TITLE Obinutuzumab, Ibrutinib, and Venetoclax for Relapsed and Previously Untreated Chronic Lymphocytic Leukemia (CLL)

SPONSOR Ohio State University

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AGENTS

Agent	Supply
Obinutuzumab	Genentech
Venetoclax	Genentech
Ibrutinib	Commercial

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PROTOCOL SYNOPSIS

This phase Ib/II study will evaluate the combination of obinutuzumab, ibrutinib, and venetoclax for the treatment of chronic lymphocytic leukemia (CLL) with the goal to establish a safe dosing regimen for the combination in relapsed and previously untreated CLL and to acquire pilot data characterizing the effectiveness of the combination in increasing the depth of response as reflected in the rate of minimal residual disease (MRD) negative complete response (CR).

Venetoclax dose will be escalated in a phase Ib trial enrolling relapsed and refractory CLL patients before proceeding to a phase II trial of the combination enrolling 2 separate cohorts: relapsed and/or refractory CLL (Cohort 1) and previously untreated CLL (Cohort 2). An additional cohort of previously untreated CLL patients (Cohort 3), to gather further toxicity and efficacy data as well as study the kinetics and biology of response.

Treatment Plan

	Cycle 1	Cycle 2	Cycle 3	Cycles 4-8	Cycles 9-14
Obinutuzumab	X	X	X	X	
Ibrutinib		X	X	X	X
Venetoclax			Intra-patient dose ramp-up to cohort dose (**Section 5.4**)	X	X

Cycle length = 28 days (except Cycle 3, which varies during Phase 1b)
Planned duration of therapy = 14 cycles

Obinutuzumab: Cycle 1: 100 mg IV D1, 900 mg IV D2, 1000 mg IV D8, D15
Cycle 2-8: 1000 mg IV D1
Maximum treatment duration = 8 cycles (6 cycles in combination)

Ibrutinib: 420 mg daily continuous
Maximum treatment duration = 13 cycles (Cycles 2-14)
(May be continued past C14 at the discretion of the treating investigator except in Cohort 3)

Venetoclax: Cohort dose- escalation to establish MTD/phase 2 dose
Maximum treatment duration = 12 cycles (Cycles 3-14)
(See **Section 5.4**, **Table 3** below)

PROTOCOL SYNOPSIS (continued)

Phase Ib study
N = 12-18
Indication = relapsed/refractory CLL
The phase Ib study will first assess the safety and tolerability of the combination using a traditional 3 + 3 phase I dose escalation design until the MTD or highest dose is established.

Phase II study
N = 75 in 3 cohorts
Cohort 1 indication = relapsed/refractory CLL (N = 25)
Cohort 2 indication = previously untreated CLL (N = 25)
Cohort 3 indication = previously untreated CLL (N = 25)

Primary Objectives
- To identify the dose of venetoclax that can be safely administered in combination with obinutuzumab and ibrutinib for the treatment of relapsed/refractory or previously untreated CLL
- Feasibility and safety of the combination in relapsed/refractory and previously untreated CLL patients
- MRD-negative CR at 8 weeks after completion of treatment

Study Assessments
- Disease response (modified IWCLL 2008 criteria) is assessed at the conclusion of obinutuzumab combination therapy (after Cycle 8) and again 8 weeks (±7 days) after the end of treatment (after Cycle 14).
- Clinical, laboratory, and CT assessments are obtained from all patients.
- Bone marrow biopsies are obtained to confirm CR meeting other criteria (modified IWCLL 2008).
- MRD will be assessed by 4-color flow cytometry (peripheral blood and marrow) at the time of both response assessments (post-Cycle 8, after Cycle 14).
- Pharmacodynamic endpoints on all patients are included.
- Quality of life metrics are assessed for all patients except for Cohort 3.

