximately 96% of the IV dose and 89% of the SC dose was recovered in urine. The parent drug accounted for a small portion of the urinary radioactivity (approximately ≤ 5%) (Celgene internal report).

In vitro, azacitidine was not an inducer of the isozymes CYP1A2, 2C19, or 3A4/5 in cultured human hepatocytes (Celgene internal report). In vitro studies showed that azacitidine (0.1 to 100 μM) did not

inhibit human CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 activities at clinically achievable plasma concentrations (Celgene internal report). Azacitidine is not metabolized by CYPs (Celgene internal report). Data from these studies suggest that azacitidine will not produce clinically relevant PK drug-drug interactions due to CYP enzyme inhibition or induction when co-administered with CYP substrates, inducers or inhibitors. An in vitro study with LLC-PK1 cells expressing P-glycoprotein found azacitidine was not a substrate of P-glycoprotein (Celgene internal report). At 50 μM, azacitidine had no notable inhibitory effect on the transport of digoxin. Based on the transport and inhibition results, azacitidine is unlikely to produce any clinically relevant interactions as a P-glycoprotein substrate or an inhibitor.

1.1.2.3 Obinutuzumab

a) Physical Properties

Obinutuzumab (Gazyva ®) is a humanized anti-CD20 monoclonal antibody of the IgG1 subclass. The molecular mass of the antibody is approximately 150 kDa. Obinutuzumab is produced by mammalian cell (CHO) suspension culture.

b) Mechanism of Action and Approved Indications

Obinutuzumab recognizes a specific epitope of the CD20 molecule found on pre B- and mature B-lymphocytes. Upon binding to CD20, obinutuzumab mediates B-cell lysis through (1) engagement of immune effector cells, (2) by directly activating intracellular death signaling pathways and/or (3) activation of the complement cascade. The immune effector cell mechanisms include antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis (Golay et al. 2013). Obinutuzumab has been approved by the FDA for the first-line treatment of CLL in combination with chlorambucil, in combination with bendamustine for relapsed FL, and in the first line in combination with chemotherapy for previously untreated FL.

c) Pharmacologic Data

Based on a population PK analysis, the geometric mean volume of distribution of obinutuzumab at steady state is approximately 3.8 L. The elimination of obinutuzumab is comprised of a linear clearance pathway and a time-dependent nonlinear clearance pathway. As obinutuzumab treatment progresses, the impact of the time-dependent pathway diminishes in a manner suggesting target mediated drug disposition. Based on a population PK analysis, the geometric mean terminal obinutuzumab clearance and half-life are approximately 0.09 L/day and 28.4 days, respectively. Age did not affect the pharmacokinetics of obinutuzumab. Volume of distribution and steady state clearance both increased with body weight; however, the expected change in exposure does not warrant a dose modification. Based on the population pharmacokinetic analysis, a baseline creatinine clearance > 30mL/min does not affect the pharmacokinetics of obinutuzumab. Obinutuzumab has not been studied in patients with a baseline creatinine clearance < 30mL/min. Obinutuzumab has not been studied in patients with hepatic impairment.

No carcinogenicity or genotoxicity studies have been conducted with obinutuzumab. No specific studies have been conducted to evaluate potential effects on fertility; however, no adverse effects on

male or female reproductive organs were observed in the 26-week repeat-dose toxicity study in cynomolgus monkeys. No formal drug interaction studies have been conducted with obinutuzumab. There are no adequate and well-controlled studies of obinutuzumab in pregnant women. In a pre- and post-natal development study, pregnant cynomolgus monkeys received weekly intravenous doses of 25 or 50 mg/kg obinutuzumab from day 20 of pregnancy until parturition. There were no teratogenic effects in animals. The high dose results in an exposure that is 2.4 times the exposure in patients with CLL at the recommended label dose. When first measured on day 28 postpartum, obinutuzumab was detected in offspring and B cells were completely depleted. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months after birth. It is not known whether obinutuzumab is excreted in human milk. However, obinutuzumab is excreted in the milk of lactating cynomolgus monkeys and human IgG is known to be excreted in human milk. The safety and effectiveness of obinutuzumab in pediatric patients has not been established.

1.1.2.4 Pharmacologic Data: Combination of Venetoclax and Obinutuzumab

Formal drug interaction studies with venetoclax and obinutuzumab have not been conducted. However, the potential for a significant protein-drug interaction between obinutuzumab and venetoclax is considered to be low. Venetoclax is a small molecule administered orally and is primarily metabolized by cytochrome P450 3A4 (CYP3A4), and obinutuzumab is a monoclonal antibody administered by IV infusion. While a transient increase in cytokine levels is observed after the first obinutuzumab administration, significant effects on CYP proteins are not anticipated and the risk for obinutuzumab to significantly alter the pharmacokinetics of venetoclax is expected to be low. Based on preliminary pharmacokinetic (PK) data from AbbVie Internal Study GP28331, obinutuzumab did not appear to affect venetoclax exposure.

1.1.2.5 Pharmacologic Data: Combination of Venetoclax and CC-486

The combination of venetoclax and azacitidine has been studied extensively in preclinical models and clinical trials of myeloid malignancies. No preclinical pharmacologic studies have been published on the combination of venetoclax and CC-486 specifically, though the combination of venetoclax and azacitidine has demonstrated a favorable safety and efficacy profile in the treatment of MDS and AML, leading to FDA approval for these indications.

1.1.3 Preclinical Data

Please refer to Investigators' Brochures for venetoclax, CC-486, obinutuzumab for a detailed summary of preclinical data for each individual agent.

1.1.3.1 Preclinical Data: Combination of Venetoclax and Obinutuzumab

In vitro studies of the combination of obinutuzumab with venetoclax showed obinutuzumab enhanced cell-death induction when combined with venetoclax in several cell lines with an additive effect (VanDerMeid et al. 2018). Importantly, venetoclax did not negatively impact the capability of obinutuzumab to induce natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity (ADCC) (VanDerMeid et al. 2018; Sampath et al. 2013). Taken together, these nonclinical in vitro data show that combination of obinutuzumab, with its more potent direct cell-death induction

compared with rituximab, with venetoclax, which lowers the apoptotic threshold, could be particularly effective for the treatment of B-cell malignancies.

The combination of obinutuzumab and venetoclax was tested in vivo in the SU-DHL-4 NHL xenograft model (Sampath et al. 2013). Daily oral administration of venetoclax at 100 mg/kg in combination with suboptimal weekly intravenous (IV) dosing of obinutuzumab at 1 mg/kg for 3 weeks resulted in enhanced tumor-growth inhibition (TGI), with 118% TGI compared with 76% and 80% TGI seen with single-agent groups, and increased tumor regressions (five partial regressions). Additionally, on Day 31, 10 days after the last dose of venetoclax, there was a prolonged TGI response of 116% in the combination group compared with the obinutuzumab (30% TGI) and venetoclax (25% TGI) single-agent groups. All dose regimens (single agent and combination) were well tolerated, resulting in < 15% average body weight loss over the duration of the study (Sampath et al. 2013).

In tumor-bearing mice, the combination of obinutuzumab and venetoclax resulted in 91% TGI over a 3-week treatment period. Notably, the latter %TGI was sustained when venetoclax only was dosed for an additional 24 days (88% TGI) following combination therapy with obinutuzumab. Prolonged treatment with venetoclax after combination treatment with obinutuzumab was well tolerated, resulting in < 10% average body weight loss over the duration of the study. Thus, maintenance therapy with venetoclax as a single agent is achievable following combination therapy with obinutuzumab in the SU-DHL-4 NHL xenograft model.

The combination of obinutuzumab and venetoclax was also tested in vivo in the s.c. Z138 MCL model (Souers et al. 2013). Daily oral administration of venetoclax at 100 mg/kg for 17 days in combination with suboptimal weekly IV dosing of obinutuzumab at 1 mg/kg for 3 weeks resulted in enhanced TGI in the combination groups compared with the respective monotherapies.

On Day 35, treatment with obinutuzumab, rituximab, venetoclax at 100 mg/kg; combination obinutuzumab with venetoclax; and combination rituximab with venetoclax resulted in 73%, 32%, 59%, 106%, and 96% TGI, respectively. All treatment groups showed a statistically significant difference compared to the vehicle group. In addition, combination obinutuzumab or rituximab, each with 100 mg/kg venetoclax, showed statistically significant antitumor activity compared with each monotherapy (Souers et al. 2013).

1.1.3.2 Preclinical Data: Combination of Venetoclax and CC-486

No published studies exist of venetoclax and azacitidine in combination in models of follicular lymphoma. However, extensive preclinical data exists supporting a synergistic effect for the combination in the treatment of other hematologic malignancies, including AML. In primary AML and myelodysplastic syndrome (MDS) samples tested in ex vivo drug dose combination response assays with venetoclax and azacitidine, all samples showed synergy (Bogenberger et al. 2015). The myeloid cell leukemia factor 1 (MCL-1) protein is a member of the BCL-2 family that promotes survival of myeloid and lymphoid malignant cells, and is a known mechanism of resistance to venetoclax therapy (Bose, Gandhi, and Konopleva 2017). MCL-1 overexpression has been found in follicular lymphoma cell lines and primary tissue (Cho-Vega et al. 2004). In vitro models have shown that azacitidine exposure lowers expression of MCL-1 and sensitizes cells to treatment with venetoclax (Tsao et al. 2012). These data suggest that the addition of oral azacitidine to venetoclax

therapy may improve the response rate and overcome resistance to venetoclax monotherapy in the treatment of follicular lymphoma.

1.1.4 Clinical Data to Date

Please refer to Investigators' Brochures for venetoclax, CC-486, obinutuzumab for a detailed summary of existing clinical data for each individual agent.

1.1.4.1 Clinical Data: Combination of CC-486 and Obinutuzumab

The combination of CC-486 and obinutuzumab has not yet been studied in patients with FL. There have been two case reports showing re-expression of CD20 and resensitization to anti-CD20 therapy after treatment with azacitidine in FL and a different B-cell lymphoma (DLBCL) (Tsutsumi et al. 2016; Hiraga et al. 2018)). Oral azacitidine was studied in combination with the anti-CD20 agent rituximab as part of standard combination chemoimmunotherapy in patients with DLBCL in a phase I/II trial (Elstrom et al. 2012), which showed the combination to be tolerable and safe.

1.1.4.2 Clinical Data: Combination of Venetoclax and Obinutuzumab

The combination of venetoclax and obinutuzumab is currently being studied in the first line treatment of FL in the SAKK 35/14 trial, with early results presented in abstract form (Stathis et al. 2019). In this open-label phase I trial, patients tolerated combined therapy at 2 dose levels of 600 mg and 800 mg continuous daily dosing along with 6 cycles of obinutuzumab dosed at 1000 mg. This resulted in 2/25 patients developing a grade 4 neutropenia and 1/25 patients developing a grade 4 thrombocytopenia. Other toxicities of grade 3 and below were manageable. There were no drug-related deaths. The CR rate was 42% with an 82% 6-month Overall Best Response Rate (ORR). In relapsed/refractory and previously untreated CLL, a single-arm, open-label, phase Ib, study investigated the maximum tolerated dose, safety, and tolerability of venetoclax when given with obinutuzumab (Flinn et al. 2019). No dose-limiting toxicities were observed. The most common grade 3-4 adverse event was neutropenia (53-58%). Rates of grade 3-4 infections were 13-29%. All infusion-related reactions were grade 1-2, except for 2 grade 3 events. No clinical tumor lysis syndrome was observed. ORR was 95% in relapsed/refractory patients and 100% in first-line patients. Similarly, in another phase I trial of first-line CLL patients with advanced age and medical comorbidities, no DLTs were observed (Fischer et al. 2017). In this study, all patients experienced at least 1 adverse event (AE), and 83.3% had at least 1 grade 3/4 AE. 58.3% had grade 3/4 neutropenia; among those patients, 25.0% had grade 3/4 febrile neutropenia. No fatal AEs were reported. The ORR was 100%. Venetoclax was been studied in combination with a similar anti-CD20 agent, rituximab, in patients with relapsed/refractory FL in the CONTALTO trial presented at ASH 2018 (Zinzani et al. 2018). In this randomized phase II trial, the combination of venetoclax and rituximab (Ven-R) was compared to venetoclax, bendamustine, and rituximab (Ven-BR) and bendamustine and rituximab (BR) alone, which found a 25% CR rate in a highly refractory population and a more tolerable side effect profile in the Ven-R cohort than the chemotherapy cohorts.

1.1.4.3 Other Clinical Data in Follicular Lymphoma

A phase I trial of venetoclax in a number of B-cell lymphoma subtypes included FL patients (n = 29) (Davids et al. 2017). AEs were reported in 97% of total patients with grade 3/4 AEs in 56% including anemia (15%), neutropenia (11%), and thrombocytopenia (9%). No DLTs were observed in the FL cohort, and the MTD was not reached. The ORR in FL was 38% and the complete response rate (CR) was 14%. Obinutuzumab has been studied in phase III trials in FL in combination with chemotherapy compared to standard-of-care rituximab anti-CD20 therapy in combination with chemotherapy (Marcus et al. 2017). In this trial, obinutuzumab-based chemotherapy resulted in a significantly lower risk of progression, relapse, or death than rituximab- based chemotherapy (estimated 3-year rate of progression-free survival, 80.0% vs. 73.3%; hazard ratio for progression, relapse, or death, 0.66). Adverse events of grade 3 to 5 were more frequent in the obinutuzumab group than in the rituximab group (74.6% vs. 67.8%), as were serious adverse events (46.1% vs. 39.9%). Based on these results and other supporting data, obinutuzumab was granted FDA approval for the first-line treatment of obinutuzumab in combination with chemotherapy for the treatment of bulky stage II, stage III or stage IV FL.

1.1.5 Rationale for Conducting this Research

Patients with FL with no or minimal pretreatment who subsequently develop indications for treatment are a common clinical scenario in hematologic oncology. Chemotherapy-sparing options would provide a benefit to patients by deferring or avoiding chemotoxicity in patients whose disease is expected to persist for a lifetime. Intervening with rationally targeted agents early in the disease course could interrupt the usual evolution of the disease and disproportionately improve outcomes. The targets for these agents have been carefully chosen based on preclinical studies of the evolution of the disease, and have previously been used in different combinations to treat patients with lymphoma. Strong scientific rationale supports combined treatment with venetoclax and obinutuzumab, as the two agents utilize different mechanisms of action and may have complementary activity that target different cellular proteins expressed on malignant lymphoid B cells. Azacitidine has been shown to sensitize malignant B-cells to treatment with anti-CD20 agents through re-expression of CD20 and to treatment with venetoclax through downregulation of MCL-1. Combinations of obinutuzumab and venetoclax and of azacitidine and venetoclax, as well as azacitidine and anti-CD20 antibodies have all been previously found safe and tolerable in early phase clinical trials, suggesting this combination may have a synergistic anticancer effect with a favorable side effect profile. If this study is successful in identifying a safe and tolerable RP2D with promising signs of efficacy in the expansion cohort, a randomized trial establishing efficacy and toxicity will follow. The end goal of this line of research is to establish a novel chemotherapy-sparing treatment option that is of equal or better efficacy as current standard of care options.

1.1.6 Dose Rationale and Risks/Benefits

1.1.6.1 Dose Rationale for Venetoclax

The dose limiting toxicity in venetoclax is primarily hematologic (cytopenias). In the CAVELLI phase Ib trial of an escalating dose of venetoclax in combination with either obinutuzumab-CHOP or rituximab-CHOP, the hematologic toxicity of venetoclax was found to be dose and time-dependent, and reductions in dosing frequency were required in combination with chemotherapy. A recommended phase 2 dose of 800 mg days 4 to 10 of cycle 1 and days 1 to 10 of cycles 2 to 8 was

established (Zelenetz et al. 2019). As monotherapy, the maximum tolerated dose was not reached in a phase I trial of venetoclax in NHL (Davids et al. 2017). However, 9 of the 51 patients treated at 1200 mg required dose reduction due to GI side effects in that trial. The combination of venetoclax and rituximab or obinutuzumab has also been studied in CONTRALTO (Zinzani et al. 2018) and SAKK 35/15 (Stathis et al. 2019) trials, both with an established recommended dose of venetoclax of 800 mg daily continuously. The optimal dose of venetoclax in combination with other targeted agents such as azacitidine is not established in FL and will be investigated in the phase I portion of this trial. The highest dose level in this trial will be 800 mg daily, due to the potentiating effect of combination therapy on both efficacy and toxicity.

1.1.6.2 Dose Rationale for Obinutuzumab

The dose of obinutuzumab will follow the FDA-approved label for monotherapy for the first 8 cycles, namely 1000 mg on day 1, 8, and 15 of the first 28-day cycle followed by 1000 mg on day 1 of cycles 2-8. After cycle 8, the label allows for therapy every 2 months for up to 2 years. To maintain synchronicity with combination therapy in this trial, obinutuzumab will be given on day 1 of cycles 4-12, and there will be no on-trial provision for maintenance of obinutuzumab after 12 months.

1.1.6.3 Dose Rationale for CC-486

CC-486 was studied with R-CHOP chemoimmunotherapy for aggressive NHL at 4 different dose levels (100, 150, 200, and 300 mg) (Martin et al. 2017). The recommended phase 2 dose (RP2D) established in this trial was 300 mg; however, 27% of patients required a dose reduction from a 300mg dose of CC-486, primarily due to neutropenia. Based on the manufacturer's analysis of efficacy and toxicity balance in this and other trials, the recommended dose for ongoing studies in NHL is 200 mg.

The schedule of CC-486 in this trial is based on pharmacodynamic data from phase I trials (Garcia-Manero et al. 2011) where the 7-per-28 day dosing of the oral drug achieved lower median reductions in methylation, as well as a smaller number of differentially methylated loci, compared to 7-day administration of the SC formulation. Bioavailability of the oral drug is lower, and given the observed exposure/PD relationship, the effect on methylation is maximized and better sustained when the oral administration schedule is extended to 14 or 21 days of a 28-day schedule (Laille et al. 2015). Duration of exposure appears to be important to achieve both depth and duration of hypomethylation. It is less clear if there is a threshold dose for this activity. Balancing the desire for a strong on-target effect with the risk of overlapping hematologic toxicities (chiefly neutropenia) with the combination of venetoclax, this trial will employ a lower maximum dose of 200mg daily but will use a 14-out-of-every-28 day schedule.