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1 OBJECTIVES

1.1 Primary Objectives

1. To identify the dose of venetoclax that can be safely administered in combination with obinutuzumab and ibrutinib for the treatment of relapsed/refractory or previously untreated CLL

2. To evaluate the feasibility, safety, and tolerability of venetoclax in combination with obinutuzumab and ibrutinib in patients with relapsed/refractory or previously untreated CLL

3. To determine the MRD-negative complete response (CR) rate after 12 cycles of treatment with venetoclax in combination with obinutuzumab and ibrutinib in patients with relapsed/refractory or previously untreated CLL

1.2 Secondary Objectives

1. To determine the overall response rate (ORR) and complete response rate (CR) of venetoclax in combination with obinutuzumab and ibrutinib in patients with relapsed/refractory or previously untreated patients with CLL

2. To estimate progression free survival (PFS) after treatment with venetoclax in combination with obinutuzumab and ibrutinib in patients with relapsed/refractory or previously untreated patients with CLL

3. To conduct pharmacokinetic and pharmacodynamic studies of venetoclax in combination with obinutuzumab and ibrutinib in patients with relapsed/refractory or previously untreated patients with CLL

4. To examine pre-treatment and serial biomarkers associated with response and mechanisms of resistance to venetoclax ,obinutuzumab and ibrutinib when given in combination for relapsed/refractory or previously untreated patients with CLL

5. To examine the natural history of patients enrolled on this trial relative to evidence of SARS-CoV-2 infection, COVID-19 syndrome, outcome from this, and ability to clear SARS-CoV-2 without convalescent plasma.

2 BACKGROUND

2.1 Chronic Lymphocytic Leukemia

CLL is the most common adult leukemia diagnosed in the Western hemisphere.

Malignant lymphocytes are characterized by a decreased susceptibility to apoptosis and although many patients respond to initial therapy, their disease becomes resistant to treatment over time.[1, 2] Patients with early stage disease have a greater than 10 year life expectancy. However, patients with more advanced disease have a median survival of only 18 months to 3 years. The development of chemoimmunotherapy regimens combining cytotoxic agents such as alkylating agents and purine nucleoside analogs with monoclonal antibodies such as rituximab has attained overall response (OR) rates of over 90% and complete response (CR) rates of over 70% in patients with previously untreated chronic lymphocytic leukemia (CLL), with similar improvement in progression free survival (PFS).[2] Notwithstanding the therapeutic advance represented by chemoimmunotherapy combinations, these treatments are not curative. Patients invariably relapse and become more refractory to treatment over time.[2, 3]

Patients with fludarabine-refractory disease, defined as any response less than a partial remission to a fludarabine-based regimen or a remission lasting <6 months on discontinuation of treatment with a fludarabine-based regimen, have a median survival of less than one year. [4] Additionally, several other prognostic factors have been identified that predict poor response to therapy as measured by response duration and shortened survival, including cytogenetic abnormalities resulting in del(17p13.1) and del(11q22.3); unmutated immunoglobulin heavy chain variable region gene (IgV_H) status; expression of ZAP-70; and expression of the cell-surface marker CD38.[5-8] Patients with del(17p13.1) treated with fludarabine, fludarabine and rituximab, or fludarabine plus cyclophosphamide, or fludarabine, cyclophosphamide, and rituximab have a shorter duration of progression-free survival and overall survival.[5] Patients with unmutated IgV_H status have been shown to be more apt to be $CD38^+$, and both sets of these patients have lower response rates to chemotherapy, including fludarabine, and lower survival rates than those patients who have mutated IgV_H status and are $CD38^-$negative.[6] Therefore, investigational agents which act through novel mechanisms and target patients with poor prognostic features are needed in this disease.

Allogeneic stem cell transplant is the only treatment option for CLL patients that is potentially curative; however, the procedure is only appropriate for a small number of younger patients and is associated with high morbidity and mortality. Thus, in almost all cases, CLL remains an incurable disease.[9] A principal complication of CLL is immunodeficiency related to myelosuppression; as a result, infection is the major cause of death in patients with CLL.[10] Many extant therapies often exacerbate disease-related immunodeficiencies, limiting their applicability in many populations. For instance, treatment options are limited in the largely elderly CLL patient population, with its characteristic limited bone-marrow reserve and decreased organ function. Therefore, there is a need for the development of novel approaches to treatment to improve response rate and survival of patients with CLL.

2.2 Venetoclax (GDC-0199, ABT-199)

Venetoclax (GDC-0199, ABT-199) is a novel, orally available small molecule Bcl-2 family protein inhibitor that binds with > 500-fold higher affinity (Ki < 0.010 nM) to Bcl-2 and with lower affinity to other Bcl-2 family proteins Bcl-X_L (Ki - 48 nM) and Bcl-w (Ki - 245 nM). Overexpression of anti-apoptotic Bcl-2 family proteins is associated with increased resistance to chemotherapy, and antagonism of the action of these proteins might enhance response to such therapy and overcome resistance. Anti-apoptotic Bcl-2 family members are associated with tumor initiation, disease progression, and drug resistance, making them compelling targets for antitumor therapy.

2.2.1 Venetoclax Pre-Clinical Pharmacokinetic Data

The pharmacokinetic profile of venetoclax was evaluated in multiple animal species. In mouse, rat, monkey and dog, the venetoclax pharmacokinetic profile was characterized by low plasma clearance and low volumes of distribution. Half-lives ranged from 2.2 hours in monkey to 12 hours in dog. Food had a marked effect on the oral bioavailability in dog.

Venetoclax has high protein binding to human, rat, dog, and monkey plasma proteins (> 99.9%). In rats, venetoclax was widely distributed into liver, kidneys, spleen, heart, lungs, small intestine, and white fat, but was poorly distributed in testes, brain, muscle, and bone. Metabolism was the major route of elimination with biliary excretion of the parent drug playing the secondary role in rats. Venetoclax showed moderate metabolic stability in *in vitro* hepatic systems across species tested, except for low to moderate stability in dog hepatocytes.

In vivo, venetoclax was metabolized by CYP3A4; it was a moderate inhibitor of CYP2C8 and a potent inhibitor of CYP2C9; it was not a potent inhibitor of CYP3A4, CYP1A2, CYP2B6, CYP2C19, or CYP2D6 (IC_{50} > 30 µM); it did not induce CYP3A4 or CYP1A2 at concentrations up to 10 µM.

2.2.2 Pre-Clinical Toxicology

The nonclinical toxicology of venetoclax has been evaluated in repeated-dose studies in mice and dogs with up to 4 weeks of once daily oral dosing (and with 4-week recovery periods) and in dogs with 2 weeks of dosing (18-week recovery period); safety pharmacology studies (cardiovascular, neurofunctional, and pulmonary); and in genetic toxicity tests (Ames and in vitro chromosome aberrations assays). The primary toxicities associated with venetoclax administration included effects on the hematologic system (lymphocytes and red blood cell parameters) in mice and dogs and on the male dog reproductive system. There was no evidence of genotoxicity of venetoclax. A severely

toxic dose (STD10) was not identified in mice up to and including the top dose of 600 mg/kg/day (overall mean AUC_{0-24} = 91.5 µg●hr/mL and C_{max} = 7.2 µg/mL). In dogs, the highest non-severely toxic dose (HNSTD) was 150 mg/kg/day, but due to overlapping exposures between the mid and high doses, the HNSTD was defined as the mid dose of 50 mg/kg/day (overall mean AUC_{0-24} = 472 µg●hr/mL and C_{max} = 27.4 µg/mL).

Venetoclax causes decreases in circulating lymphocytes and lymphocytes in lymphoid tissue. After 4 weeks of dosing, the lymphocyte effects were reversible or partially reversible in the mouse but generally were less reversible in the dog at the end of a 4-week recovery period. However, in a 2-week dog study focused on lymphocyte recovery over an extended (18-week) period, reversibility of lymphocyte effects were demonstrated. Immunophenotyping was used to assess changes in peripheral blood lymphocyte subsets (i.e., mature T cells, helper T cells, cytotoxic T cells, and mature B cells). At the end of the 18-week recovery period, both total and lymphocyte subset counts returned to within range of baseline and control values, and all effects on lymphoid tissue reversed. The venetoclax–related decreases in lymphocytes in blood and lymphoid tissues are considered pharmacologically mediated and non-adverse.[11]

Additional hematological effects of venetoclax treatment included reversible decreases in red blood cell parameters (primarily, hematocrit and hemoglobin concentration) in mice and dogs. The decreases in red cell parameters were adverse only at the high dose levels in the 4-week studies (i.e., at 600 mg/kg/day in mice and at 150 mg/kg/day in dogs, but all red cell parameters were reversible at the end of a 4-week recovery period. Effects on both lymphocytes and red cell mass are readily monitored in subjects.

Male dog reproductive effects consisted of markedly reduced numbers of spermatogonia in the testes at all venetoclax dose levels after 4 weeks of dosing, with progression to severe decreases in the numbers of all germ cells in testes during the 4-week recovery period. Male mice did not have testicular changes associated with venetoclax administration. The translatability of the testicular findings in dogs to humans is unknown, but this change may be related to venetoclax pharmacology, as one or more members of the Bcl-2 family of proteins play a role in spermatogenesis.[12-14] In view of the potential treatment benefits of venetoclax, this finding is anticipated not to impact the treatment of subjects with advanced hematologic malignancies.