1.1.7 Rationale for Research Design and Population

BCL2 rearrangement is a very early event in the development of FL, preceding any clinical manifestation (Mamessier, Broussais-Guillaumot, et al. 2014). At the time of clinically meaningful disease, additional mutations are typically found, most commonly in epigenetic regulatory factors (Okosun et al. 2014; Korfi et al. 2017). An increasing understanding of FL biology and pathogenesis over the past several years has resulted in a consensus model of FL common progenitor cells which

contain a core set of shared mutations and characteristics, likely live in the bone marrow, and shuttle in and out of lymph node germinal centers (Burkhard et al. 2015; Mamessier, Song, et al. 2014). In germinal centers, the early malignant cells undergo repeated antigenic stimulation and hypermutation, resulting in increasingly deleterious mutations and activation of additional survival pathways through epigenetic modification (Basso and Dalla-Favera 2015). Late in the course of some patients' disease, certain subclones develop oncogenic mutations in proliferative pathways associated with histologic transformation to aggressive lymphoma (Scherer et al. 2016; Loeffler et al. 2015). Based on these preclinical models, we hypothesize that targeting epigenetic reprogramming of malignant cells along with the Bcl-2 survival signal in early stages of the disease course, before additional oncogenic mutations accumulate in aggressive clones, may restore the anti-cancer effect of Bcl-2 inhibition in this disease.

Routine testing of total mutational burden in the treatment of B-cell lymphomas is not performed in any clinical setting, and there are no established biomarkers for response to venetoclax, IV or oral azacitidine, or antiCD20 agents in the treatment of non-Hodgkin lymphoma. In order to provide a study results which are generalizable to typical clinical practice, we will target a clinically-defined population which will serve as a surrogate for FL that is at an earlier stage in clonal evolution and potentially more susceptible to specific targeted therapies aimed at early events in clonal evolution. These assumptions regarding mutational status will be tested as exploratory endpoints in the trial, but enrollment in the trial will not be dependent on molecular analysis.

The study design consists of two arms. First, in the dose-finding arm aimed at establishing a recommended phase 2 dose and uncovering dose limiting toxicities in a novel triplet combination therapy, all three investigational agents will be given together starting in cycle 1. This will allow early assessment of toxicity from the three-drug combination and efficient progression through dose levels in a standard "3 + 3" design.

In the expansion cohort, a "window" design will be used to explore the efficacy of the combination of venetoclax and CC-486 alone before obinutuzumab is added in cycle 4. The efficacy of anti-CD20 therapy in FL is already well-established, and this design will provide an opportunity to assess the effects of a novel two-drug combination independent of confounding effects of an agent known to be effective for many patients. To minimize the chance of exposing patients to a futile treatment, the expansion cohort will follow a Simon two-stage design for an interim assessment of efficacy based on response to the three-drug combination at 6 months. The study will be halted for futility if the criteria for early efficacy are not met.

1.2 OBJECTIVES

1.2.1 Overall Study Hypothesis

A safe and tolerable dose of combination venetoclax, CC-486 and obinutuzumab can be found, which demonstrates treatment efficacy equal to or better than historical results of other non-chemotherapy agents for first-line therapy of FL.

1.2.2 Objectives for Dose Finding Cohort

1.2.2.1 Co-Primary Objective of the Dose Finding Cohort

Determine the RP2D of combined venetoclax/CC-486 in patients with minimally pre-treated FL.

Hypothesis: Dose limiting toxicities will not be uncovered at the maximum recommended doses discussed with the manufacturer; an RP2D will be established at 800 mg venetoclax and 200 mg CC-486.

1.2.2.2 Co-Primary Objective of the Dose Finding Cohort

Determine the safety and tolerability of combined venetoclax, CC-486, and obinutuzumab in human subjects.

Hypothesis: Based on the previously reported early discontinuation rates of 11% with chemotherapy-sparing frontline therapy for FL (Morschhauser et al. 2018), we expect discontinuation rates less than 15% for the combination of venetoclax and CC-486, as well as the three-drug combination. Prior studies of front-line chemotherapy and chemotherapy-sparing agents have reported a rate of 65% for grade 3-4 reactions, and 99% for any grade adverse reaction (Morschhauser et al. 2018). We hypothesize grade 3-4 reactions will occur in fewer than 70% of enrolled patients.

1.2.2.3 Exploratory objective of the Dose Finding Cohort

Elucidate pharmacodynamic effects of CC-486 in combination through cell-free DNA methylation profiling using the Nano-Seal 5-hmc assay (Han et al. 2016).

Hypothesis: Exposure to the standard dose of CC-486 will result in measurable and prolonged changes in circulating methylation profiles in treated patients which will not be significantly different by differing doses of venetoclax.

1.2.3 Objectives for Expansion Cohort

1.2.3.1 Primary Objective of the Expansion Cohort

Determine the CR rate per Lugano Criteria (B. D. Cheson et al. 2014) of combination oral therapy with CC-486 and obinutuzumab assessed by PET/CT whole body scan after 6 total cycles of therapy.

Hypothesis: Based on prior studies of chemotherapy-sparing front-line agents in FL (Morschhauser et al. 2018), a successful combination will demonstrate a complete response rate of greater than 50%. An ineffective combination will demonstrate a complete response rate of less than 30%.

1.2.3.2 Secondary Objectives of the Expansion Cohort

a) Determine median overall survival (OS) and median progression-free survival (PFS) of patients treated at the MTD/RP2D.

Hypothesis: Prior studies of front-line therapies have demonstrated 5-year PFS and OS of 50% and 90% at 5 years, and 3-year PFS of approximately 75% (Tomita et al. 2013; Morschhauser et al. 2018). Our study will demonstrate expected PFS greater than 75% at the study conclusion, and estimates of 5 year PFS and OS greater than 50% and 90%, respectively.

b) Determine CR rate at 30 months after initiation of therapy (CR30) as defined by Lugano Criteria and assessed with PET-CT whole-body scan.

Hypothesis: Using the CR30 as a surrogate for PFS as previously defined (Shi et al. 2017) will yield estimates for 5-year PFS in excess of 50%.

c) In the expansion cohort, determine the CR rate (by Lugano Criteria) of combination oral therapy, assessed with PET-CT whole-body scan after 3 cycles of venetoclax/CC-486 alone.

Hypothesis: Venetoclax monotherapy and the combination of venetoclax and rituximab in relapsed/refractory FL have shown CRrates of 14% (Davids et al. 2017). In the first-line setting, the combination of venetoclax and obinutuzumab produced a CR rate of 45% (95% CI: 17% - 77%) (Stathis et al. 2019). Given the shorter 3 month window to imaging and the lack of previous trial data for the combination of venetoclax and CC-486, we hypothesize the oral combination will have a CR superior to 25% as measured by whole-body PET/CT imaging..

1.2.3.3 Exploratory Objectives of the Expansion Cohort

a) Elucidate specific pre-treatment somatic mutations enriched in responders or non-responders, and analyze CR rates separately in patients without mutations associated with late or transformed disease.

Hypothesis: Somatic mutations will associate with responders or non-responders, and can be used for further studies of predictive biomarkers. CR rates in patients without canonical "late" mutations will be superior to the primary analysis. For the purposes of this study, canonical "late" mutations will be considered to be:

- *TP53* loss of function mutations - found in 30% of transformed disease or TFL and 15% in non-transformed FL (Pasqualucci et al. 2014; Sander et al. 1993; Lo Coco et al. 1993; Kridel et al. 2016)
- *MDM2* gain of function mutations - overexpression seen in 80% of TFL and 0% in FL (Moller, Nielsen, and Pedersen 2002)
- *CDKN2A* mutations - found in 46% of TFL and 0-8% of FL 26 48
- *FAS* mutations - found in 33% of TFL (Pasqualucci et al. 2014; Alhejaily et al. 2014)
- *B2M* loss of function mutations - found in 33% of TFL and 10% of FL (Kridel et al. 2016)
- *CD58* mutations - found in 5% of TFL and 0% of FL

- *MYC* amplifications or translocations - found in 58% of TFL and 0% of FL (Kridel et al. 2016; Pasqualucci et al. 2014)

b) Correlate changes in cell-free DNA methylation profile compared to a baseline, pre-treatment sample with response to therapy as a potential pharmacodynamic marker.

Hypothesis: Global demethylation changes as measured by cell-free DNA methylation profiling will be detected at the first assessment after initiation of CC-486 and will correlate with ongoing disease response on serial assessment during and after completion of therapy.

c) Correlate minimal residual disease status as measured by circulating tumor DNA with progression-free survival and response by imaging criteria, including 30-month complete response.

Hypothesis: Patients who have detectable post-treatment tumor-associated mutations -- either matching mutations identified on pre-treatment circulating tumor DNA B-cell lymphoma-specific multigene next generation sequencing panel (ctDNA panel) or novel tumor-associated mutations – will be significantly more likely to experience relapse during the study period, have a significantly shorter progression-free survival, and be more significantly more likely to have detectable disease on the 30-month PET scan (CR30 assessment).

2 STUDY DESIGN

2.1 TYPE OF STUDY

The study will consist of two sequential single arms. Patients meeting enrollment criteria will be assigned non-randomly to the study arms based on order of enrollment. Neither patients nor investigators will be blinded to the assignment. First, a dose finding arm with a standard "3 + 3" design will use venetoclax, CC-486, and obinutuzumab combination therapy in three dose levels and two optional dose de-escalation levels to establish the RP2D and assess toxicity and tolerability of the triplet. Dose-limiting toxicity will be assessed during the 28 days of Cycle 1. If a safe and tolerable RP2D is established, the study will proceed with an expansion cohort using Simon two-stage and window designs. In the expansion cohort, the first three cycles will consist of a combination of venetoclax and CC-486 before obinutuzumab is added in cycle 4. Disease assessment will take place after cycle 3 and cycle 6 and will be graded according to the Lugano Criteria (B. D. Cheson et al. 2014). Adverse events (AEs) will be monitored throughout the trial, and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. This trial will be conducted in accordance with Good Clinical Practices.

2.2 DURATION OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis (i.e., PET 30-month post treatment initiation) or safety follow-up is received from the last patient, whichever occurs later. The minimum

required safety follow up for all AEs is 30 days, though a subset of AEs will remain reportable indefinitely. The total duration of the study, from screening of the first patient to LPLV is expected to be 55 months or less, with an estimated 24 months to full accrual and 31 months from enrollment of the last patient to LPPV.

2.3 Schedule of Events

For each study visit, basic information including body measurements and vital signs will be recorded. Symptoms of the disease and treatment-related toxicities will be collected and recorded by a licensed medical provider. A physical exam will be performed and documented by a licensed medical provider. Scheduled laboratory assessments will be drawn on the day of the appointment. The assessments and procedures conducted at each visit will follow the study schema shown in **Appendix A**.

The schedule will proceed as follows: first there will be a screening visit within 28 days prior to Cycle 1 to determine eligibility and review the protocol. A 28-day supply of venetoclax and 14-day supply of CC-486 will be given to the patient on Day 1 of each cycle. Cycle 1 will require visits on Day 1, 8, 15, and 22 for treatment, laboratory assessments, and assessment. In the dose-finding cohort only, infusional therapy with obinutuzumab will be given on Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 15 in the dose-finding arm. In the expansion cohort, no obinutuzumab will be given in Cycle 1, but the patient will be assessed for toxicity weekly.

Cycle 2 will require visits on Day 1 and Day 15. Infusional therapy with obinutuzumab will be given on Cycle 2 Day 1 in the dose-finding arm only. Cycle 3 through 12 will require visits on Day 1 only in the dose finding arm. The last dose of obinutuzumab will be given on Cycle 9 Day 1 in the dose finding arm. In the expansion cohort, obinutuzumab treatment will start in Cycle 4, with infusions and laboratory studies on Day 1, Day 8, and Day 15; subsequent Cycles through Cycle 12 will include an obinutuzumab infusion on Day 1 only. The end-of-treatment visit will occur within 4 weeks of completion of treatment on Cycle 12, Day 28. Follow-up visits will occur every 8-12 weeks until 18 months post-treatment, and every 6 months thereafter until the close of the trial or disenrollment of the patient.

2.4 Sequence and Duration of all Study Periods

Patients will undergo an initial screening phase within 28 days prior to treatment allocation. Treatment will consist of twelve 28-day cycles for a total of 336 days. Follow-up after completion of treatment will extend to the final disease response assessment at 30 months following initiation of treatment. Post-study follow-up for progression of disease, death, secondary malignancies, next treatment delivered, and late treatment-related toxicities will continue by telephone survey every 6 months until the close of the trial or disenrollment of the subject.

2.5 Method for Assigning Subjects to Study Groups

Subjects will be assigned to the dose-finding arm in cohorts of 3 patients until the RP2D is established (estimated 12-18 subjects). The next 15 enrolled subjects will be assigned to the expansion cohort, stage 1. The following 17 enrolled subjects will be assigned to the expansion

cohort, stage 2. Once the expansion cohort has reached a goal of 32 total patients, further enrollment will be closed. Patients will not be randomized and will be assigned to arms, cohorts and stages by the order of enrollment alone. No placebos will be used.

2.6 BLINDING

Neither subjects nor investigators will be blinded to the investigational agents in this study.

2.7 PRIMARY STUDY ENDPOINTS

Dose-finding cohort:

- Recommended phase 2 dose, defined as the maximum tolerated dose up to dose level 3 (see Table 2)
- Rate of grade 3/4 adverse events
- Rate of discontinuation

Expansion cohort:

- Six-month complete metabolic response rate assessed by PET scan

2.8 SECONDARY STUDY ENDPOINTS

- Overall survival both at the end of the trial and as a 5-year estimate
- Progression-free survival both at the end of the trial and as a 5-year estimate
- "CR30" complete metabolic response rate at 30 months post-treatment initiation
- Three-month CR rate after 3 cycles of treatment with venetoclax and CC-486 alone (expansion cohort only)

2.9 EXPLORATORY STUDY ENDPOINTS

- Evaluation of pre-treatment tumor mutations by next generation sequencing of the tumor material for specific mutations (see Section 1.2.3.3)
- Measurement of minimal residual disease (MRD) via circulating tumor DNA
- Pharmacodynamic assessment of the effect of oral azacitidine on the circulating cell-free DNA methylation profile over time

3 SUBJECT SELECTION AND WITHDRAWAL

3.1 NUMBER OF SUBJECTS

Twelve to eighteen subjects from any of the study sites are expected in the dose-finding arm, and 32 in the expansion cohort for a total of 44-50 patients.

3.2 GENDER, AGE, RACIAL AND ETHNIC ORIGIN OF SUBJECTS

The age of the participants in this trial will be 18 years and older. Follicular lymphoma is very rare in children and consists of a particular subtype which is biologically distinct from slow-developing adult

FL (Louissaint et al. 2016). The preclinical data supporting this trial were derived from adult FL, and do not provide adequate support for including pediatric-type nodal follicular lymphoma in this trial. Obinutuzumab has not previously been studied in a pediatric population, and there is no available safety or efficacy data for this drug in children.

Non-pregnant, non-breastfeeding women and minority populations will be included in the trial without restriction. There is inadequate safety data for the approved agents for use in pregnant and breastfeeding women, and the potential benefits of treatment. The patient population at University of Chicago Medicine is diverse in race, sex, and socioeconomic status, which will allow for generalizability of findings.

3.3 INCLUSION CRITERIA

Participants are eligible to be included in the study if all of the following criteria apply:

1. Male and female subjects who are at least 18 years of age with a histologic diagnosis of grade 1-3a FL by 2017 World Health Organization criteria. A prior tissue or bone marrow biopsy may be used for histologic confirmation if collected within 90 days of the initiation of therapy.

2. Treatment-naive or fewer than two prior lines of anti-CD20 monotherapy consisting of a total of 16 or fewer doses.

3. Ann Arbor Stage II-IV disease on screening PET imaging with measurable disease, defined as at least one lesion that can be accurately measured in at least two dimensions and quantifiable avidity to FDG. Minimum measurement must be >15 mm in the longest diameter by >10 mm in the short axis.

4. Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less as defined in Appendix B. Performance status must be evaluated within 28 days prior to treatment initiation.

5. There must be an indication for treatment, either by meeting one or more of the GELF criteria for treatment (Brice et al. 1997), the existence of cancer-related pain or other uncontrollable symptom, or in the judgment of the primary oncologist based on pace of disease progression or other clinical criteria. Patients must have documented progression of disease.

6. Not be a candidate for standard-of-care chemoimmunotherapy in the judgment of the primary oncologist OR standard chemoimmunotherapy was discussed with the primary oncologist and declined by the subject.

7. A male participant must agree to use contraception as detailed in Appendix D of this protocol during the treatment period, and for at least 90 days after the last dose of venetoclax or 18 months after the last dose of obinutuzumab, whichever is longer, and refrain from donating sperm during this period. With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 6 months after the last dose of obinutuzumab to avoid exposing the embryo.

8. A female participant is eligible to participate if she is not pregnant (see Appendix D), not breastfeeding, and at least one of the following conditions applies:

a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix D

b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix D during the treatment period and for at least 30 days after the last dose of venetoclax or 18 months after the last dose of obinutuzumab, whichever is longer.

c.) Subjects must have a negative pregnancy test within 72 hours of beginning treatment if WOCBP.

9. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.

10. Have adequate organ function as defined in Table 1 within 28 days prior to treatment initiation.

Table 1. Adequate Organ Function Laboratory Values

Hematological	
Absolute neutrophil count	> 1500 cells per microliter unless due to bone marrow involvement
Hemoglobin	> 9 g/dL
Platelet count	> 75,000 platelets per microliter
Renal	
Creatinine clearance	> 60 mL per minute by Cockcroft-Gault equation
Hepatic	
Total bilirubin	≤ 1.5 × Upper limit of normal (ULN) OR direct bilirubin ≤ ULN for participants with total bilirubin levels > 1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN, or ≤3 x ULN for patients with documented Gilbert syndrome, or ≤5 × ULN for participants with documented liver metastases

Coagulation	
International normalized ratio (INR) OR prothrombin time (PT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
Activated partial thromboplastin time (aPTT)	

3.4 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

1. A WOCBP who has a positive urine pregnancy test within 72 hours prior to treatment allocation (see Appendix D). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Note: in the event that 72 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for the subject to start receiving study medication. Women who are known to be pregnant or who are breastfeeding are excluded from the study (lactating women must agree not to breastfeed for the duration of the trial).

2. Has received any prior systemic therapy other than anti-CD20 monoclonal antibody or radiotherapy prior to the first dose of study medication. Subjects must not have had a prior dose of anti-CD20 monoclonal antibody therapy within 28 days prior to the first dose of study medication.

3. Known hypersensitivity or allergy to any of the study drugs, xanthine oxidase inhibitors and/or rasburicase, mannitol, murine products, or any components of the drug formulations.