Dogs at the high dose of 150 mg/kg/day in the 4-week study had clinical signs of itching and swelling of the skin on the ears, head (cranial area), and forepaws and/or hindpaws. Most of the animals (8 of 10 dogs) were affected. The clinical signs were mild to moderate in severity, transient and sporadic in occurrence, and were absent during the recovery period. The swelling reactions were observed after the first dose in 3 dogs, and therefore not consistent with drug-induced immediate (IgE-mediated, Type I) hypersensitivity; however, other immune-mediated mechanisms could be involved.

Although the basis for the swelling reactions was not established, there were no signs of anaphylaxis. Any occurrences of swelling reactions in patients can be monitored and treated.

In an ongoing 9-month chronic toxicity study of dogs with venetoclax, hypopigmented (white) facial hair was observed after approximately 3 months of dosing [ongoing study Abbott R&D/12/384]. The finding was limited to the mid and high doses (6 and 20 mg/kg/day), and was observed in both males and females. Evidence from Bcl-2 knockout mouse (bcl-$2^{-/-}$) studies indicates that hair hypopigmentation is consistent with the pharmacological effect of Bcl-2 functional loss, and occurs due to loss of hair follicle melanocytes dependent on Bcl-2 for survival.[15] A dedicated physical examination of the skin and extensive ophthalmic examinations determined that pigmentation of the skin and in the eye (particularly in the iris and fundus) appear unaffected. The potential for development of white (hypopigmented) hair in humans is unknown.

In an anesthetized dog cardiovascular model given intravenous doses of venetoclax, mild reductions in myocardial contractility (maximum rate of rise of left ventricular pressure [dP/dt_{max}]: –6% to –13%) and cardiac output (–11% to –19%) were observed at plasma concentrations of ≥ 16 µg/mL and ≥ 32 µg/mL, respectively. However, no effects on blood pressure, heart rate, or electrocardiogram (ECG) parameters were observed relative to baseline or controls in either the anesthetized dog study or in the conscious dog cardiovascular study using telemeterized animals at maximum drug concentrations of 46 µg/mL and 16 µg/mL, respectively.

Venetoclax was tested in a battery of safety pharmacology assays and produced no effects in central nervous system/neurobehavioral, or respiratory studies in mice at oral doses up to 600 mg/kg. In dogs, mild reductions in cardiac contractility and cardiac output were observed at plasma concentrations of ≥ 16 µg/mL. However, no effects on blood pressure, heart rate, or electrocardiogram (ECG) parameters were observed in dogs at a maximum drug concentration of 46 µg/mL.

On the basis of nonclinical safety pharmacology and toxicology evaluations of venetoclax, and on the basis of nonclinical and human studies of related anti-apoptotic Bcl-2 family protein inhibitors, potential mechanism-based toxicities may include lymphopenia and neutropenia,[16] signs of tumor lysis, reduction in red cell mass, decreased spermatogenesis, skin swelling, and hair hypopigmentation. Thrombocytopenia has not been observed in toxicology studies in mice and dogs. These findings are consistent with venetoclax as a Bcl-2 specific (Bcl-X_L sparing) inhibitor. Consequently, thrombocytopenia is not expected to be a dose limiting toxicity (DLT) clinically.

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology can be found in the Investigator's Brochure.

2.2.3 Pre-Clinical Efficacy

In vitro, venetoclax demonstrated broad cell killing activity against a panel of lymphoma and leukemia cells including B-cell follicular lymphomas (FLs), mantle cell lymphomas (MCLs), diffuse large B-cell lymphomas (DLBCLs), and acute myeloid leukemias (AMLs). Venetoclax was especially potent against cell lines expressing high levels of Bcl-2. Leukemia and lymphoma cell lines bearing the t(14;18) translocation were significantly more sensitive to venetoclax than non-mutated cell lines.

Venetoclax exhibited potent activity against patient-derived CLL cells treated *ex vivo*, killing these cells with an average concentration required for 50% effect (EC_{50}) of 0.006 µM (n = 35; note that not all subject samples are from venetoclax trials). Venetoclax was equally potent against the subset of CLL samples bearing the high-risk 17p deletion, with an average EC_{50} of 0.008 µM (n = 5), indicating that venetoclax may have a significant utility in treating subjects with this high-risk disease.

2.2.4 Venetoclax Clinical Data

As of 3 February 2014, 267 patients have received venetoclax either as monotherapy or in combination with other agents across different trials for multiple oncology indications. Five ongoing studies have enrolled 160 patients with relapsed/refractory CLL/small lymphocytic lymphoma (SLL) (95 patients in M12-175, 38 patients in M13 365, 17 patients in M13-982, 8 patients in GP28331, and 2 patients in GO28440). The first in-human venetoclax monotherapy dose-escalation study (Study M12-175) is ongoing in patients with relapsed or refractory CLL/SLL and NHL. Study M13-365 (venetoclax in combination with rituximab in relapsed/refractory CLL), Study M13-982 (venetoclax monotherapy in relapsed/refractory CLL harboring 17p deletion), and Study GP28331 (venetoclax in combination with obinutuzumab), and Study GO28440 (venetoclax in combination with bendamustine plus rituximab) are also ongoing.

Preliminary safety, PK, and efficacy data are summarized below on the basis of on data cutoff dates of February 20143 for safety listings (see the venetoclax Investigator's Brochure for details on clinical studies). Dose-limiting toxicity (DLT) assessments are available for patients enrolled in Study M12-175 (through Cohort 8 with a target venetoclax dose of 1200 mg) and in Study M13-365 (through Cohort 35 with a target venetoclax dose of 400600 mg).

Study M13-982 includes relapsed or refractory CLL patients harboring the 17p deletion. The primary objective of this study is to evaluate the efficacy of venetoclax

monotherapy in patients with relapsed or refractory CLL harboring the 17p13 (TP53 locus) deletion (17p deletion). Efficacy will be measured by ORR. The secondary objectives are to evaluate the CR, PR, duration of response, PFS, TTP, OS and percent of patients who move on to stem cell transplant. Patients will receive venetoclax orally QD continuously. To mitigate the risk for TLS, a lead-in period (up to 5 weeks) is employed to evaluate a step-wise dose escalation. Patients start with 20 mg of venetoclax on Week 1 Day 1 and, if no significant findings occur, receive 50 mg venetoclax QD for the remainder of Week 1. After 1 week at 50 mg, the dose is increased weekly first to 100 mg, then 200 mg, then 400 mg (or additional lead-in steps to designated 400-mg dose), as tolerated. A lower starting dose and/or modification to the lead-in regimen may be implemented for individuals at particularly high risk for TLS.

Study GP28331 is an open-label, dose-finding and safety study of venetoclax in combination with obinutuzumab in relapsed/refractory and previously untreated CLL patients. Venetoclax is administered in escalating doses over 2 to 5 weeks with target doses of venetoclax ranging from 100 mg/day to 600 mg/day. Patients receive 6 cycles of obinutuzumab (28-day cycles). Obinutuzumab infusions occur on Days 1, 2, 8 and 15 of Cycle 1 and on Day 1 of Cycles 2 to 6. Following completion of 6 cycles of combination therapy, patients will continue on venetoclax as a single agent at the target venetoclax dose to which they were assigned until disease progression or end of study (whichever occurs first). Following completion of the dose-finding stage in each patient population (relapsed/refractory and previously untreated CLL), a dose and schedule will be selected for use in the expansion stage of the study. The expansion stage for each patient population will have at least 14 patients.

Study GO28440 is an open-label, dose-finding and safety study of venetoclax in combination with BR in relapsed/refractory and previously untreated CLL patients. Venetoclax is administered in escalating doses over 2 to 5 weeks with target doses of venetoclax ranging from 100 mg/day to 600 mg/day. Rituximab is administered IV once every 28-day cycle for up to 6 cycles. The initial dose is 375 mg/^{m2} in Cycle 1, followed by 500 mg/m^2 in Cycles 2 to 6. Bendamustine is administered IV at 70 mg/m^2 for 2 consecutive days of each 28-day cycle for 6 cycles in patients with relapsed/refractory CLL, and at 90 mg/m^2 in previously untreated patients with CLL. Following completion of 6 cycles of combination therapy, patients will continue on venetoclax as a single agent at the target venetoclax dose to which they were assigned until disease progression or end of study (whichever occurs first). Following completion of the dose finding stage in each patient population (relapsed/refractory and previously untreated CLL), a dose and schedule will be selected for use in the expansion stage of the study. The expansion stage for each patient population will have at least 14 patients.