4. History of severe allergic or anaphylactic reaction to humanized or murine monoclonal antibodies.

5. History of other malignancy that could affect compliance with the protocol or interpretation of results.

   a.) Patients with a history of curatively treated basal or squamous cell carcinoma or stage 1 melanoma of the skin or in situ carcinoma of the cervix are eligible.

   b.) Patients with a malignancy that has been treated with surgery alone with curative intent will also be excluded. Individuals in documented remission without treatment for 2 years prior to enrollment may be included at the discretion of the sponsor-investigator.

6. Has histologic or clinical evidence of transformation to an aggressive lymphoma subtype including grade 3b FL.

7. Received the following agents within 7 days prior to the first dose of venetoclax:
   a.) Steroid therapy for anti-neoplastic intent
   b.) A strong or moderate CYP3A inhibitor (see Appendix H)
   c.) CYP3A inducers (see Appendix H)

d.) Consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruit within 3 days prior to the first dose of venetoclax.
e.) P-gp inhibitors or narrow therapeutic index P-gp substrates

8. Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results or that could increase risk to the patient, including renal disease that would preclude chemotherapy administration or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm).

9. Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1, Day 1. Uncontrolled systemic fungal, bacterial or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy and/or other treatment) will result in study exclusion. Caution should be exercised when considering the use of any of the study medication in patients with a history of recurring or chronic infections.

10. Clinically significant history of liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis.

11. Presence of positive test results for hepatitis B virus (HBV), hepatitis B surface antigen (HBsAg), or hepatitis C (HCV) antibody. Patients who are positive for HCV antibody must be negative for HCV by polymerase chain reaction (PCR) to be eligible for study participation. Patients with occult or prior HBV infection (defined as positive total hepatitis B core antibody [HBcAb] and negative HBsAg) may be included if HBV DNA is undetectable. These patients must be willing to undergo monthly HBV DNA testing.

12. Receipt of live-virus vaccines within 30 days prior to the initiation of study treatment

13. Malabsorption syndrome, inability to swallow a large number of pills, or other condition that precludes enteral route of administration.

14. A history of progressive multifocal leukoencephalopathy (PML) or known prior infection with the John Cunningham (JC) virus.

15. Significant active cardiac disease within the previous 6 months including New York Heart Association class 4 heart failure, unstable angina, or myocardial infarction.

3.5 VULNERABLE SUBJECTS

No children, pregnant women, fetuses, or prisoners will be included in this study. Persons with cognitive impairment who are found to have capacity for medical decision making and who can provide their own informed consent will be allowed to participate in the study. Economically disadvantaged persons will not be specifically targeted or excluded from the study. Patients will be

recruited from the diverse general population of FL patients requiring treatment at University of Chicago Medicine and other study sites to allow for generalizable results to routine community practice.

3.6 Subject Identification & Recruitment

Patients will be identified by primary oncologists and study investigators in the ordinary course of care for FL patients. The trial will be publicized to community physicians through fliers and lectures, and will be publicized with regional academic centers through academic gatherings and meetings.

3.7 Location

Patients will be seen for each study visit in the Duchossois Center for Advanced Medicine at the University of Chicago Hyde Park Campus, or the equivalent primary oncology clinic at each participating site. Infusional therapy will be administered in the outpatient intravenous therapy center of each participating site.

3.8 Notification of Primary Physician

The primary treating oncologist for each subject will be notified of successful enrollment in the study and provided with detailed study information regarding the schedule and investigational agents. There is no mandated participation from the primary treating physician, though subjects will be encouraged to maintain their relationship with the primary oncologist through periodic visits. Following study completion, the primary oncologist will be provided a summary of the treatments administered and the outcomes of assessments.

3.9 Payment to Subjects

No payments will be made to subjects.

3.10 Informed Consent Process

The site investigator will make certain that an appropriate informed consent process is in place to ensure that potential research subjects, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research subjects. The site investigator, or a sub-investigator(s) designated by the site investigator, will obtain the written, signed informed consent of each subject prior to performing any study-specific procedures on the subject. The date and time that the subject signs the informed consent form and a narrative of the issues discussed during the informed consent process will be documented in the subject's case history. The site investigator will retain the original copy of the signed informed consent form, and a copy will be provided to the subject.

The site investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled subjects are adequately addressed and that the subjects are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit

ratio of study participation, the site investigator will obtain the informed consent of enrolled subjects for continued participation in the clinical study.

3.11 Subject Withdrawal Following Study Completion

The final study assessment will be at 30 months post initiation of treatment (18 months following treatment completion) and will consist of a clinical assessment, laboratory, and imaging studies as detailed in the Study Schema (Appendix A) and Section 5.7. After the end of treatment, each subject will be followed for the occurrence of adverse events and ongoing disease response with post-treatment visits and assessments as outlined in detail in Section 5.8. Post-treatment visits will continue until the study formally ends, the patient dies, the patient experiences disease progression requiring an alternative therapy, or the subject voluntarily withdraws prior to study completion.

3.12 Subject Withdrawal Before Study Completion

Participants may discontinue study treatment at any time for any reason, and may also be discontinued from study treatment at the discretion of the site investigator should any untoward effects occur. In addition, a participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Confirmed radiographic disease progression
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Unacceptable adverse events
- The participant has a medical condition or personal circumstance which, in the opinion of the site investigator and/or Lead PI, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with study treatment or procedure requirements
- Administrative reasons

3.13 Data Collection and Follow-up on Early Treatment Termination Subjects

Subjects who are withdrawn from active treatment due to an AE or an SAE will remain enrolled in the trial for the purposes of tracking ongoing toxicity. Subjects will continue with the usual schedule of follow-up visits as feasible and will be included in the intention-to-treat analysis. Subjects who have voluntarily withdrawn from the active treatment will be asked to continue scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care under medical supervision until the symptoms of any AE resolve or the subject's condition becomes stable.

Subjects who discontinue treatment for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects, including those who withdraw due to disease progression or complete the planned follow-up period, will be followed by telephone until death, withdrawal of consent, or the end of the study.

Subjects may be replaced in the trial as needed to ensure that the required number of evaluable subjects is achieved for the designated statistical analyses as put forth in Section 6.

4 STUDY DRUG

4.1 FORMULATION OF STUDY DRUGS

4.1.1 Formulation of Venetoclax

Venetoclax is available in its commercial formulation as a coated tablet with strength of 10, 50, and 100 mg. Excipients include copovidone, colloidal silicon dioxide, polysorbate 80, sodium stearyl fumarate, calcium phosphate dibasic. The 10 mg and 100 mg tablets' coating contains iron oxide yellow, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc. The 50 mg tablet's coating contains iron oxide yellow, iron oxide red, iron oxide black, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc.

4.1.2 Formulation of CC-486

Azacitidine has been developed for clinical investigation in strengths of 20, 60, 100, 150, 200, and 300 mg tablets. The oral azacitidine formulations may use any of the following excipients: mannitol USP, silicified microcrystalline cellulose NF, crospovidone NF, magnesium stearate NF, croscarmellose sodium, vitamin E TPGS NF, methacrylic acid copolymer (enteric coating) NF, Opadry coating, triethyl citrate NF, talc USP, hydroxypropyl cellulose NF, and hard gelatin capsule.

4.1.3 Formulation of Obinutuzumab

The manufacturing process of the obinutuzumab drug substance consists of cell culture and purification process. Obinutuzumab is provided as a single 1000 mg dose liquid concentrate with a strength of 25 mg/mL. It is supplied in 50 mL glass vials containing 40 mL of the 25 mg/mL liquid concentrate. In addition to the antibody, the liquid also contains histidine/histidine-HCl, trehalose, poloxamer 188 and water for injection. Water meets the specified limits for "Water for Injections" according to Ph. Eur. monograph and "Water for Injection" according to USP monograph.

4.2 DRUG REGIMEN

4.2.1 Summary of Drug Regimen

4.2.1.1 Summary of Drug Regimen for Dose Finding Cohort

In the dose-finding cohort, there will be three escalating dose levels of the three drug combination, and two optional dose de-escalation levels if needed (see Table 2). Venetoclax will be dosed by mouth once daily on days 1-28 or days 1-10 of each 28-day cycle. CC-486 will be dosed by mouth once daily on days 1-14. The doses and days of administration of CC-486 and venetoclax for each dose level are found in Table 2. Obinutuzumab will be administered intravenously at a fixed dose of 1000 mg on days 1, 8, and 15 of cycle 1, and on day 1 of each subsequent cycle. 12 total cycles will

be completed of venetoclax and CC-486. Obinutuzumab will be administered for 9 total cycles (cycle 1-9) and omitted from cycle 10-12. Definition of DLT is in Section 6.2.1.

Table 2: Levels for dose finding

Dose Level	Venetoclax	CC-486	Obinutuzumab
DL 1	400 mg days 1-28	200 mg days 1-14	1000 mg
DL 2	600 mg days 1-28	200mg days 1-14	1000 mg
DL 3	800 mg days 1-28	200 mg days 1-14	1000 mg
DL -1	400 mg days 1-28	150 mg days 1-14	1000 mg
DL -2	400 mg days 1-10	150 mg days 1-14	1000 mg

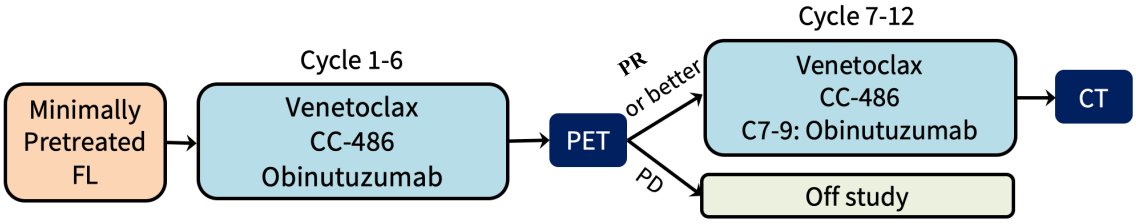

Figure 3: Treatment plan for dose-finding arm

4.2.1.2 Summary of Drug Regimen for Expansion Cohort

In the expansion cohort, the RPD2 established in the dose-finding cohort will be used. Venetoclax will be taken once daily by mouth at the RP2D every day of a 28-day cycle. CC-486 will be taken once daily by mouth at the RP2D on days 1-14 of a 28-day cycle. Obinutuzumab will be omitted from cycle 1-3. In cycle 4, obinutuzumab will be administered intravenously on days 1, 8, and 15. In cycle 5-12, obinutuzumab will be administered intravenously on day 1 only.

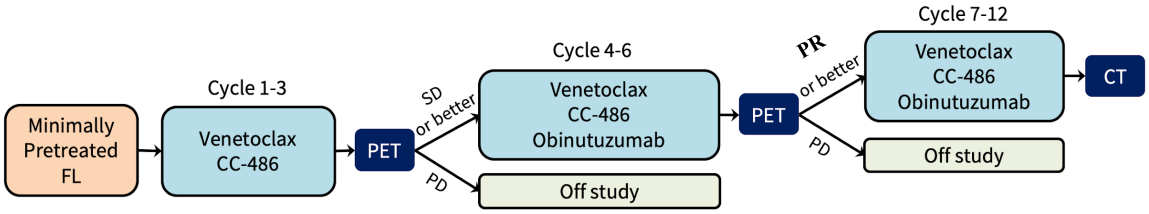

Figure 4: Treatment plan for expansion cohort

4.2.2 Administration Details for CC-486 for Expansion Cohort

All efforts should be made to administer CC-486 on all scheduled days. A dose missed earlier in a day can be administered later that day as long as it is taken at least 8 hours before the next scheduled dose. Any missed dose should not be taken beyond the last scheduled day of CC-486 administration

for the cycle, but should be returned by the subject for CC-486 accountability. If vomiting occurs after a dose of CC-486 is administered, that dose should not be made up later that day. The subject should continue with the dosing schedule on the next day and inform the treating investigator about the vomiting event at the next visit.

For the purposes of dose adjustment, unacceptable toxicity will be defined as any treatment related AE that is deemed by the treating investigator to be related to CC-486 and/or to the combination of CC-486 with venetoclax and/or obinutuzumab, and that poses a medical risk or substantial discomfort to the subject including, but not limited to, Grade 3 or 4 hematologic or non-hematologic toxicity. CC-486 dosing may be re-escalated (up to the planned dose level in the dose-finding cohort or the RP2D in the expansion cohort) at the discretion of the treating investigator. See Dose Modification Table 3 and Table 4 in Section 4.2.5.

4.2.3 Administration Details for Venetoclax for Expansion Cohort

The dosing of venetoclax in this trial assumes the drug will be administered with a meal, and patients will be instructed to take venetoclax immediately prior to a meal. On days when venetoclax is taken with CC-486, venetoclax should be given first.

If vomiting occurs within 15 minutes after taking venetoclax and all expelled tablets are still intact, another dose may be given. Otherwise, no replacement dose is to be given. In cases where a dose of venetoclax is missed or forgotten, the patient should take the dose as soon as possible and ensure that the minimal interval between the current dose and the next dose is at least 16 hours in order to avoid excessive drug accumulation after the next dose.

All patients must receive prophylaxis for tumor lysis syndrome (TLS) with antihyperuricemics (e.g., allopurinol or rasburicase) and ensure adequate hydration prior to start of venetoclax therapy (see Section 7.4.1 and Appendix G for further details). If TLS is diagnosed by laboratory criteria only AND resolves within 48 hours, venetoclax may be resumed at the prior dose without adjustment. If TLS is diagnosed by laboratory criteria AND lasts greater than 48 hours before full resolution OR TLS is diagnosed by clinical criteria, the dose of venetoclax should be reduced following Table 4.

For the purposes of dose adjustment, unacceptable toxicity will be defined as any treatment related AE that is deemed by the treating investigator to be related to venetoclax and/or to the combination of venetoclax with CC-486 and/or obinutuzumab, and that poses a medical risk or substantial discomfort to the subject including, but not limited to, grade 3 or 4 hematologic or non-hematologic toxicity. Treatment should be delayed if there is any evidence of infection until the resolution of any infection-related symptoms. After an episode of unacceptable toxicity resolves or after the first episode of an infectious complication which resolves within 3 weeks, venetoclax may be resumed or re-escalated to the prior dose at the discretion of the treating investigator. After a second or greater episode of an infectious complication which resolves within three weeks, the venetoclax dose should be adjusted as shown in Table 3 and Table 4. Treatment with investigational agents should not be resumed after an infectious complication that remains symptomatic for greater than 3 weeks.

Patients who require -azole antifungal prophylaxis will require a dose reduction of 75% or more of the original dose and should not follow the schedule in Table 3. The final dose for patients requiring -

azole prophylaxis will be agreed upon by study investigators on a case-by-case basis. See Section 7.4.4.1 for details.

Obinutuzumab will not be subject to dose adjustment. See Dose Modification Guidelines in Section 4.2.5.

4.2.4 Administration Details for Obinutuzumab for Expansion Cohort

The recommended dosage of obinutuzumab is 1000 mg administered on Day 1, Day 8 and Day 15 of the first treatment cycle, followed by 1000 mg administered on Day 1 only for each subsequent 28-day treatment cycle.

Required premedication for management of infusion-related reactions is outlined in Section 7.4.2. Hypotension may occur during obinutuzumab IV infusions. Consider withholding antihypertensive treatments for 12 hours prior to and throughout each obinutuzumab infusion, and for the first hour after administration.

All patients in the dose-finding arm will receive TLS prophylaxis prior to cycle 1 day 1. Subjects in the expansion cohort who start obinutuzumab in cycle 4 will be considered for TLS prophylaxis on a case-by-case basis. Those with high tumor burden, high circulating absolute lymphocyte counts (>25 $x10^9$/L), or renal impairment are considered at risk for TLS and should receive prophylaxis prior to cycle 4 day 1 if they are not already on appropriate TLS prophylaxis. Continue prophylaxis prior to each subsequent obinutuzumab infusion, as needed. During the initial days of obinutuzumab treatment, monitor the laboratory parameters of patients considered at risk for TLS (labs on Day 1, 2, 8, and 15). See Section 7.4.1 and Appendix G for details of TLS prophylaxis.

No dose reductions will be allowed for obinutuzumab on this protocol. For patients with toxicity potentially attributable to obinutuzumab including grade 3 or 4 neutropenia and/or febrile neutropenia, doses of obinutuzumab should be delayed up to two weeks until the toxicity improves to grade 1 or 2, or permanently discontinued if recovery does not occur within a two-week window. Patients who develop PML should be permanently discontinued from obinutuzumab therapy. Patients who develop a grade 4 infusion-related reaction or recurrent grade 3 infusion-related reactions should be discontinued permanently from obinutuzumab treatment on this trial.

4.2.5 Dose Modification Guidelines for Expansion Cohort

General principals/stopping rules: Dose Levels for the phase I portion of the study are as per Table 2. During the Expansion Cohort portion of the trial, dose delays/modifications are per the tables below and should be used as long as patients are deriving clinical benefit from the treatment regimen. Once the dose of an agent has been reduced, no dose re-escalation is permitted. If a scheduled dose is delayed for more than 6 weeks due to treatment-related toxicity, remove the patient from protocol therapy. No more than three dose reductions are permitted. A missed dose should not be made up, so that cycle lengths are always 28 days irrespective of the number of doses delivered in that cycle.

There will be no dose reductions for obinutuzumab. Dose reductions for CC-486 and venetoclax are per Table 4 below.

NOTE: Dose delays/dose reductions for the Dose Expansion portion of the study will be re-evaluated at the conclusion of the phase I portion of the study, and the following section is subject to revision.

Table 3A. Dose Modifications for Hematologic Toxicities. See Dose Levels for venetoclax and CC-486 in Table 4.

Observation	Action	Comments
Neutropenia ≥ gr 3	• Hold venetoclax, CC-486, and obinutuzumab (if applicable) • Resume therapy at same dose level once neutropenia resolves to ≤ grade 2 • If recurs, reduce by one dose level. • If recurs again, reduce by one additional dose level. • If recurs again, reduce by one additional dose level.	Monitor CBC weekly. Consider use of growth factor support. If treatment is delayed by more than 6 weeks due to treatment-related toxicity, remove patient from study No more than 3 dose reductions are allowed
Thrombocytopenia ≥ gr 3	• Hold venetoclax, CC-486, and obinutuzumab (if applicable) • Resume therapy at same dose level once thrombocytopenia resolves to ≤ grade 2 • If recurs, reduce by one dose level. • If recurs again, reduce by one additional dose level. • If recurs again, reduce by one additional dose level.	Monitor CBC weekly. No more than 3 dose reductions are allowed If treatment is delayed by more than 6 weeks due to treatment-related toxicity, remove patient from study
Anemia ≥ grade 3	• For first instance of grade 3 and 4 anemia, transfuse PRBC's as required • If recurs, hold treatment and evaluate etiology (drug-related or not). If drug-related,	Monitor CBC weekly. No more than 3 dose reductions are allowed If treatment is delayed by more than 6 weeks due to treatment-related toxicity, remove patient from study

	decrease by one dose level. • If recurs again, reduce by one additional dose level. • If recurs again, reduce by one additional dose level.	