See the venetoclax Investigator's Brochure for more details on these and additional studies.

2.2.4.1 Venetoclax Preliminary Clinical Pharmacokinetics Summary

Preliminary pharmacokinetic data with venetoclax are available from ongoing oncology Studies M12-175, M12-630, M13-365, and M13-367, and GP28331 in subjects with hematologic malignancies.

The venetoclax formulation currently used in clinical studies is a tablet formulation with strengths of 10, 50, and 100 mg. The tablet formulation was orally administered after a low-fat meal. Food increased the bioavailability of venetoclax by 3- to 4-fold. Preliminary pharmacokinetic results indicated that the absorption of venetoclax after the oral dosing was relatively slow. Venetoclax plasma concentrations peaked at approximately 6 hours after dosing. The mean harmonic terminal phase elimination half-life of venetoclax was approximately 17 hours and the mean oral clearance was approximately 13 L/hr after a single dose. Preliminary data did not suggest apparent pharmacokinetics differences among subjects with CLL/small lymphocytic leukemia (SLL), NHL, or multiple myeloma (MM). The combined data from subjects with CLL/SLL and NHL suggested that venetoclax exposure was approximately dose proportional across the 150 to 1200 mg dose levels at steady state. Co-administration of bendamustine and rituximab did not show apparent impact on venetoclax pharmacokinetics. On the basis of limited preliminary data from Cohort 1 of Study GP28331 (venetoclax administered alone and in combination with obinutuzumab), obinutuzumab did not appear to affect venetoclax exposure.

2.2.4.2 Venetoclax Preliminary Safety Data Summary

This section summarizes safety events observed in patients with relapsed/refractory CLL/SLL enrolled in Studies M12-175, M13-365, M13-982, GP28331, and GO28440.

Study M12-175
Preliminary safety data as of February 2014 for 95 patients with CLL/SLL enrolled in Study M12-175 study are summarized below. The data include patients treated at dose-escalation cohorts with target doses from 50 to 1200 mg of venetoclax.
The most common adverse events, occurring in≥10% of patients, were diarrhea (38.9%), neutropenia (37.9%), nausea (34.7%), upper respiratory tract infection (30.5%), fatigue (27.4%), and cough (20%). The most common Grade 3/4 and above adverse events were neutropenia (4.7%) and anemia (10.5%). The most frequently reported (≥10%) adverse events considered possibly or probably related to venetoclax include neutropenia (34.7%), nausea (22.1%), diarrhea (24.2%), and fatigue (5.8%),
Serious adverse events were reported in 36 patients (37.9%). Those reported in more than one2 patients were febrile neutropenia (5.3%), autoimmune thrombocytopenia (3.2%), and TLS (3.2%). One serious adverse event resulted in death: a patient with an ongoing event of TLS experienced sudden death

A total of 6 patients (6.3%) experienced adverse events that led to death: malignant neoplasm progression (2), multi-organ failure (1), sudden death (1), small intestinal obstruction (1), and mental status changes (1).

A total of 611 patients (11.6%) experienced adverse events that led to study discontinuation. These adverse events included: thrombocytopenia, general physical health deterioration, sudden death, multi-organ failure, mental status change, esophageal adenocarcinoma, and diarrhea.

In addition, Richter's transformation had been noted at the time of disease progression for 14 (14.7%) patients with CLL.

Study M13-982

In study M13-982, 15 out of the 17 patients enrolled (88.2%) reported treatment emergent adverse events. The most common adverse events were nausea (35.3%) and neutropenia and fatigue (23.5% each). Seven (41.2%) patients experienced adverse events Grade 3 or above. The most common adverse events Grade 3 and above were anemia and neutropenia (17.6% each) and thrombocytopenia and lymphocyte count decreased (11.8% each). Seven patients (41.2%) experienced serious adverse events. Serious adverse events of anemia, febrile neutropenia, and abdominal pain upper were considered to have a reasonable possibility of being related to venetoclax. No patients experienced adverse events that resulted in venetoclax discontinuation or death.