Table 3B. Dose Modifications for non-Hematologic Toxicities. See Dose Levels for venetoclax and CC-486 in Table 4.

Observation	Action	Comments
AE resolves promptly with supportive care	Maintain dose level	
Febrile neutropenia or neutropenia with infection	• Withhold all agents until resolution of fever and infection (as applicable)	
Grade 3 or higher non-hematologic AE that does not resolve to grade 2 or below within one week despite maximum supportive care	• Hold venetoclax, CC-486, and obinutuzumab (if applicable) • Resume therapy at same dose level once AE resolves to ≤ grade 2 • If recurs, reduce by one dose level. • If recurs again, reduce by one additional dose level. • If recurs again, reduce by one additional dose level	Monitor CBC and CMP weekly. No more than 3 dose reductions are allowed If treatment is delayed by more than 6 weeks due to treatment-related toxicity, remove patient from study

Table 4. Venetoclax and CC-486 Dose Levels to be used if dose modifications are needed as per Tables 3A and 3B in the Expansion Cohort.

Agent	Starting Dose	Dose Reduction #1	Dose Reduction #2	Dose Reduction #3
Venetoclax	RP2D dose and schedule	RP2D dose on Days 1-10 only	50% reduction in dose, on Days 1-10 only	75% reduction in dose, on Days 1-10 only

CC-486	RP2D dose and schedule	25% dose reduction, same schedule	50% dose reduction, same schedule	50% dose reduction with every other day dosing

4.3 Preparation and Administration of Study Drug

Venetoclax and CC-486 tablets will be delivered to, stored, and dispensed from the University of Chicago Medicine Investigational Drug Service (IDS) Pharmacy. A 28-day supply of each drug will be provided to patients in bottles. Obinutuzumab vials will be delivered to, stored, and dispensed from the IDS and administered intravenously in the infusion center of University of Chicago Medicine or the participating study sites.

4.4 Subject Compliance Monitoring

For the oral medications CC-486 and venetoclax, study personnel will review the dosing instructions with the subject prior to dispensing the study drug. The subject will be instructed to return any unused study drugs to the site at the next visit. Subject compliance will be noted on the appropriate CRFs and source records based on a tablet count. To monitor treatment compliance, reconciliation of tablet will be done at each scheduled study visit. Exposure to the therapy will also be assessed by a reliable history, diary, and expected pharmacologic effect during the follow-up visits.

4.5 Concomitant Medications and Therapies

All treatments that the treating investigator considers necessary for a participant's welfare may be administered at the discretion of the treating investigator in keeping with the standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF. All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and Adverse Events of Special Interest.

Participants are prohibited from receiving the following therapies during the screening and treatment phase of this trial:

- Anti-neoplastic biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy
- Steroid therapy for anti-neoplastic intent
- Investigational agents other than venetoclax, CC-486, or obinutuzumab
- Radiation therapy
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. See Section 3.4. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are

allowed; however, intranasal influenza vaccines (eg,FluMist®) are live attenuated vaccines and are not allowed.

- Strong and moderate CYP3A inhibitors (see Appendix H)
- CYP3A inducers (see Appendix H)
- Warfarin or warfarin derivatives
- P-gp inhibitors or narrow therapeutic index P-gp substrates

NOTE: There is an interaction between P-gp substrates/inhibitors and venetoclax. If these agents become required, reduce the venetoclax dose by at least 50%.

In addition, in order to avoid overestimation of the MTD, moderate or strong CYP3A inducers are prohibited during the DLT Evaluation Period.

Concomitant medications that fall into the categories below could potentially lead to adverse reactions and should be considered cautionary (except where noted). If a potential study patient is taking any of the medications in the categories described below, the treating investigator must assess and document the use of medications known or suspected to fall in the following medication categories:

- Moderate/weak CYP3A inducers such as efavirenz and oxcarbazepine
- CYP2C8 substrates such as thiazolidinediones (glitazones) and select statins (because of expected inhibition of the metabolism of CYP2C8 substrates) by venetoclax
- CYP2C9 substrates such as tolbutamide (because of expected inhibition of the metabolism of CYP2C9 substrates by venetoclax). It is recommended to exclude CYP2C9 substrates with a narrow therapeutic index such as phenytoin.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

4.5.1 Monitoring and Treatment for Hepatitis B Reactivation

Patients who are both HBsAg negative and hepatitis B core antibody (anti-HBc) positive may be included in this study. These patients should have HBV DNA levels obtained monthly for at least 12 months after the last cycle of therapy by means of real-time PCR with the use of an assay that has a sensitivity of at least 10 IU/mL.

If the HBV DNA assay becomes positive and is above the World Health Organization's cutoff of 100 IU/mL, treatment with immunochemotherapy should be held and the patient should be treated (for at least 1 year after the last dose of obinutuzumab) with an appropriate nucleoside analogue and immediately referred to a gastroenterologist or hepatologist for management. Patients may resume immunochemotherapy once HBV DNA levels decrease to undetectable levels.

If the HBV DNA assay becomes positive and is $\leq$ 100 IU/mL, the patient should be retested within 2 weeks. If the assay is still positive, treatment with obinutuzumab must be held and the patient should be treated with an appropriate nucleoside analogue (for at least 1 year after the last dose of obinutuzumab) and immediately referred to a gastroenterologist or hepatologist for management. Patients may resume obinutuzumab once the HBV DNA levels decrease to undetectable levels.

If a patient's HBV DNA level exceeds 100 IU/mL while the patient is receiving antiviral medication, treatment with immunochemotherapy must be permanently discontinued.

4.6 PACKAGING AND LABELING

4.6.1 Venetoclax

Venetoclax tablets will be packaged in high-density polyethylene plastic bottles to accommodate the study design. Each bottle will be labeled with the manufacturer name, address and telephone number, the protocol number, drug name, dosage form and strength (where applicable), amount of drug per container, lot number, expiration 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. A desiccant canister may be included in the bottle. If supplied with a desiccant, the desiccant canister should be returned to the bottle directly after each tablet removal.

For further details regarding venetoclax formulation, see the Venetoclax IB.

4.6.2 CC-486

CC-486 tablets will be packaged in blister cards. Each bottle will be labeled with the manufacturer name, address and telephone number, the protocol number, drug name, dosage form and strength (where applicable), amount of drug per container, lot number, expiration date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable, including the warning, "Caution: New Drug — Limited by Federal (or United States) law to investigational use."

Only sufficient drug for one cycle of treatment will be provided to each subject at the start of each treatment cycle. All tablets should be swallowed whole, and should not be broken or chewed.

4.6.3 Obinutuzumab

Obinutuzumab is provided as a single 1000-mg dose liquid concentrate with a strength of 25 mg/mL. It is supplied in 50-mL glass vials containing 40 mL of the 25-mg/mL liquid concentrate. In addition to the antibody, the liquid also contains histidine/histidine-HCl, trehalose, poloxamer 188, and highly purified water which meets the specified limits according to Pharm. Eur. and USP.

4.7 RECEIPT OF DRUG SUPPLIES

Investigational agents will be received by the Investigational Drug Services (IDS) pharmacy at each participating site. The drug supply will be requested as each patient clears screening at each individual site. If subjects are assigned to a study cohort but withdraw prior to receiving drug, the tablets and vials will be returned to the supplying company or destroyed pending instructions from the supplying companies. When a new patient is assigned in replacement, supplies for the first cycle will be requested at that time.

4.8 Product Storage and Stability

CC-486 tablets should be stored at 25 ºC (77 ºF), excursions permitted to 15 ºC to 30 ºC (59 ºF to 86 ºF). Venetoclax tablets must be stored at 15 °C-25 °C (59 °F - 77 °F). The recommended storage conditions for obinutuzumab drug products are between 2 °C and 8 °C, protected from light. For further instructions for obinutuzumab storage as well as information on in-use stability, see the packaging label. The storage area should be secure and have limited access.

4.9 Dispensing of Study Drug

When a patient presents for a study visit at which oral investigational agents are to be dispensed (see Section 5 for a detailed schedule of drug dispensing), the IDS Pharmacy will be alerted of the patients' arrival with enough lead time to secure delivery of materials. The clinical investigation staff will have responsibility for the agent until it is given to the patient. The clinical investigation staff and patient will each mark receipt in a Drug Accountability Log. The number and strength of the tablets and/or capsules will be noted.

On days where study subjects are scheduled for obinutuzumab administration, the IDS Pharmacy representative will deliver the single full dose directly to the IV therapy nurse who will administer the drug to the patient.

Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.

4.10 Return or Destruction of Study Drug

At the close of the study, a detailed inventory of all remaining study drugs will be undertaken at all study sites. Any remaining study drugs will be returned or destroyed on site per instructions from the supplying companies.

5 STUDY PROCEDURES

5.1 Informed Consent

Study documentation including informed consent documents will be reviewed in detail and the potential subject given opportunity to ask detailed questions regarding the study. A schedule of events will be provided to the potential subject. If the subject elects to sign the informed consent documents and undergo screening, the assessments and procedures listed below with proceed.

5.2 Visit 1: Screening

5.2.2 Screening Visit Methods and Procedures

The screening visit will take place in the oncology clinic space at participating trial sites. The visit must take place no more than 28 days prior to the planned initiation of therapy. A full medical history

will be obtained and recorded in the clinical record by the treating investigator or qualified designee, as well as detailed information about current medications, allergies, oncology treatment history, family history, social history and history of surgeries. Current symptoms will be elucidated and recorded in the clinical record.

5.2.3 Screening Visit Scales and Assessments

The treating investigator or qualified designee will take vital signs including temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only. The body mass index (BMI) and body surface area (BSA) will be calculated.

- The Follicular Lymphoma International Prognostic Index (FLIPI) score (Solal-Céligny et al. 2004) will be assessed and recorded by the treating investigator or qualified designee (Appendix C).
- The treating investigator or qualified designee will assess ECOG status (Appendix B) at screening.
- A pretreatment whole-body PET scan will be obtained prior to the initiation of therapy.
- Formalin-fixed, paraffin-embedded slides and/or tissue block containing a tumor biopsy dated within 90 days prior to of the initiation of screening, or up to 28 days after screening initiation but prior to the start of therapy, will be obtained and sent to hematopathology at University of Chicago Medicine Hyde Park Campus for central pathology review (see Section 5.10 for instructions). The tumor biopsy material also will undergo next generation DNA sequencing of a targeted panel of cancer-related genes.
- Blood samples for correlative studies are to be provided to the main University of Chicago site for circulating methylation profiling and circulating tumor DNA analysis (see Section 5.10 for instructions).

5.2.4 Screening Visit Examinations and Questionnaires

The treating investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. The treating investigator or qualified designee may use standard intake forms to facilitate the collection of a detailed past medical history, family history, and medication list. These must be verified in a face-to-face encounter. No additional questionnaires are required.

5.2.5 Screening Visit Laboratory Studies

The following laboratory studies should be drawn within 28 days of the start of therapy:

- Complete blood count (CBC) with differential counts including hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, white blood cell count, platelet count, absolute and relative neutrophil count, absolute and relative lymphocyte count, absolute and relative monocyte count, and absolute and relative eosinophil count.
- Complete metabolic panel including serum glucose, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, total protein, albumin, alanine transaminase, aspartate transaminase, and alkaline phosphatase.
- Serum uric acid level

- Serum lactate dehydrogenase level
- Serum beta-2 microglobulin level
- Prothrombin (PT) and activated partial thromboplastin (aPTT) times
- Hepatitis B core antibody (total)
- Hepatitis B surface antigen
- HIV 1/2 4th generation antibody and p24 antigen test
- Hepatitis C antibody screening
- A blood sample stored for testing if the patient develops a viral infection on study (e.g., cytomegalovirus, varicella zoster virus, herpes simplex virus, or Epstein–Barr virus).
- Pregnancy testing (see Appendix D for more details)

5.2.6 Screening Visit Medications

a) Medications to begin:
    - TLS prophylaxis per Section 7.4.1.1. TLS prophylaxis should be continued at least through the end of Cycle 1.
    - Infectious prophylaxis per Section 7.4.4.1

b) Medications to discontinue (in cooperation with primary treating physicians):
    - Strong CYP3A4 inhibitors such as fluconazole, ketoconazole, and clarithromycin
    - Strong CYP3A4 inducers such as rifampin and carbamazepine

5.2.7 Plan for unscheduled visits

Study subjects will be provided with contact information for the clinic, including but not limited to access to the electronic health records messaging portal, business hour phone numbers for the clinic, and pager numbers for treating investigators. Study subjects will be provided with instructions to call for specific symptoms or any health concerns after the screening visits. Unscheduled visits may occur throughout the study period when concerns raised by patient contact or abnormal assessments indicate the necessity for such an encounter. Unscheduled visits may consist of laboratory draws only, a clinic visit, or an admission to an inpatient unit depending on the judgment of the treating investigator.

5.3 Cycle 1 Visits

Patients will be assessed and/or treated in the clinic at the appropriate study site on the following days during the 28-day Cycle 1:

- Day 1
- Day 8
- Day 15
- Day 22

Visits should ideally occur exactly on the scheduled date but are permitted to be rescheduled within a window of +/- 3 days.

5.3.1 Cycle 1 Methods and Procedures

Cycle 1 visits will take place in the oncology clinic space at participating trial sites. A focused medical history will be obtained and recorded in the clinical record by the treating investigator or qualified designee, as well as any changes in concomitant medical conditions, current medications, allergies, or social history. Current symptoms will be elucidated and recorded in the clinical record.

5.3.2 Cycle 1 Scales and Assessments

The treating investigator or qualified designee will take vital signs including temperature, pulse, respiratory rate, weight and blood pressure. The body mass index (BMI) and body surface area (BSA) will be calculated. The treating investigator or qualified designee will assess ECOG status (Appendix B) at each visit.

5.3.3 Cycle 1 Examinations and Questionnaires

The treating investigator or qualified designee will perform a focused physical exam during each visit. Clinically significant abnormal findings should be recorded as medical history. The treating investigator or qualified designee may use standard intake forms to facilitate the collection of changes in medical history, and medication list. These must be verified in a face-to-face encounter. No additional questionnaires are required.

5.3.4 Cycle 1 Laboratory Studies

On Days 1, 8, 15, and 22, the following studies should be obtained and reviewed prior to administration of any treatment scheduled for that day:

- Complete blood count (CBC) with differential counts including hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, white blood cell count, platelet count, absolute and relative neutrophil count, absolute and relative lymphocyte count, absolute and relative monocyte count, and absolute and relative eosinophil count.
- Complete metabolic panel including serum glucose, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, total protein, albumin, alanine transaminase, aspartate transaminase, and alkaline phosphatase.
- Serum lactate dehydrogenase level.
- Serum uric acid level on Day 1 only, repeat as needed (see Appendix G)
- Serum beta-2 microglobulin level on Day 1 only.

5.3.5 Cycle 1 Medications

Cycle 1 Day 1:

- A 5 to 28-day supply of venetoclax at the appropriate dose level will be distributed to the subject.
- 14 doses (28-day supply) of CC-486 at the appropriate dose level will be distributed to the subject.
- Obinutuzumab 1000 mg IV (dose-finding cohort only).

Cycle 1 Day 8:

- Obinutuzumab 1000 mg IV (dose-finding cohort only)

Cycle 1 Day 15:

- Obinutuzumab 1000 mg IV (dose-finding cohort only)

Cycle 1 Day 22: No facility-administered medications

5.4 CYCLE 2 AND 3 VISITS

There will be three study visits during Cycles 2 and 3. Each subject will be assessed and/or treated in the clinic at the appropriate study site on Day 1 and Day 15 during Cycle 2 and on Day 1 only during Cycle 3. Visits should ideally occur exactly on the scheduled date but are permitted to be rescheduled within a window of +/- 3 days.

5.4.1 Cycle 2-3 Methods and Procedures

Cycle 2 and 3 visits will take place in the oncology clinic space at participating trial sites. A focused medical history will be obtained and recorded in the clinical record by the treating investigator or qualified designee, as well as any changes in concomitant medical conditions, current medications, allergies, or social history. Current symptoms will be elucidated and recorded in the clinical record.

5.4.2 Cycle 2-3 Scales and Assessments

The treating investigator or qualified designee will take vital signs including temperature, pulse, respiratory rate, weight and blood pressure. The body mass index (BMI) and body surface area (BSA) will be calculated.

- The treating investigator or qualified designee will assess ECOG status (Appendix B) at each visit.
- A blood sample for correlative studies is to be provided to the main University of Chicago site for circulating methylation profiling (see Section 5.10) on Cycle 3 Day 1 only.

5.4.3 Cycle 2-3 Examinations and Questionnaires

The treating investigator or qualified designee will perform a focused physical exam during each visit. Clinically significant abnormal findings should be recorded as medical history. The treating investigator or qualified designee may use standard intake forms to facilitate the collection of changes in medical history, and medication list. These must be verified in a face-to-face encounter. No additional questionnaires are required.

5.4.4 Cycle 2-3 Laboratory Studies

On Day 1 (both Cycle 2 and 3) and Day 15 (Cycle 2 only), the following studies should be obtained and reviewed prior to administration of any treatment scheduled for that day:

- Complete blood count (CBC) with differential counts including hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, white blood cell count, platelet count, absolute

and relative neutrophil count, absolute and relative lymphocyte count, absolute and relative monocyte count, and absolute and relative eosinophil count.
- Complete metabolic panel including serum glucose, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, total protein, albumin, alanine transaminase, aspartate transaminase, and alkaline phosphatase.
- Serum lactate dehydrogenase level.
- Serum uric acid level on Day 1 only, repeat as needed (see Appendix G).
- Serum beta-2 microglobulin level on Day 1 only.

5.4.5 Cycle 2-3 Medications

Cycle 2 Day 1:
- A 5 to 28-day supply of venetoclax at the appropriate dose level will be distributed to the subject.
- 14 doses (28-day supply) of CC-486 at the appropriate dose level will be distributed to the subject.
- Obinutuzumab 1000 mg IV (dose-finding cohort only)
- TLS prophylaxis may be continued, restarted or discontinued after Cycle 1 is completed per the judgment of the treating investigator.

Cycle 2 Day 15: no facility-administered medications

Cycle 3 Day 1:
- A 5 to 28-day supply of venetoclax at the appropriate dose level will be distributed to the subject
- 14 doses (28-day supply) of CC-486 at the appropriate dose level will be distributed to the subject.
- Obinutuzumab 1000 mg IV (dose-finding cohort only)

5.5 Cycle 4 Visits

Patients will be assessed and/or treated in the clinic at the appropriate study site on the following days during the 28-day Cycle 4:
- Day 1
- Day 8 (expansion cohort only)
- Day 15 (expansion cohort only)

5.5.1 Cycle 4 Methods and Procedures

Cycle 4 visits will take place in the oncology clinic space at participating trial sites. A focused medical history will be obtained and recorded in the clinical record by the treating investigator or qualified designee, as well as any changes in concomitant medical conditions, current medications, allergies, or social history. Current symptoms will be elucidated and recorded in the clinical record.

5.5.2 Cycle 4 Scales and Assessments

The treating investigator or qualified designee will take vital signs including temperature, pulse, respiratory rate, weight and blood pressure. The body mass index (BMI) and body surface area (BSA) will be calculated.

- The treating investigator qualified designee will assess ECOG status (Appendix B) at each visit.
- Prior to the Cycle 4 Day 1 visit, the first interim PET imaging for disease response (secondary outcome assessment) must be completed. See Appendix E for details of PET interpretation and response assessment.

5.5.3 Cycle 4 Examinations and Questionnaires

The treating investigator or qualified designee will perform a focused physical exam during each visit. Clinically significant abnormal findings should be recorded as medical history. The treating investigator or qualified designee may use standard intake forms to facilitate the collection of changes in medical history, and medication list. These must be verified in a face-to-face encounter. No additional questionnaires are required.

5.5.4 Cycle 4 Laboratory Studies

On Day 1 (both dose-finding and expansion cohorts) and 8, and 15 (expansion cohort only), the following studies should be obtained and reviewed prior to administration of any treatment scheduled for that day:

- Complete blood count (CBC) with differential counts including hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, white blood cell count, platelet count, absolute and relative neutrophil count, absolute and relative lymphocyte count, absolute and relative monocyte count, and absolute and relative eosinophil count.
- Complete metabolic panel including serum glucose, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, total protein, albumin, alanine transaminase, aspartate transaminase, and alkaline phosphatase.
- Serum lactate dehydrogenase level.
- Serum uric acid level on Day 1 only, repeat as needed (see Appendix G).
- Serum beta-2 microglobulin level on Day 1 only.

5.5.5 Cycle 4 Medications

Cycle 4 Day 1:

- A 5 to 28-day supply of venetoclax at the appropriate dose level will be distributed to the subject
- 14 doses (28-day supply) of CC-486 at the appropriate dose level will be distributed to the subject.
- Obinutuzumab 1000 mg IV (expansion and dose-finding cohorts)

Cycle 4 Day 8:

- Obinutuzumab 1000 mg IV (expansion cohort only)

Cycle 4 Day 15:

- Obinutuzumab 1000 mg IV (expansion cohort only)

5.6 CYCLE 5-9 VISITS

Patients will be assessed and/or treated in the clinic at the appropriate study site on Day 1 of the 28-day Cycles 5, 6, 7, 8, and 9. Visits should ideally occur exactly on the scheduled date, but are permitted to be rescheduled within a window of +/- 3 days.

5.6.1 Cycle 5-9 Methods and Procedures

Visits during Cycles 5-9 will take place in the oncology clinic space at participating trial sites. A focused medical history will be obtained and recorded in the clinical record by the treating investigator or qualified designee, as well as any changes in concomitant medical conditions, current medications, allergies, or social history. Current symptoms will be elucidated and recorded in the clinical record.

5.6.2 Cycle 5-9 Scales and Assessments

The treating investigator or qualified designee will take vital signs including temperature, pulse, respiratory rate, weight and blood pressure. The body mass index (BMI) and body surface area (BSA) will be calculated.

- The treating investigator or qualified designee will assess ECOG status (Appendix B) at each visit.
- Prior to the Cycle 7 Day 1 visit, the second interim PET imaging for disease response (primary outcome assessment) must be completed. See Appendix E for details of PET interpretation and response assessment.
- A blood sample is to be provided to the main University of Chicago site for circulating methylation profiling (see Section 5.10) on Cycle 6 Day 1 only.

5.6.3 Cycle 5-9 Examinations and Questionnaires

The treating investigator or qualified designee will perform a focused physical exam during each visit. Clinically significant abnormal findings should be recorded as medical history. The treating investigator or qualified designee may use standard intake forms to facilitate the collection of changes in medical history, and medication list. These must be verified in a face-to-face encounter. No additional questionnaires are required.

5.6.4 Cycle 5-9 Laboratory Studies

On Day 1 of Cycles 5-9, the following studies should be obtained and reviewed prior to administration of any treatment scheduled for that day:

a) Complete blood count (CBC) with differential counts including hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, white blood cell count, platelet count, absolute and relative neutrophil count, absolute and relative lymphocyte count, absolute and relative monocyte count, and absolute and relative eosinophil count.

b) Complete metabolic panel including serum glucose, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, total protein, albumin, alanine transaminase, aspartate transaminase, and alkaline phosphatase.
c) Serum lactate dehydrogenase level.
d) Serum uric acid level.
e) Serum beta-2 microglobulin level.

5.6.4 Cycle 5-9 Medications

Cycle 5 Day 1:
- A 5 to 28-day supply of venetoclax at the appropriate dose level will be distributed to the subject
- 14-day supply of CC-486 at the appropriate dose level will be distributed to the subject.
- Obinutuzumab 1000 mg IV

Cycle 6 Day 1:
- A 5 to 28-day supply of venetoclax at the appropriate dose level will be distributed to the subject
- 14-day supply of CC-486 at the appropriate dose level will be distributed to the subject.
- Obinutuzumab 1000 mg IV

Cycle 7 Day 1:
- A 5 to 28-day supply of venetoclax at the appropriate dose level will be distributed to the subject
- 14-day supply of CC-486 at the appropriate dose level will be distributed to the subject.
- Obinutuzumab 1000 mg IV

Cycle 8 Day 1:
- A 5 to 28-day supply of venetoclax at the appropriate dose level will be distributed to the subject
- 14-day supply of CC-486 at the appropriate dose level will be distributed to the subject.
- Obinutuzumab 1000 mg IV

Cycle 9 Day 1:
- A 5 to 28-day supply of venetoclax at the appropriate dose level will be distributed to the subject
- 14-day supply of CC-486 at the appropriate dose level will be distributed to the subject.
- Obinutuzumab 1000 mg IV

5.7 Cycle 10-12 Visits

Patients will be assessed and/or treated in the clinic at the appropriate study site on Day 1 of the 28-day Cycles 10, 11, and 12. Visits should ideally occur exactly on the scheduled date, but are permitted to be rescheduled within a window of +/- 3 days.

5.7.1 Cycle 10-12 Methods and Procedures

Visits during Cycles 10-12 will take place in the oncology clinic space at participating trial sites. A focused medical history will be obtained and recorded in the clinical record by the treating investigator or qualified designee, as well as any changes in concomitant medical conditions, current medications, allergies, or social history. Current symptoms will be elucidated and recorded in the clinical record.

5.7.2 Cycle 10-12 Scales and Assessments

The treating investigator or qualified designee will take vital signs including temperature, pulse, respiratory rate, weight and blood pressure. The body mass index (BMI) and body surface area (BSA) will be calculated.

- The treating investigator or qualified designee will assess ECOG status (Appendix B) at each visit.

5.7.3 Cycle 10-12 Examinations and Questionnaires

The treating investigator or qualified designee will perform a focused physical exam during each visit. Clinically significant abnormal findings should be recorded as medical history. The treating investigator or qualified designee may use standard intake forms to facilitate the collection of changes in medical history, and medication list. These must be verified in a face-to-face encounter. No additional questionnaires are required.

5.7.4 Cycle 10-12 Laboratory Studies

On Day 1 of Cycles 10-12, the following studies should be obtained and reviewed prior to administration of any treatment scheduled for that day:

a) Complete blood count (CBC) with differential counts including hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, white blood cell count, platelet count, absolute and relative neutrophil count, absolute and relative lymphocyte count, absolute and relative monocyte count, and absolute and relative eosinophil count.
b) Complete metabolic panel including serum glucose, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, total protein, albumin, alanine transaminase, aspartate transaminase, and alkaline phosphatase.
c) Serum lactate dehydrogenase level.
d) Serum uric acid level on Day only, repeat as needed (see Appendix G).
e) Serum beta-2 microglobulin level on Day 1 only.

5.7.5 Cycle 10-12 Medications

Cycle 10 Day 1:

- A 5 to 28-day supply of venetoclax at the appropriate dose level will be distributed to the subject
- 14-day supply of CC-486 at the appropriate dose level will be distributed to the subject.
- Obinutuzumab 1000 mg IV (expansion cohort only)

Cycle 11 Day 1:

- A 5 to 28-day supply of venetoclax at the appropriate dose level will be distributed to the subject
- 14-day supply of CC-486 at the appropriate dose level will be distributed to the subject.
- Obinutuzumab 1000 mg IV (expansion cohort only)

Cycle 12 Day 1:

- A 5 to 28-day supply of venetoclax at the appropriate dose level will be distributed to the subject
- 14-day supply of CC-486 at the appropriate dose level will be distributed to the subject.
- Obinutuzumab 1000 mg IV (expansion cohort only)

5.8 End of Treatment Visit

The end of treatment visit will be scheduled in the clinic at the appropriate study site within one calendar month of the last administered treatment (Cycle 12, Day 28). Patients who discontinue therapy due to adverse events or disease progression will be moved immediately to the end-of-treatment visit.

5.8.1 End of Treatment Methods and Procedures

An updated complete medical history will be obtained and recorded in the clinical record by the treating investigator or qualified designee, as well as any changes in concomitant medical conditions, current medications, allergies, or social history. Current symptoms will be elucidated and recorded in the clinical record.

5.8.2 End of Treatment Scales and Assessments

The treating investigator or qualified designee will take vital signs including temperature, pulse, respiratory rate, weight and blood pressure. The body mass index (BMI) and body surface area (BSA) will be calculated.

- The sponsor-investigator or qualified designee will assess ECOG status (Appendix B) at each visit.
- A CT scan with intravenous contrast of the chest, abdomen, pelvis (as well as the neck if previously involved with disease) is recommended at the time of the end-of-treatment visit as a standard-of-care disease assessment approximately one year into therapy, but is not required per the study protocol.
- A blood sample is to be provided to the main University of Chicago site for circulating methylation profiling (see Section 5.10)

5.8.3 End of Treatment Examinations and Questionnaires

The treating investigator or qualified designee will perform a focused physical exam during each visit. Clinically significant abnormal findings should be recorded as medical history. The treating investigator or qualified designee may use standard intake forms to facilitate the collection of changes

in medical history, and medication list. These must be verified in a face-to-face encounter. No additional questionnaires are required.

5.8.4 End of Treatment Laboratory Studies

At the end of treatment visit, the following studies should be obtained:

- Complete blood count (CBC) with differential counts including hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, white blood cell count, platelet count, absolute and relative neutrophil count, absolute and relative lymphocyte count, absolute and relative monocyte count, and absolute and relative eosinophil count.
- Complete metabolic panel including serum glucose, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, total protein, albumin, alanine transaminase, aspartate transaminase, and alkaline phosphatase.
- Serum lactate dehydrogenase level.
- Serum beta-2 microglobulin level.

5.8.5 End of Treatment Medications

Antiviral prophylaxis may be continued for up to 6 months following the end of treatment, within the judgment of the treating investigator. Antibiotic and antifungal prophylaxis may be discontinued when any ongoing neutropenia improves to Grade 1-2 or better. TLS prophylaxis, if still ongoing this point, may be discontinued after the last dose of venetoclax or obinutuzumab.

5.9 Post Treatment Follow Up

Post-treatment follow-up visits shall occur every 8-12 weeks until 18 months post-treatment, and every 6 months thereafter until the subject is lost to follow-up, dies, withdraws from the study protocol, or the end of the study is reached. Patients who discontinue therapy due to adverse events or disease progression will be moved immediately to the end-of-treatment visit and then the post-treatment follow-up schedule. Procedures for early subject withdrawal and data collection from withdrawn patients can be found in Section 3.12 and Section 3.13.

5.9.1 Post Treatment Methods and Procedures

A focused medical history will be obtained and recorded in the clinical record by the treating investigator or qualified designee, as well as any changes in concomitant medical conditions, current medications, allergies, or social history. Current symptoms will be elucidated and recorded in the clinical record.

5.9.2 Post Treatment Scales and Assessments

The treating investigator or qualified designee will take vital signs including temperature, pulse, respiratory rate, weight and blood pressure. The body mass index (BMI) and body surface area (BSA) will be calculated.

- The treating investigator or qualified designee will assess ECOG status (Appendix B) at each visit.

- A CT scan with intravenous contrast of the chest, abdomen, pelvis (as well as the neck if previously involved with disease) is recommended at the time of the end-of-treatment visit as a standard-of-care disease assessment at approximately 18 months following treatment initiation (6 months post treatment competition), but is not required per the study protocol.
- A blood sample is to be provided to the main University of Chicago site for circulating methylation profiling (see Section 5.10) at approximately 18 months following treatment initiation (6 months post treatment completion) and again at 30 months post treatment initiation (18 months post treatment completion).
- At 30 months post treatment initiation (18 months post treatment completion) PET imaging for disease response (secondary outcome assessment) must be completed. See Appendix E for details of PET interpretation and response assessment.

5.9.3 Post Treatment Examinations and Questionnaires

The treating investigator or qualified designee will perform a focused physical exam during each visit. Clinically significant abnormal findings should be recorded as medical history. The treating investigator or qualified designee may use standard intake forms to facilitate the collection of changes in medical history, and medication list. These must be verified in a face-to-face encounter. No additional questionnaires are required.

5.9.4 Post Treatment Laboratory Studies

At each post-treatment visit, the following studies should be obtained:

- Complete blood count (CBC) with differential counts including hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, white blood cell count, platelet count, absolute and relative neutrophil count, absolute and relative lymphocyte count, absolute and relative monocyte count, and absolute and relative eosinophil count.
- Complete metabolic panel including serum glucose, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, total protein, albumin, alanine transaminase, aspartate transaminase, and alkaline phosphatase.
- Serum lactate dehydrogenase level.

5.10 Sample Shipping Instructions

5.10.1 Tissue for Correlative and Central Pathology Review

Archival tissue from a diagnostic tumor biopsy should be obtained and sent to the University of Chicago Study Coordinator during the pre-screening phase of the trial. Please send all stained slides, as well as 10 to 20 formalin-fixed paraffin-embedded (FFPE) unstained slides of 4 to 5μm thickness and/or the paraffin-embedded tissue block, if available (see below). If 10 to 20 unstained FFPE slides are not available, please provide any number of slides that may be available. Please ensure that all slides are properly labeled and that appropriate inventory sheet (see Appendix I) is included in each shipment. Please ensure that each slide is labeled with the following information: subject initials, subject ID number, date of biopsy, and specify biopsy site if slides from different origins are being submitted.

Tissue blocks are preferred to unstained slides if available, and can also be submitted to the University of Chicago in order for sections to be cut. All tissue blocks will be returned to the originating institute as

instructed on the inventory sheet (Appendix I). A copy of the completed inventory sheet should be made and filed in the corresponding subject's study files. Please refer to Section 5.10.3 for more details on how processed samples should be shipped.

5.10.2 Blood Specimen Collection and Processing for Correlative Studies

The blood draw for the correlative studies will occur at the screening visit, cycle 4 day 1, cycle 6 day 1, end-of-treatment visit, 18 months after treatment initiation, and 30 months after treatment initiation (see Appendix A). At each time point, 20mL blood in lavender-top BD Vacutainer K2 EDTA tubes will be drawn. The blood specimen for plasma isolation should be processed on site ***within 2 hours*** from the time of collection according to the following protocol:

- Place the lavender-top tube on ice after draw and centrifuge within 1-2 hours
- Centrifuge at 4˚ C at 1000 x g for 15 minutes
- Remove the plasma supernatant and store at -80˚C in 1-2 mL aliquots.
    i) In order to avoid breakage during freezing or leaking during thaw for analysis, please do not overfill the aliquots.

Please ensure that each aliquot is labeled with the following information: subject initials, subject identification number, visit, and aliquot identifier (e.g. a, b, c, etc.). All correlative specimens that are processed on-site should be sent in batches every 2 to 3 months on dry ice via overnight to the University of Chicago. All shipments must be accompanied with the appropriate inventory sheet (Appendix J). A copy of the completed inventory sheet should be made and filed in the corresponding subject's study files. Please refer to Section 5.10.3 for more details on how processed samples should be shipped.

5.10.3 General Shipping Instructions

Please arrange all shipments so that they are sent out to the University of Chicago Monday through Thursday. No shipments should be sent out on Fridays or the day prior to a holiday as shipments cannot be received on weekends and/or holidays. Shipments should be packaged in accordance with the appropriate regulations as specified by the carrier.

Please ensure that all aliquots are properly labeled and that the appropriate inventory sheet (Appendix I or Appendix J) is included in each shipment. In order to alert the study team of an upcoming shipment, please email the details of the shipment to the University of Chicago Study Coordinator, at PhaseIICRA@medicine.bsd.uchicago.edu. The email should contain the completed inventory sheet, or if the sheet cannot be emailed it should be faxed to: 773-702-4889.

Shipment should be sent to the following address:

University of Chicago Medicine
Attention: Jessica Robertson
5841 S. Maryland Avenue
MC-2115, Room I-207
Chicago, IL 60637
Business Phone 773-702-1264
Business Fax 773- 702-4889

Email: PhaseIICRA@medicine.bsd.uchicago.edu

6 STATISTICAL PLAN AND CONSIDERATIONS

6.1 Sample Size Determination

The sample size of the dose-finding arm may vary based on the number of adverse events in the lower dose levels, with an estimated size of 12-18 subjects. The number of subjects for the expansion cohort was calculated using $\alpha = 0.1$, $\beta = 0.2$, power (1- β) = 0.8, a dichotomous study outcome, null hypothesis (H0) proportion of 0.3, and an alternative hypothesis proportion of 0.5. Enrolling 32 patients in a Simon two-stage design yields an α of 0.0997, 1- β = 0.8038, and a probability of correctly stopping after 15 patients if the null hypothesis is true of 72.16%.

6.2 Statistical Methods

6.2.1 Dose Finding Cohort

A 3+3 trial design with 3 dose levels and 2 optional dose de-escalation levels will be used (see Section 4.2 for details). This rule-based design proceeds with cohorts of three patients; the first cohort is treated at a starting dose that is considered to be safe based on prior human studies, and the subsequent cohorts are treated at increasing dose levels that have been fixed in advance (Storer 1989). Safety and tolerability for the purpose of dose-finding for the three-drug combination will be assessed in the first 28-day cycle of therapy.