Study M13-365

As of February 2014, preliminary safety results are available for 38 patients enrolled in Study M13-365. Six patients were enrolled in Cohort 1 (designated venetoclax cohort dose of 200 mg), 10 patients were enrolled in Cohort 2 (designated venetoclax cohort dose of 300 mg), 7 patients were enrolled in each of Cohorts 3, 4, and 5 (designated venetoclax cohort doses of 400, 500, and 600 mg, respectively). Most patients (94.7%) reported at least one treatment-emergent adverse event. The most common adverse events were neutropenia (50%), nausea (2.1%), diarrhea and headache (28.9% each), cough (26.3%), and thrombocytopenia, fatigue, and pyrexia, and upper respiratory tract infection (23.7% each).

Twenty-seven patients (71.1%) were reported to have Grade ≥ 3 adverse events. The most commonly reported Grade ≥ 3 adverse events occurring in more than 2 patients were neutropenia (50%), thrombocytopenia (18.4%), and anemia (10.5%). Serious adverse events were reported in 14 patients (36.8%). TLS was reported in 2 patients (5.3%), and each of the following events was reported in 1 patient (2.6%) each: febrile neutropenia, histiocytosis hematophagic, lower gastrointestinal hemorrhage, non-cardiac chest pain, pyrexia, bronchitis bacterial, influenza, lung infection, pneumonia hemophilus, rotavirus infection, infusion-related reaction, hyperkalemia, lymphoma transformation, Richter's syndrome, and pulmonary mass. Both events of TLS and

individual events of bronchitis bacterial, pneumonia hemophilus, rotavirus infection, and hyperkalemia were considered to have a reasonable possibility of being related to venetoclax.

As described above, 1 patient experienced a serious adverse event of hyperkalemia in a setting of TLS that resulted in study discontinuation and death. Two additional patients experienced adverse events that resulted in discontinuation of venetoclax (lymphoma transformation, and Richter's syndrome).

Study GP28331

In Study GP28331, 45 of the 8 patients who received venetoclax reported treatment-emergent adverse events. In this study, the most commonly reported adverse events related to venetoclax were diarrhea and IRR (in 3 patients; 37.5%) and hyperphosphatemia, anemia, flatulence, pollakiuria, and fatigue (in 2 patients; 25.0%). Hyperphosphatemia was reported as a serious event in the setting of laboratory TLS that occurred after the third dose of venetoclax in a patient who had not received obinutuzumab. The event resolved with IV hydration and discontinuation of study therapy.

Study GO28440

Two patients have been enrolled in the study and had data available. Study enrollment is continuing. No treatment-emergent adverse events have been reported in the 2 enrolled patients.

See the venetoclax Investigator's Brochure for more details on these studies.

2.2.4.3 Summary of TLS Events in CLL Patients Treated with venetoclax

In Study M12-175, substantial antitumor activity was observed in the first 3 patients with CLL following a single dose of venetoclax of 100-200 mg. Within 24 hours, dramatic reductions in lymphocyte count (> 95%) were observed in the 2 patients with pretreatment lymphocytosis, and laboratory TLS developed in all 3 patients (per Cairo Bishop Criteria [see Cairo et al. 2004]).

Following the two fatal events in December 2012, the dose of venetoclax was reduced in all active patients to 600 mg or less. Overall, six DLTs of TLS and two DLTs of fatalities in the setting of TLS were reported in the venetoclax clinical program (Arm A of Study M12-175 and Study M13-365). Details of these events are provided in the venetoclax Investigator's Brochure. Based on data of 77 CLL/SLL patients treated in the program up to that point, protocol amendments were then implemented in patients with CLL/SLL to include:

- Modified venetoclax dosing regimens (i.e., a reduction in the starting dose to 20 mg, implementation of a more gradual 5-step dose ramp-up of 20, 50, 100, and 200 mg up to the final dose) and with a maximum dose of 600 mg allowed.
- Guidance regarding identification of TLS risk categories:
  TLS low-risk: All measurable lymph nodes with the largest diameter < 5 cm AND < 25 X 10^9/L absolute lymphocyte count (ALC)
  TLS medium-risk: Any measurable lymph node with the largest diameter ≥ 5 cm and <10 cm OR ≥ 25 X 10^9/L ALC
  TLS high-risk: Any measurable lymph node with the largest diameter ≥ 10 cm OR ≥ 25 X 10^9/L ALC AND any measurable lymph node with the largest diameter ≥ 5 cm but < 10 cm
- Enhanced TLS prophylaxis and monitoring measures

Clinical hold was released in May 2013 and all studies globally were able to fully resume as of that time with new TLS measures in place. The safety profile of venetoclax with regard to TLS has now been further characterized in 58 patients with relapsed/refractory CLL/SLL treated with venetoclax and who completed the monotherapy ramp-up period with the above TLS measures in place (data cutoff date 17 January 2014).