The definition of dose limiting toxicity (DLT) is as follows:

- Grade 3 or 4 treatment-related non-hematologic toxicity with the exceptions of fatigue, anorexia, nausea, and fever without neutropenia
- Grade 4 treatment-related hematologic toxicity (anemia, thrombocytopenia and/or neutropenia) either lasting > 7 days despite supportive care or complicated by hemorrhage
- Any grade 5 toxicity.

If none of the three patients in the first cohort experiences a DLT within a 28-day cycle, the dose level will be advanced to DL2. If one or more of the patients at a certain dose level experiences a dose-limiting toxicity, three more patients will be treated at the same dose level. If there are two or more DLTs in a cohort of 3-6 patients at dose level 1, three patients will be enrolled at DL-1. If there are two more DLTs at dose level -1, three patients will be enrolled at DL-2.

If the dose level has been advanced to level 2 already, and two or more patients in a cohort of 3-6 patients experience dose-limiting toxicity, the RP2D will be defined as dose level 1. If a dose level has been lowered to DL-1 or DL-2 and no patients experience a DLT, that dose will be the RP2D. If one patient in a cohort at DL-1 and DL-2 experiences a DLT, another three patients will be enrolled. If none of the subsequent cohort experience a DLT, the dose level will be taken as the RP2D.

If there are no DLTs at DL2, DL2 will be the RP2D.

NOTE: The RP2D will be determined based on an integrated evaluation of the efficacy, safety, and tolerability of all evaluated dosing cohorts.

6.2.2 Expansion Cohort

Prior to start of the expansion cohort, there will be a review of the dose modification plan for the expansion cohort by the PI and co-I's. Based on prior studies of chemotherapy-sparing front-line agents in FL (Morschhauser et al. 2018), we hypothesize a successful combination will demonstrate a complete response rate of greater than 50%, while an ineffective combination will demonstrate a complete response rate of less than 30%. Simon's two-stage design (Simon 1989) will be used to test the primary outcome of 6-month CR rate defined for each subject as a binary categorical variable using Lugano response criteria applied to the 6 month PET disease assessment. The null hypothesis that the true 6-month CR rate is 30% or lower will be tested against a one-sided alternative. In the first stage, 15 patients will be accrued. If there are 5 or fewer responses in these 15 patients, the study will be stopped. Otherwise, 17 additional patients will be accrued for a total of 32. The null hypothesis will be rejected if 13 or more responses are observed in 32 patients. This design yields a type I error rate of 0.10 and power of 0.80 when the true response rate is 50%. Patients treated at the MTD/RP2D in the Dose Finding Cohort will contribute towards the accrual goal for the Expansion Cohort.

6.3 Subject Population(s) for Analysis

In the dose finding cohort, all enrolled patients who receive investigational agents will be subjected to study analysis. The all-treated population will be analyzed for the primary study outcomes of safety, tolerability and RP2D. In the expansion cohort, the intention-to-treat population of patients assigned to the treatment arm and who received at least one dose of an investigational agent will be used for analysis of the primary study outcome of CR rate as well as all secondary outcomes. The evaluable population will include patients who have completed 3 cycles of treatment and have a first interim response assessment data available, as well as patients with early progression and off-schedule disease assessment.

7 RISKS AND BENEFITS

7.1 Risk Summary

Risks to the subject have been minimized, but not eliminated. Risks include expected or unexpected toxicity due to treatment with investigational agents, with particular attention towards febrile neutropenia, tumor lysis syndrome, and infusion-related reactions. Anticipated therapy-related toxicities and detailed management plans are found in Section 7.4.

Study associated risks also include vascular injury or bruising associated with venipuncture to obtain the whole blood specimen. Data privacy risks will also be largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is a risk that the information, like all medical information, may be misused.

It is necessary for subject-related data (i.e., ethnicity, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure database. Specimens will be stripped of subject identifiers for downstream analysis. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

7.2 Likelihood of Occurrence

The risks of therapy-related toxicity are unknown, but based on previously reported early discontinuation rates of 11% with chemotherapy-sparing frontline therapy for FL (Morschhauser et al. 2018), we expect discontinuation rates less than 15% for the three-drug combination. Prior studies of front-line chemotherapy and chemotherapy-sparing agents have reported a rate of 65% for grade 3-4 reactions, and 99% for any grade adverse reaction (Morschhauser et al. 2018). We hypothesize grade 3-4 reactions will occur in fewer than 70% of enrolled patients. The likelihood of vascular injury due to venipuncture is very low. The risk of a data breach from secured, institutionally monitored servers is low.

7.3 Potential Direct Benefits to Subject

The therapeutic benefit to study subjects is unknown. Preclinical experience and the success of combinations of two of the three drugs used in this study in other hematologic malignancies suggests outcomes may be similar or better than existing therapies for FL. If successful, this study may lead to the development and eventual approval of a novel chemotherapy-sparing regimen for the treatment of chronic disease, which can lower the population exposure to chemotoxicity in patients with FL.

7.4 Risks Associated with Investigational Agents

Important risks identified in clinical investigations with obinutuzumab were: IRRs, TLS, thrombocytopenia (including acute thrombocytopenia), neutropenia (including prolonged and late onset neutropenia), prolonged B cell depletion, infections (including hepatitis B reactivation and PML), worsening of pre-existing cardiac conditions and GI perforation. See the obinutuzumab IB for additional details.

Based on nonclinical and clinical findings, the potential overlapping toxicities with the addition of venetoclax to obinutuzumab include B cell depletion, neutropenia, and TLS. Given that venetoclax and obinutuzumab target different B-cell subsets and result in an additive pharmacological effect in disease models when combined, it is possible that the rapid, marked depletion of B cells (and total lymphocytes for venetoclax) could lead to increased cases of TLS and infection, and that full reversibility of normal B cells may require a prolonged period without treatment. See the venetoclax IB for additional details.

Oral and intravenous azacitidine has been associated with multilineage cytopenia in preclinical models and clinical trials, particularly neutropenia, through a different mechanism. Studies of the combination of azacitidine and venetoclax in the treatment of myeloid malignancies have highlighted

a risk of febrile neutropenia which is partially abrogated by limiting maximum doses, as has been done in this study. (Jilg et al. 2019). See the azacitidine IB for additional details.

Potential therapy-related risks are described in detail below along with suggested management guidelines.

7.4.1 Tumor Lysis Syndrome

Tumor Lysis Syndrome, or TLS, is a known risk for patients with CLL who are treated with high cell killing agents, including venetoclax or obinutuzumab. TLS can be defined either by laboratory criteria or by clinical criteria following the guidelines of (Howard, Jones, and Pui 2011):

- Two of the following laboratory criteria must be present in serum studies in the same 24-hour window from the time of 3 days prior to therapy until 7 days after initial therapy:
    - Uric acid > 8 mg/dL
    - Phosphorus > 4.5 mg/dL
    - Potassium > 6 mmol/L
    - Corrected calcium < 7 mg/dL or ionized calcium < 4.5 mg/dL
- One of the following clinical criteria is sufficient to diagnose TLS in the 3 days prior to initial therapy or 7 days after initial therapy:
    - Cardiac dysrhythmia at least probably attributable to hyperkalemia
    - Cardiac dysrhythmia, seizure, neuromuscular irritability, hypotension or heart failure at least probably attributable to hypocalcemia
    - Acute kidney injury, defined by increase in serum creatinine level > 0.3 mg/dL from baseline, a single creatinine value > 1.5x the upper age-adjusted limit of normal, or oliguria defined as < 0.5 mL/kg/hr urine production for at least 6 hours

The risk of TLS is expected to be lower in FL than CLL based on prior studies of each agent individually (Davids et al. 2017; Marcus et al. 2017), but the exact nature of the risk of the combination in FL is unknown. Changes in blood chemistry consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax or obinutuzumab. The risk of TLS exists as a continuum based on multiple factors, including tumor burden and comorbidities. Risk is highest for those with bulky disease, elevated leukocyte count, elevated pretreatment LDH levels, compromised renal function, and dehydration. Perform tumor burden assessment with CT scan and CBC with WBC differential, assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) in all patients and correct pre-existing chemistry abnormalities prior to initiation of treatment with venetoclax or obinutuzumab.

7.4.1.1 TLS Prophylaxis

In the dose-finding cohort, **all patients must receive prophylaxis for TLS** before the initiation of the first dose of combination therapy with venetoclax and obinutuzumab on Cycle 1 Day 1.

In the expansion cohort, **all patients must receive prophylaxis for TLS** prior to venetoclax administration on cycle 1 day 1. Those with high tumor burden, high circulating absolute lymphocyte counts (> 25 x109/L), or renal impairment are considered at risk for TLS and must receive

prophylaxis prior to initiation of obinutuzumab on Cycle 4 Day 1 if they are not already on appropriate TLS prophylaxis. For subjects enrolled in the expansion cohort who do not meet those criteria at the time of initiation of obinutuzumab, the need for TLS prophylaxis will be left to the clinical judgement of the treating investigator.

Prophylaxis will include the following:

- Appropriate hydration, consisting of a fluid intake of approximately 2 to 3 L/day starting 24 to 48 hours before the start of treatment.
- Administration of an agent to reduce uric acid (such as allopurinol 300 mg/day orally beginning 72 hours before dose and continuing for 37 days afterwards) or rasburicase IV (for those high risk patients with elevated uric acid levels before treatment, or when otherwise judged to be appropriate by the treating investigator) until normalization of serum uric acid and other laboratory evidence of TLS (e.g., elevated serum LDH levels). Patients with an allergy to allopurinol should receive an alternative TLS prophylaxis regimen such as febuxostat.
- Laboratory results should be reviewed and electrolyte values should not demonstrate any clinically significant abnormalities before the first dose of venetoclax or obinutuzumab, or the patient should receive additional prophylactic treatment and hydration before the initiation of dosing.

On the day of the first administration of venetoclax and/or obinutuzumab, serial vital signs will be measured, and serum chemistry and hematology samples will be drawn before venetoclax and/or obinutuzumab dosing (see Appendix A). These samples are to be sent immediately to the laboratory and the treating investigator or designee must review the results promptly. Laboratory values obtained before the dose of venetoclax and/or obinutuzumab are to be used to determine whether a patient developed a change related to TLS. Additional laboratory studies including post-dose studies are up to the judgement of the treating investigator but are not required by the study protocol. Patients who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring per Appendix G.

7.4.1.2 Guidelines for Hospitalization Due to TLS Risk

Patients exhibiting specific characteristics at screening or initiation of treatment are considered to be at high risk of developing TLS and must be hospitalized for more intensive prophylaxis and monitoring for the initial dose of venetoclax and/or obinutuzumab. These patients are identified by the presence of any of the following:

- Any lymphoid mass > 10 cm on the screening CT scan.
- Any lymphoid mass > 5 cm on the screening CT scan AND an absolute lymphocyte count > 25,000 cells /ul on peripheral cell count.

In addition to characteristics requiring mandatory hospitalization, other patient characteristics may suggest an increased risk of TLS. These include, but are not limited to, the following:

- Overall disease burden (e.g., several enlarged lymph nodes, even if none reaching 10 cm)
- Elevated LDH levels.
- Compromised renal function, as evidenced by creatinine clearance < 80 mL/min
- Extensive bone marrow involvement.

- Dehydration or concern about patients' inability to meet oral hydration requirements (approximately 2 to 3 L/day starting 24 to 48 hours before the start of treatment, with continued intake during therapy).

Hospitalization is not mandatory for patients exhibiting these characteristics, but these and any other factors considered relevant to TLS should be considered in an overall assessment of the patient's state and their risk of TLS. Investigators should use their judgment in assessing TLS risk for their patients and may optionally hospitalize any patient they consider to be at risk for TLS for the first dose of venetoclax, with the approval of the lead PI.

7.4.1.3 Hospitalization Procedures

For patients requiring hospitalization for the administration of venetoclax, hospitalization will begin the evening before the first dose of venetoclax and continue for 24 hours after. Upon admission, serum chemistry and hematology laboratory samples should be drawn at least 4 hours prior to a planned dose of venetoclax. IV hydration should be started at the time of admission with a target of 150 - 200 mL/hr or as clinically appropriate. Laboratory results should be reviewed, and electrolyte values should not demonstrate clinically significant abnormalities before the first dose of venetoclax; otherwise, the patient should receive additional prophylactic treatment and hydration before the initiation of dosing. The nephrology (or acute dialysis) service must be consulted/contacted on hospital admission (per institutional standards) to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Dosing should not be initiated until the laboratory abnormalities resolve. Telemetry should also be considered.

Serial vital signs and TLS laboratory samples will be drawn (serum chemistry as defined in Section 5.2.4 before the first dose of venetoclax. These studies will be repeated only for hospitalized patients at 8-, 12-, and 24-hour following the dose of venetoclax. Additionally, a complete blood count with differential as defined in Section 5.2.4 will be drawn at 8- and 24-hours post-dose (see Appendix G). These samples are to be sent immediately to the laboratory and the treating investigator or designee must review the results promptly. Laboratory values obtained before the dose of venetoclax are to be used to determine whether a patient developed a change related to TLS. Laboratory results of the 24-hour post-dose must be reviewed before receiving the dose of venetoclax for the next day. Patients who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring per Appendix G. Patients felt by the treating-investigator to have particularly high risk of TLS may, in addition to hospitalization, start at a lower dose of venetoclax at the treating investigator's discretion, following discussion with the lead PI.

7.4.2 Infusion-Related Reactions

Obinutuzumab can cause severe and life-threatening Infusion-Related Reactions (IRRs); 65% of patients with CLL experienced a reaction to the first 1000 mg infused of obinutuzumab, and 38% of indolent non-Hodgkin lymphoma patients experienced a reaction on Day 1 of obinutuzumab infusion. IRRs within 24 hours of receiving obinutuzumab have occurred. 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). Most frequently reported

symptoms include nausea, fatigue, dizziness, vomiting, diarrhea, hypertension, flushing, headache, pyrexia, and chills.

Management of patients with IRRs includes the following:

- Premedicate 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.
- For patients with any Grade 4 IRRs, including but not limited to anaphylaxis, acute life-threatening respiratory symptoms, or other life-threatening IRR, stop the obinutuzumab infusion and 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 IRRs and manage symptoms.
- For patients with preexisting cardiac or pulmonary conditions, monitor more frequently throughout the infusion and the post-infusion period because patients may be at greater risk of experiencing more severe reactions.1 Hypotension may occur as part of the obinutuzumab IRR. Consider withholding antihypertensive treatments for 12 hours prior to administration, during each obinutuzumab infusion, and for the first hour after administration until blood pressure is stable.
- For patients at increased risk of hypotensive crisis, consider the benefits versus the risks of withholding antihypertensive medication as suggested above.

7.4.3 Neutropenia

Severe and life-threatening neutropenia, including febrile neutropenia, has been reported during treatment with obinutuzumab, venetoclax and CC-486. Patients with grade 3 or 4 neutropenia should be monitored frequently with regular laboratory tests until resolution. Anticipate, evaluate, and treat any symptoms or signs of developing infection. Consider administration of granulocyte colony-stimulating factors (G-CSF) in patients with grade 3 or 4 neutropenia. Neutropenia can also be of late onset (occurring more than 28 days after completion of treatment) and/or prolonged (lasting longer than 28 days).

Consider dose delays of obinutuzumab and dose reduction of CC-486 followed by venetoclax in the case of grade 3 or 4 neutropenia (see Section 4.2 for details). Antimicrobial prophylaxis should be administered as outlined in Section 7.4.4.1.

7.4.4 Infections Including Febrile Neutropenia

Serious, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of any investigational therapy in this protocol. Fatal infections have been reported. Specifically, serious infections have been reported in patients treated with venetoclax in combination with other agents, including obinutuzumab. Subjects with a history of recurring or chronic infections may be at increased risk of infection. Neutropenia is not an independent risk factor for infections in patients treated with venetoclax. All subjects with or without neutropenia must be carefully monitored for signs of active or imminent infection at each study visit.

7.4.4.1 Antimicrobial Prophylaxis

Previous studies have demonstrated a heightened risk for viral, fungal and bacterial infections with single agent and combination therapy using the agents under investigation in this protocol. This risk may be partially mitigated by the use of appropriate antimicrobial prophylaxis. The choice of agents and timing of prophylaxis are up to the clinical judgment of the treating physician. However, the following guidance and suggestions are provided for antimicrobial prophylaxis:

- There is low risk compared to significant possible benefit for acyclovir or valacyclovir antiviral prophylaxis. 400 mg acyclovir PO twice daily or equivalent dose is recommended for all patients undergoing active treatment from the screening visit until 6 months after the last dose of investigational agents, unless there is a competing risk.
- Patients with severe and long lasting (1 week) neutropenia are strongly recommended to receive antimicrobial prophylaxis until resolution of neutropenia to grade 1 or 2. The choice of prophylactic agent may be individualized within the current National Comprehensive Cancer Network guidelines (National Comprehensive Cancer Network 2017), and should be at least equivalent in coverage and potency to 500mg levofloxacin PO daily. Patients with transient or no neutropenia can be considered on a case-by-case basis for antibacterial prophylaxis based on the treating investigator's estimation of the baseline infection risk.
- Antifungal prophylaxis is complicated by drug-drug interactions between venetoclax and the -azole class of antifungal agents. In prior studies in AML patients of hypomethylating agents such as azacitidine alone, the rate of invasive fungal infections in patients not on antifungal prophylaxis was 4.1% (Pomares et al. 2016), which rose to 8% Grade 3/4 fungal infections in AML patients treated with a combination of venetoclax and azacitidine (DiNardo et al. 2019). Complicating the assessment of this risk is that 46% of the patients on the latter trial received non-azole antifungal prophylaxis. Real-world analysis of patients treated with venetoclax for CLL showed lower rates of invasive fungal infection (1.4%) (Mato et al. 2018).
    - For this protocol, the following antifungal prophylaxis is recommended for all patients with Grade 3/4 neutropenia lasting longer than one week: 300 mg micafungin IV infusion three times per week (Muilwijk et al. 2018; Neofytos et al. 2015).
    - Patients requiring posaconazole or other -azole prophylaxis will require a dose reduction of venetoclax of 75% or more (Agarwal et al. 2017). The venetoclax dose for these particular patients should be agreed upon by study investigators on a case-by-case basis.

7.4.4.2 Management of Infections

The following guidance is provided for infections that occur during the study:

- Patients with uncontrolled systemic infection are excluded from the trial.
- Blood counts should be closely monitored for evidence of infection throughout the trial.
- All patients should be monitored closely for infection and treated aggressively according to institutional guidelines, including growth factor and transfusion support.
- If grade 2−4 infection occurs, treatment (any or all study treatments) may be delayed for a maximum of 4 weeks after the last dose, regardless of presence or absence of neutropenia. If the infection has not resolved after 3 weeks, study treatment must be discontinued. It is strongly recommended that sites delay study treatment when presented with evidence of infection.

- After the first occurrence of an infection which resolves within three weeks, venetoclax and other study drugs can be resumed at the prior dose. After the second occurrence of an infection that resolves within three weeks, the dose of venetoclax should be adjusted per Section 4.2.3.
- Patients being treated with an -azole antifungal agent must cease study drug administration while under active antimicrobial treatment and must not resume venetoclax until 3 posaconazole half-lives have passed (approximately 96 hours).
- Signs and/or symptoms of infection should result in prompt evaluation and appropriate samples for bacteriological investigation prior to starting antibiotic or other treatment.
- A blood sample should be collected at screening and stored for testing if the patient develops a viral infection on study (e.g., cytomegalovirus, varicella zoster virus, herpes simplex virus, or Epstein–Barr virus).
- Grade 4 infection should be reported to the lead PI expeditiously.

7.4.5 Thrombocytopenia

Severe and life-threatening thrombocytopenia has been reported during treatment with obinutuzumab in combination with chlorambucil or bendamustine, and has also been reported with intravenous azacitidine in prior studies and in commercial use. Fatal hemorrhagic events during Cycle 1 have also been reported in patients with CLL treated with obinutuzumab. Cytopenias, including thrombocytopenia, are also a known risk of venetoclax and azacitidine in combination.

Monitor all patients frequently for thrombocytopenia and hemorrhagic events, especially during the first cycle of obinutuzumab administration. In patients with Grade 3 or 4 thrombocytopenia, monitor platelet counts more frequently until resolution and consider subsequent dose delays of obinutuzumab or dose reductions of oral investigational therapy per Section 4.2. Transfusion of blood products (i.e., platelet transfusion) may be necessary. Consider withholding concomitant medications which may increase bleeding risk (e.g. platelet inhibitors, anticoagulants), especially during the first cycle.

7.4.6 Lymphopenia

Lymphopenia has been observed in nonclinical studies with venetoclax and obinutuzumab. While opportunistic infections have been reported in the clinical program, data are confounded by patients' underlying disease and prior therapies. Antimicrobial prophylaxis should be given per the guidelines in Section 7.4.4.1.

7.4.7 Hepatitis B 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 anti-Hepatitis B core Antibody (HBc) positive. Reactivation has also occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive, and hepatitis B surface antibody [anti HBs] positive). HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and

anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels and, in severe cases, increase in bilirubin levels, liver failure, and death. Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with obinutuzumab. For patients who show evidence of hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy.

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

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

7.4.8 Progressive Multifocal Leukoencephalopathy

John Cunningham Virus (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 preexisting neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging, and lumbar puncture. Discontinue obinutuzumab therapy and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

7.4.9 Reproductive Effects

Based on nonclinical studies, there is a potential for decreased spermatogenesis with exposure to venetoclax. Nonreversible depletion of testicular germ cells has been observed in dogs at all doses tested after 4 weeks of dosing. Male patients should be instructed to consider sperm banking before treatment with venetoclax if they are considering preservation of fertility.

7.4.10 Treatment-Emergent Malignancies (Second Primary Malignancies)

Events of second primary malignancies have been reported as rare events with all three investigational agents. No pattern has been observed. The possibility of second primary malignancies should be closely monitored.

7.4.11 Immunizations

The safety and efficacy of immunization with live or attenuated viral vaccines during or following obinutuzumab, venetoclax or CC-486 therapy have not been studied. Immunization with live-virus vaccines is not recommended during treatment or until B-cell recovery following treatment.

7.4.12 Gastrointestinal toxicity

The most commonly reported gastrointestinal (GI) adverse reactions associated with azacitidine, venetoclax, and obinutuzumab therapy include constipation, diarrhea, nausea and vomiting. Gastrointestinal adverse events associated with azacitidine mainly occurred during the first 2 cycles and tended to decrease with subsequent cycles. They occurred more frequently during the first week of the cycle, coinciding with the days of treatment. The majority of these AEs were mild or moderate in severity, transient, and nonserious. Patients should be monitored for these GI toxicities closely and managed symptomatically with antiemetics for nausea and vomiting; antidiarrheals for diarrhea, and laxatives and/or stool softeners for constipation.

7.4.13 Renal Adverse Reactions

Renal abnormalities, ranging from elevated serum creatinine, renal failure and death were reported rarely in patients treated with azacitidine in combination with other chemotherapeutic agents. In addition, renal tubular acidosis defined as a fall in serum bicarbonate < 20 mEq/L in association with alkaline urine, and hypokalemia (serum potassium < 3 mmol/L), developed in subjects with chronic myelogenous leukemia (CML) treated with azacitidine and etoposide. If unexplained reductions in serum bicarbonate (< 20 mmol/L) or elevations of serum creatinine or BUN occurs, the dose of CC-486 should be reduced, or administration delayed. See Section 4.2.2 for suggestions for dose modification.

8 DOCUMENTING AND REPORTING ADVERSE EVENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following characteristics of an observed AE (Section 8.1) will determine whether the event requires expedited reporting in addition to routine reporting.

8.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5. A copy of the CTCAE version 5 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

- **Attribution** of the AE:
  - Definite (5) – The AE *is clearly related* to the study treatment.
  - Probable (4) – The AE *is likely related* to the study treatment.
  - Possible (3) – The AE *may be related* to the study treatment.
  - Unlikely (2) – The AE *is doubtfully related* to the study treatment.
  - Unrelated (1) – The AE *is clearly NOT related* to the study treatment.

8.2 ADVERSE EVENT DEFINITIONS

8.2.1 Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (including a laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

At each evaluation patients should be interviewed in a non-directed manner to elicit potential adverse reactions from the patient. The occurrence of an adverse event will be based on changes in the patient's physical examination, laboratory results, and/or signs and symptoms, and review of the patient's own record of adverse events.

Adverse events will be followed until resolution while the patient remains on-study. Once the patient is removed from the study, events thought to be related to the study medication will be followed until resolution or stabilization of the adverse event, or until the patient starts a new treatment regimen, or death, whichever comes first. Subjects will be followed for AEs/SAEs for 30 days after their last dose of study drug(s). At the end of treatment and after the adverse event period has ended, the lead investigator should continue to report all deaths, (regardless of cause), and any serious adverse event including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject and including pregnancy occurring in the partner of a male study subject who participated in the study that is believed to be related to prior exposure to CC-486, venetoclax and/or obinutuzumab.

8.2.2 Serious Adverse Event

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) Life-threatening (e.g. places subject at <u>immediate</u> risk of death, this does not include events that might have caused death if they occurred at greater severity)
3) Results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect or death of a neonatal infant within 28 days of birth.

Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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.

8.2.3 Unexpected Events

Unexpected events are those not listed at the observed specificity or severity in the protocol (Section 8.3.4), informed consent, investigator brochure, or FDA-approved package insert. An event is considered unexpected if it is listed as occurring within the class of drugs or otherwise expected from the drug's pharmacological properties but has not been previously observed with this specific investigational agent.

8.2.4 Adverse Drug Reactions

An adverse event is considered to be an adverse drug reaction if there is evidence to suggest a causal relationship to the study agent(s). This may include a single occurrence of an event strongly associated with drug exposure (e.g. Stevens-Johnson Syndrome), one or more occurrence of an event otherwise uncommon in the study population, or an aggregate analysis of specific events occurring at greater than expected frequency

8.2.5 Adverse Events of Special Interest (AESI)

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

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law.
- Suspected transmission of an infectious agent by the study drug, as defined below
    - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Additional events of special interest related to venetoclax are:
    - Tumor lysis syndrome (any grade and regardless of attributed cause)
- Additional events of special interest related to CC-486 are:
    - Grade 3 or 4 neutropenia
    - Grade 3 or 4 thrombocytopenia
    - Grade 3 or 4 anemia
- Additional events of special interest related to obinutuzumab are:
    - Tumor lysis syndrome (any grade and regardless of attributed cause)
    - Secondary malignancy (any neoplastic diagnosis other than the study indication that is made after enrollment on the trial)

These events should be reported as an SAE as described in Section 8.2.2.

8.2.6 Other Special Events Requiring Reporting

Any reports of the following events should be recorded and reported to the Lead PI in an expedited fashion as described in Section 8.4.

- Pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the study drug(s). See Sections 8.4.2 and 8.4.3 for additional information.
- Use of the study drug(s) in participant that is actively breastfeeding
- Overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors). See Section 8.4.1 for additional information.
- Product complaints: any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a population.

8.2.7 Other Selected Adverse Events

Selected adverse events (events for which additional data collection or analyses will be performed; but no special case handling or follow-up is required) include the following:

- Infusion related reactions
- Infections (including progressive multifocal leukoencephalopathy)
- Neutropenia (including late-onset neutropenia, defined as neutrophil count <1000 cells/mm^3, occurring 28 days or more after obinutuzumab treatment has been completed or stopped; prolonged neutropenia, defined as neutrophil count <1000 cells/mm^3, that does not resolve after 28 days (without obinutuzumab treatment)
- Thrombocytopenia (including acute thrombocytopenia occurring during and within 24 hours post obinutuzumab infusion)
- Hepatitis B reactivation
- Cardiac events
- Second malignancies
- GI perforation

8.3 Adverse Event Reporting Requirements

8.3.1 Routine Adverse Event Reporting

All Adverse Events must be reported in routine study data submissions. AEs reported using the Serious Event Reporting Form and/or MedWatch Form discussed below must also be reported in routine study data submissions.

All adverse events (except grade 1 and 2 laboratory abnormalities that do not require an intervention), regardless of causal relationship, are to be recorded in the case report form and source documentation. The investigator must determine the intensity of any adverse events

according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 and their causal relationship.

8.3.2 Serious Adverse Event Reporting

Use the UC CCC protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

All serious adverse events (as defined in Section 8.2.2) and all adverse events of special interest (as defined in Section 8.2.5) occurring on this study require expedited reporting to the University of Chicago Comprehensive Cancer Center (UC CCC). The responsible Research Nurse or other designated individual at the treating site should report the SAE to the Study Lead Investigator, the University of Chicago CRA and the CCTO by the end of the business day when s/he becomes aware of the event. Events occurring after business hours should be reported to the CCTO by 12pm (noon) the next business day. Reports should be made using the 'Serious Event Report' Form. Please scan and send via email (preferred) or fax to the following:

University of Chicago Phase II CRA General:
PhaseIICRA@medicine.bsd.uchicago.edu
Phone: 773-834-1746
Fax: 773-702-4889

UC CCC Cancer Clinical Trials Office Quality Assurance:
qaccto@bsd.uchicago.edu

All unexpected adverse reactions must be reported to Dr. Sonali Smith so that the University of Chicago CCTO can inform the FDA. The responsible Research Nurse or other designated individual at the treating site should provide a complete written report using the FDA MedWatch 3500A form. The completed form should be sent to the CCTO at qaccto@bsd.uchicago.edu and to the Phase II CRA at PhaseIICRA@medicine.bsd.uchicago.edu within the specified timelines above regardless of whether all information regarding the event is available. If applicable, a follow-up report should be provided if additional information on the event becomes available.

Participating sites should not forward any adverse event reports directly to the FDA. The CCTO will report all events to the FDA as per the current FDA guidelines.

All serious adverse events and all adverse events of special interest should also be reported to the local IRB of record according to their policies and procedures.

8.3.3 Other Events Requiring Expedited Reporting

All other special events requiring expedited reporting (as defined in Section 8.2.6)

) should be reported to the Lead PI and UCCCC by the designated individual at the treating site within 5 calendar days of site awareness of the event. Events should be reporting using the email addresses in Section 8.3.2.

All such events should also be reported to the local IRB of record according to their policies and procedures.

8.3.4 Serious and Unexpected Adverse Event reporting by the Coordinating Center

The designated UC CCC Regulatory Manager will notify all participating sites of all unexpected and serious adverse reactions that occur on this clinical trial and which are reported to the FDA and/or UC Institutional Review Board (IRB). When reported to the FDA, a copy of the completed MedWatch Form 3500A will be provided to the responsible Regulatory Manager by the CCTO IND Coordinator for distribution to all participating sites.

8.3.5 Expedited Reporting to Collaborators

The sponsor-investigator will report all protocol-defined Serious Adverse Events (SAEs), AEs of Special Interest (AESIs), and Other Special Events as defined in this protocol to Genentech and Celgene within the timelines described below. The completed MedWatch Form or Celgene/Genentech approved reporting forms should be faxed/emailed immediately upon completion to Celgene/Genentech at the following contacts:

- All protocol-defined SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints with or without an AE should be sent to both of the following:
  - **Genentech:** fax (650) 238-606 or email usds_aereporting-d@gene.com
  - **Celgene:** fax: (908) 673-9115 or email: drugsafety@celgene.com

- All Product Complaints related to obinutuzumab and/or venetoclax without an AE should be sent to the following email:
  - kaiseraugst.global_impcomplaint_management@roche.com

It is understood and agreed that the Sponsor-Investigator will be responsible for the evaluation of AEs/SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the study. These reports will be exchanged between the parties as outlined below so that regulatory obligations are met.

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

- **Serious Adverse Drug Reactions (SADRs):** Serious AE reports (as defined in Section 8.2.4) that are related to the Product shall be transmitted to Celgene and Genentech within fifteen (15) calendar days of the coordinating center's awareness date.

- **Other SAEs:** Serious AE reports (as defined in Section 8.2.7) that are unrelated to the study agent(s) shall be transmitted to Celgene and Genentech within thirty (30) calendar days of the coordinating center's awareness date.
- **AESIs:** AESIs (as defined in section 8.2.5) shall be forwarded to Genentech and Celgene within fifteen (15) calendar days of the coordinating center's awareness date.
- **Pregnancy reports:** Any reports of pregnancy (as defined in Section 8.4.2) shall be transmitted to Celgene and Genentech within thirty (30) calendar days of the coordinating center's awareness date.
- **Product Complaints:** All Product Complaints (as defined in Section 8.3.5) shall be forwarded to Celgene and/or Genentech within fifteen (15) calendar days of the coordinating center's awareness date.
- **Other Expedited Event Reports:** In addition, all other events requiring expedited reporting (as defined in Section 8.2.6) will be transmitted to Celgene and Genentech within thirty (30) calendar days of the coordinating center's awareness date.

8.3.6 Case Transmission Verification of Single Case Reports

The Lead PI agrees to conduct the Case Transmission verification to ensure that all events requiring expedited reporting have been adequately received by Genentech and Celgene via the sponsor-investigator emailing Genentech and Celgene a quarterly line-listing documenting single case reports sent by the sponsor-investigator to Genentech and Celgene in the preceding time period. The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Lead PI and Genentech and/or Celgene 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.

Following Case Transmission Verification, reports which have not been received by Genentech or Celgene shall be forwarded by the Lead PI to the company within five (5) calendar days from request by Genentech or Celgene.

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

8.4 Guidance for Specific Situations in Completing Case Reports

8.4.1 Overdose

Overdose, as defined for this protocol, refers to CC-486, venetoclax, and obinutuzumab dosing only. On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of CC-486, venetoclax, and/or obinutuzumab assigned to a given patient, regardless of any associated adverse events or sequelae.

- PO any amount over the protocol-specified dose

- IV 10% over the protocol-specified dose

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

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

8.4.2 Pregnancy in Study Subjects

If a female subject becomes pregnant (including elevated βhCG or positive pregnancy test in a female subject of reproductive potential, regardless of disease state) while receiving venetoclax, obinutuzumab and/or CC-486 or within 180 days after the last dose of venetoclax, obinutuzumab and /or CC-486, a report should be completed and expeditiously submitted to both Genentech and Celgene. The female subject should be immediately discontinued from any study therapy and should be referred to an obstetrician-gynecologist, (preferably one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Lead PI will follow the female subject until completion of the pregnancy outcome and 1 additional year after the initial report of pregnancy to ensure complete reporting of outcomes. The Lead PI must notify Celgene and Genentech Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form and Infant Follow-Up Form, or approved equivalent form.

If the outcome of a pregnancy is abnormal (e.g. spontaneous or therapeutic abortion, stillbirth, neonatal death, or congenital anomaly) in a female subject exposed to venetoclax, CC-486, and/or obinutuzumab as part of this study, the Lead PI should always report the abnormal outcome as serious, and report the event as an SAE within 24 hours of the sponsor-investigator's knowledge of the event using the appropriate SAE reporting procedures as outlined in Section 8.3.2.

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 Lead PI suspects is related to the in utero exposure to the study drug(s) should also be reported to Genentech and Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Lead PI's knowledge of the event using the SAE Report Form, or approved equivalent form.

8.4.3 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the treating investigator if their partner becomes pregnant during the study or within 180 days after the last dose of CC-486, venetoclax, and/or obinutuzumab. A Clinical Trial Pregnancy

Reporting Form should be completed and submitted to Celgene and Genentech within thirty (30) calendar days of the awareness date.

8.5 Data Safety Monitoring Plan

8.5.1 Study Initiation Procedures

This study will be remotely monitored by the designated University of Chicago Clinical Research Associate (CRA) in accordance with the University of Chicago Section of Hematology/Oncology standard operating procedure titled Monitoring of Multi- Institutional Investigator Initiated Clinical Trials. Prior to subject recruitment, and unless otherwise specified, each participating site will undergo a Site Initiation Teleconference to be conducted by the designated University of Chicago research team. The site's principal investigator and his or her study staff must attend the site initiation meeting.

8.5.2 Study Monitoring

Oversight of the study while it is open will be carried out in the multi-institutional data and safety monitoring teleconference through the Lymphoma Clinical Research Group as specified by the UC CCC NCI approved Data and Safety Monitoring Plan. See Section 10.1 for details of the study monitoring plan.

8.5.3 Study Closing Procedures

Participating sites will also undergo a site close-out teleconference upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and to ensure that the site investigator is aware of his/her ongoing responsibilities. Any study report submitted to the FDA by the Lead PI should be copied to Genentech and Celgene. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any publications that are a result of the study should be sent to Celgene and Genentech.

9. DATA HANDLING AND RECORD KEEPING

9.1 Data Management Responsibilities

Record-keeping for this study will be carried out by the designated University of Chicago Clinical Research Associate (CRA) in accordance with the University of Chicago, Section of Hematology/Oncology standard operating procedure titled Monitoring of Multi- Institutional Investigator Initiated Clinical Trials. Investigators at each site will be responsible for ensuring the timely reporting of clinical trial data to the CRA for central record-keeping. Review of data will be the responsibility of the PI and sub-investigators.

9.2 Data Capturing Methods

Data reporting will be performed utilizing the Research Electronic Data Capture (REDCap) electronic data capture system. The University of Chicago CRA will provide outside sites with the applicable user registration information. All required data must be recorded in the REDCap database at the completion of each cycle. AEs are to be entered in real time. SAEs are to be entered on the Serious Event Form within 24 hours of the site's knowledge of the event and sent via email (preferred) or fax to the University of Chicago. All case report forms must be completed by designated study personnel. Each screened (consented) patient is to be entered into REDCap within 48 hours of patient registration.

9.3 SOURCE DOCUMENTS

Before the study can be initiated at any site, the following documentation must be provided to the Cancer Clinical Trials Office (CCTO) at the University of Chicago Comprehensive Cancer Center.

- A copy of the official IRB approval letter for the protocol and informed consent IRB membership list
- Curriculum vitae and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation,
- CAP and CLIA Laboratory certification numbers and institution lab normal values.
- Investigational drug accountability standard operating procedures.
- Additionally, before the study can be initiated at any site, the required executed research contract/subcontract must be on file with the University of Chicago.

In addition to direct data entry, supporting clinical source documentation may be required. Source records are original documents, data, and records (e.g., medical records, raw data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. Each site will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical trial. Source records must be adequate to reconstruct all data transcribed onto the case report form.

9.4 RECORDS RETENTION

It is the Lead PI's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Institutional policy requires that all study records be kept for a minimum of seven years.

9.5 CONFIDENTIALITY

Information about study subjects should be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996. All subjects participating in this trial will have signed a subject authorization form, included in the consent form, informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the Lead PI, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, an attempt will be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10 STUDY MONITORING, AUDITING, AND INSPECTING

10.1 STUDY MONITORING PLAN

Subject eligibility will be determined by the CRA at the central (University of Chicago) site after central pathology review of the tumor sample for eligible histology. A second review on an as-needed basis will be carried out by the study investigators.

Throughout the course of the study, monitoring of all study sites will be conducted by the site investigators and designated CRA to verify the following:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Compliance with regulations
- Submission of required source documents
- Completeness and accuracy of signed informed consent forms

This protocol will undergo weekly review at the multi-institutional data and safety monitoring teleconference as per procedures specified by the UC CCC NCI-approved Data and Safety Monitoring Plan. The conference will be attended by protocol-specified investigators at the designated CRA. During the conference, the following topics will be reviewed:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (Serious Adverse Event & Adverse Event reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

Protocol deviations are to be documented using the Protocol Deviation Form and sent via email to PhaseIICRA@medicine.bsd.uchicago.edu. Deviations that are considered major because they impact subject safety or alter the risk/benefit ratio, compromise the integrity of the study data, and/or affect subjects' willingness to participate in the study must be reported within 7 days. The University of Chicago CRA (PhaseIICRA@medicine.bsd.uchicago.edu) should be contacted with any questions about how to report deviations. All major protocol deviations should also be reported to the local IRB of record according to their policies and procedures.

10.2 AUDITING AND INSPECTING

The Lead PI will permit study-related monitoring, audits, and inspections by the OCR, IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study-related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The Lead PI will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 ETHICAL CONSIDERATIONS

11.1 INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL

The Lead PI will obtain, from the University of Chicago Institutional Review Board (IRB), prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, Lead PI will promptly notify the University of Chicago IRB of the deviation.

The University of Chicago IRB operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (CGP).

In the event that the University of Chicago IRB requires, as a condition of approval, substantial changes to a clinical protocol submitted under an FDA-accepted IND application, or in the event of a sponsor-investigator's decision to modify the previously accepted clinical protocol:

The Lead PI will submit (i.e., in advance of implementing the change) a Protocol Amendment to the IND describing any change to the Phase 1 clinical protocol that significantly affects the safety of the subjects. For changes that do not affect critical safety assessments, the revisions to the clinical protocol will be addressed in the Annual Report to the IND.

11.2 ETHICAL AND SCIENTIFIC CONDUCT OF THE CLINICAL STUDY

The clinical study will be conducted in accordance with the current IRB-approved clinical protocol; ICH Guidelines on GCP; and relevant policies, requirements, and regulations of the University of Chicago IRB, University of Chicago and UCMC, State of Illinois, and applicable federal agencies.

12 STUDY FINANCES

12.1 FUNDING SOURCE

Funding for this study will be provided jointly by Celgene Corp. and Genentech Inc.

13 PUBLICATION PLAN

This study will be subject to the publication policies of the University of Chicago Biological Sciences Division. The Sponsor-Investigator, Dr. Sonali Smith and a Co-Investigator, Dr. Michael Leukam, will together hold primary responsibility for publication of the results of the study. The trial will be submitted for peer review and consideration for publication at high-impact hematology-oncology journals such as the *New England Journal of Medicine*, *Journal of Clinical Oncology*, *Blood*, or *Lancet Oncology*.

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15 APPENDICES

APPENDIX A: SCHEDULE OF STUDY EVENTS (SCHEMA)

Days	Screening	Day 1	Day 8	Day 15	Day 22	End of treatment visit	Post-treatment follow-up
Cycles (Dose finding arm)	Before C1	Cycle 1-12	Cycle 1 only	Cycle 1, 2	Cycle 1 only	N/A	N/A
Cycles (Expansion cohort)	Before C1	Cycle 1-12	Cycle 1, 4	Cycle 1, 2 and 4	Cycle 1 only	N/A	N/A
Window	Within 4 weeks	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	Within 4 weeks of last treatment	Every 8-12 weeks until 18 months post- treatment, every 6 months thereafter
Infusional therapy (obinutuzumab)		X	Cycle 1 (dose finding), Cycle 4 (expansion)	Cycle 1 (dose finding), Cycle 4 (expansion)			
Physical exam, vital signs, height, weight, performance status, BMI, BSA	X	X	X	X	X	X	X
Collection of AE		X	X	X	X	X	X
CBC, CMP, LDH	X	X	X	X	X	X	X
Beta-2 microglobulin	X	X				X	
Uric acid	X	X					
Hepatitis B and C, HIV serology	X						
Pathology review for eligibility	X						
Pregnancy testing	X	X					
PET whole body lymphoma study	X	Prior to cycle 4 and cycle 7					At 30 months after treatment initiation (CR30)
CT chest, abdomen, pelvis						X	At 18 months after treatment initiation
Oncoplus NGS panel (tumor)	X						
Blood draw for correlative studies	X	Prior to cycle 4, cycle 6				X	At 18 months and 30 months after treatment initiation

APPENDIX B: ECOG PERFORMANCE STATUS

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

APPENDIX C: FOLLICULAR LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX

One point is assigned for each of the following adverse prognostic factors:

- Age > 60 years
- Ann Arbor stage III-IV
- Hemoglobin level < 12.0 g/dL
- Number of nodal areas > 4
- Serum LDH level above normal

Three risk groups are defined: low risk (0-1 adverse factors), intermediate risk (2 factors), and poor risk (≥ 3 adverse factors). Individual risk factors will be reported in this trial at the time of data collection for the pretreatment visit and recorded in REDCap.

APPENDIX D: CONTRACEPTIVE GUIDANCE AND PREGNANCY TESTING

Definition of a Woman of Childbearing Potential (WOCBP): A woman is considered fertile following menarche and until becoming post-menopausal
unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
      Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 8 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
    - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the below table during the protocol-defined time frame.

Appendix D Table 1:

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestin- containing) hormonal contraception [b] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestin-only hormonal contraception [b] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b] ● Intrauterine hormone-releasing system (IUS) ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● Vasectomized partner A vasectomized partner is a highly effective contraception method, provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.
a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing:

WOCBP should only be included in the trial after a negative highly sensitive urine or serum pregnancy test.

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected; at the time points specified in the Study Schema (Appendix A), including at the start of each cycle; and as required locally. A positive urine pregnancy test must be followed by a confirmatory serum test.

APPENDIX E: ASSESSING RESPONSE BY LUGANO RESPONSE CRITERIA

Adapted from:

> Van Heertum RL, Scarimbolo R, Wolodzko JG, Klencke B, Messmann R, Tunc F, Sokol L, Agarwal R, Strafaci JA, O'Neal M. Lugano 2014 criteria for assessing FDG-PET/CT in lymphoma: an operational approach for clinical trials. Drug Des Devel Ther. 2017 Jun 13;11:1719-1728. doi: 10.2147/DDDT.S136988. PMID: 28670108; PMCID: PMC5479259.
>
> Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, Lister TA; Alliance, Australasian Leukemia and Lymphoma Group; Eastern Cooperative Oncology Group; European Mantle Cell Lymphoma Consortium; Italian Lymphoma Foundation; European Organization for Research; Treatment of Cancer/Dutch Hemato-Oncology Group; Grupo Español de Médula Ósea; German High-Grade Lymphoma Study Group; German Hodgkin's Study Group; Japanese Lymphoma Study Group; Lymphoma Study Association; NCIC Clinical Trials Group; Nordic Lymphoma Study Group; Southwest Oncology Group; United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014 Sep 20; 32(27):3059-68. doi: 10.1200/JCO.2013.54.8800. PMID: 25113753; PMCID: PMC4979083.

Modified Lugano 5-point scale (5PS)

Score	Description
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately increased above liver at any site
5	Markedly increased uptake above liver at any site
NE	Not evaluable
X	Any areas of uptake not likely to be related to lymphoma

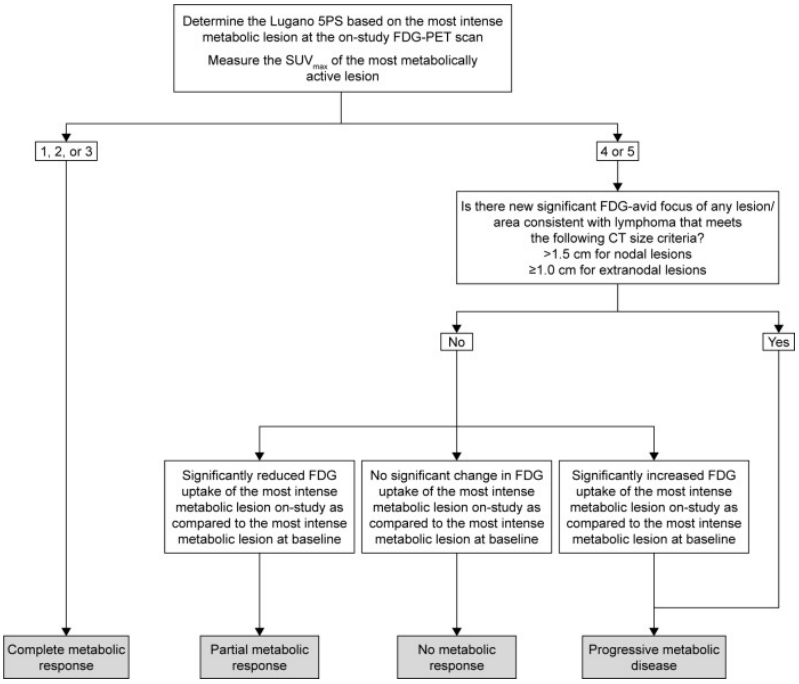
Baseline assessment

At baseline, a maximum of six sites with most metabolically active FDG-avid disease (classified as index [or target] lesions) should be selected which, when possible, include the largest lesions most representative of the patient's overall tumor burden. When possible, index lesions should be chosen from disparate regions of the body and include mediastinal and retroperitoneal areas of disease. These lesions must meet the minimum size requirement of being >15 mm in longest diameter (LDi) for nodal disease, or >10 mm in LDi for extranodal lesions. The LDi and shortest diameter should be recorded for each index lesion. All other disease, consisting of up to ten individual or grouped sites, should be selected at baseline as non-index (or non-target) disease. These can include nodal or extranodal lesions or groups of lesions which are not measurable (or measurable beyond the six sites chosen to be followed as index lesions). In addition, non-index disease can include markedly diffuse FDG uptake in the liver or spleen and marked focal FDG uptake in the BM. All selected sites of disease should be followed throughout the course of treatment.

Each designated index and non-index CT lesion should be correlated to the corresponding and co-registered PET lesion. A visual assessment using the 5PS should then be performed on the most metabolically active lesion out of all index and non-index disease. In addition, a quantitative standardized uptake value (SUV) measurement, which represents the maximum SUV (SUV_{max}), should also be documented for this lesion. The SUVmax will be used to calculate the change in uptake compared to post-baseline TPs.

On-study assessment

At each on-study TP, the index and non-index lesions identified at baseline are assessed on the PET/CT exam. The most metabolically active lesion is again assessed using the 5PS approach and the SUV_{max} of that lesion is determined. Of note, it is possible that the most metabolically active lesion identified on-study, when a subject is undergoing treatment, may be different from the most metabolically active lesion which had been identified at the baseline TP. The on-study SUV_{max} measurement is then utilized to perform the on-study response assessment. The response will be recorded for each PET-based disease assessment following the flow diagram in Appendix E, Figure 1.



Appendix E, Figure 1: Flowchart for defining metabolic response. Reproduced from Van Heertum et al. *Drug Des Devel Ther*. 2017.

APPENDIX F: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting (http://ctep.cancer.gov/reporting/ctc.html).

APPENDIX G: ELECTROLYTE IMBALANCES AND PREVENTION OF TUMOR LYSIS SYNDROME

Within the first 24 hours after the first dose or dose increase of any investigational agent in this protocol, if any laboratory criteria below are met, the patient should be hospitalized for monitoring and the investigator notified. No additional doses of investigational agents should be administered until resolution. Following resolution, investigational agents may be resumed following the dose modification guidelines in Section 4.2.2 and Section 4.2.3.

A rapidly rising serum potassium level is a medical emergency.

Guidelines for management are as follows:

- Nephrology (or acute dialysis service) must be consulted/contacted on admission (per institutional standards to ensure emergency dialysis is available).
- IV fluids (e.g., D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/h rounded to the nearest 10 mL (target 150 to 200 mL/h; not 50 mL/h). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of TLS (e.g., fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesia, mental status changes, confusion, and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour.
- Vital signs should be taken at time of all blood draws or any intervention.
- The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multi-disciplinary management will be per institutional protocols.

Specific recommendations:

Abnormality	**Management Recommendations**
Hyperkalemia (including rapidly rising potassium)	
Potassium > 0.5 mmol/L increase from prior value (even if potassium within normal limits)	• Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour. If further 0.2 mmol/L increase in potassium, but still upper limit of normal (ULN), manage per potassium ULN. Otherwise recheck in 1 hour. • Resume per protocol testing if change in potassium is 0.2 mmol/L, and potassium ULN, and no other evidence of tumor lysis. • At the discretion of the treating investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the

	discretion of the investigator. Potassium, phosphorus, uric acid, calcium, and creatinine must be rechecked within 24 hours.
Potassium > upper limit of normal	● Perform immediate ECG and commence telemetry. ● Nephrology notification with consideration of initiating dialysis ● Administer Kayexalate 60 g (or Resonium A 60 g). ● Administer furosemide 20 mg IV once ● Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. ● Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour. ● If potassium > ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 1, 2, and 4 hours later, if no other evidence of tumor lysis.
Potassium > 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	● Perform immediate ECG and commence telemetry. ● Nephrology assessment with consideration of initiating dialysis ● Administer Kayexalate 60 g (or Resonium A 60 g). ● Administer furosemide 20 mg IV once. ● Administer insulin 0.1 U/kg IV D25 2 mL/kg IV. ● Administer sodium bicarbonate 1 to 2 mEq/kg IV push. ○ If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. ● Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. ● Recheck potassium, phosphorus, uric acid, calcium, and creatinine every hour.

Hyperuricemia	
Uric acid > 8.0 mg/dL (476 mol/L)	● Consider rasburicase (dose per institutional guidelines). ○ If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. ● Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour.
Uric acid > 10 mg/dL (595 µmol/L) OR Uric acid > 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase > 0.3 mg/dL (0.027 mmol/L) from pre-dose level	● Administer rasburicase (dose per institutional guidelines). ○ If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. ● Consult nephrology. ● Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour. ● If uric acid 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Hypocalcemia	
Corrected calcium > 7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias) in the presence of hypocalcemia	● Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. ● Telemetry. ● Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour. ● If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. ● Calculate corrected calcium and ionized calcium if albumin is low.
Hyperphosphatemia	
Phosphorus > 5.0 mg/dL (1.615 mmol/L) with > 0.5 mg/dL (0.16 mmol/L) increase	● Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate).

	● Nephrology notification (dialysis required for phosphorus 10 mg/dL) ● Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour. ● If phosphorus 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Creatinine	
Increase > 25% from baseline	● Start or increase rate of IV fluids. ● Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 to 2 hours.
IV = intravenous; ULN = upper limit of normal; WNL = within normal limits.	

APPENDIX H: STRONG AND MODERATE CYTOCHROME P (CYP) 3A ENZYME INDUCERS AND INHIBITORS

Source: Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). "https://drug-interactions.medicine.iu.edu" Accessed 6/1/2020.

Strong inhibitors (cause a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance in the substrate drug).

- ribociclib
- telithromycin
- clarithromycin
- indinavir
- itraconazole
- ketoconazole
- nefazodone
- nelfinavir
- ritonavir
- saquinavir
- idelalisib

Moderate inhibitors (cause a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance in the substrate drug)

- netupitant/palonosetron
- verapamil
- voriconazole
- diltiazem
- erythromycin
- fluconazole
- grapefruit juice

Inducers:

- barbiturates
- brigatinib
- carbamazepine
- efavirenz
- enzalutamide
- glucocorticoids
- modafinil
- nevirapine
- oxcarbazepine
- phenobarbital
- phenytoin
- pioglitazone
- rifabutin
- rifampin
- troglitazone

APPENDIX I: TISSUE INVENTORY SHEET

Name of Site: _____

Date of Shipment: _____

Site Contact Name: _____

Phone #:_____

Email: _____

Please ensure a de-identified copy of the corresponding pathology report is included with the shipment.

Subject ID # _____ **Subject Initials** _____

Sample type	Number of slides or blocks included in shipment	Date of biopsy	Biopsy site
[ ] Stained slides **[ ] Unstained slides** **[ ] Block**			

If tissue blocks were submitted, please provide address the tissue block should be returned to as well any other instructions that should be followed:
Address:

_____
_____
_____
_____
_____

Instructions:

_____
_____
_____
_____
_____

APPENDIX J: BLOOD INVENTORY SHEET

Name of Site: _____

Date of Shipment: _____

Site Contact Name: _____

Phone #:_____

Email: _____

Subject ID #	**# of Aliquots included in shipment & identifier**	**Visit**	**Date/Time of Collection**	**Date/Time of Processing**
		[ ] Screening [ ] Cycle 4 Day 1 [ ] Cycle 6 Day 1 [ ] End of Treatment [ ] 18 months [ ] 30 months	Date: _____ Time: _____am/pm	Date: _____ Time: _____am/pm