There was a marked reduction in severity and frequency of TLS per Cairo-Bishop (Cairo et al. 2004) and Howard definitions (Howard et al. 2011) in the analysis for these 58 patients with CLL/SLL who received venetoclax using the mentioned TLS prophylaxis and monitoring measures as compared with the findings in the 77 patients with CLL/SLL in the previous analysis.

None of the 58 patients experienced any serious (including fatal) or non-serious event of clinical TLS (CTLS) or laboratory TLS (LTLS) or had study treatment discontinued because of TLS. Eight patients (13.8%) were determined to have LTLS (per Cairo Bishop definition) after medical adjudication: none in 13 low-risk patients, 5 in 19 medium risk patients (26.3%), and 3 in 26 high-risk patients (11.5%). Three of the 8 patients had a non-serious Grade 1 adverse event related to an electrolyte change; no adverse event was reported in the other 5 patients. One additional high-risk patient had a serious adverse Grade 2 event of cytokine release syndrome considered to be in the TLS setting with no electrolyte changes. These findings differ from those in the previous analysis (N = 77) where 3 high-risk patients (3.9%) experienced CTLS and 16 patients (20.8%) experienced LTLS (6 in 27 medium-risk patients [22.2%] and 10 in 25 high-risk patients [40.0%]). When using the Howard definition for TLS (Howard et al. 2011), which requires both electrolyte changes to be outside the Cairo Bishop thresholds, none of the 58 patients experienced CTLS or LTLS, whereas 3 (3.9%) and 7 (9.1%) patients experienced CTLS and LTLS, respectively, among the 77 patients with CLL/SLL in the previous analysis.

Moreover, consistent with the previous analysis, the risk of TLS with venetoclax in patients with CLL/SLL is characterized as highest when initiating venetoclax dosing and with a higher initial dose of venetoclax as well as higher in patients with a large tumor burden. In addition, there were no adverse events of TLS identified in the period after completion of the ramp-up when patients received venetoclax monotherapy at the target dose or were dosed with combination agents in all ongoing clinical studies evaluating venetoclax in patients with CLL/SLL. On the basis of the recent analysis, further modifications to the TLS prophylaxis measures for patients with CLL are done in this protocol.

More details of TLS events associated with venetoclax are provided in the venetoclax Investigator's Brochure.

2.2.4.4 Preliminary Efficacy Data for venetoclax in CLL/SLL

Study M12-175

Preliminary efficacy data for the patients in the CLL/SLL arm of Study M12-175 are available as of 17 January 2014. A total of 93 patients were enrolled, with a median time on study of 6.1 months (range: 0-27 months). Twenty-three patients (24%) had CLL with 17p13 (TP53 locus) deletion (17p deletion), 55 subjects (59%) had fludarabine refractory CLL, and 32 of the 42 patients with available status had unmutated IGHV. The median number of prior therapies was 4 (range: 1-11).

Seventy patients were evaluable for overall response based on the 2008 updated International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria. The ORR (complete response [CR]/CR with incomplete bone marrow recovery [Cri] PR) was 76% (53 of 70 evaluable patients), with CR/CRi in 14 patients (20%) and PR in 39 patients (56%). This included 17 of 23 patients with unmutated IGHV (74% ORR, with 4 CR/CRi), 15 of 21 patients with 17p deletion (71% ORR, with 3 CR/CRi), and 29 of 39 patients with fludarabine-refractory CLL (74% ORR, 6 CR/CRi).

The median duration of response (DOR) was 20.5 months [95% CI; 13.8,] for the 53 responding patients. At 12 months, 91% of patients with CR and 67% of patients with PR remained progression-free. Of the 14 subjects with CR/CRi, 9 were evaluated in local labs by flow cytometry for MRD; 5 were MRD negative and of these, 2 were IGHV unmutated, 4 were fludarabine-refractory, and 1 had 17p deletion.

Study M13-365

Preliminary efficacy data for Study M13-365 are available as of 17 January 2014. A total of 37 patients were enrolled, with a median time on study of 4.8 months (range: 0 to 15.2 months). Nine patients (24%) had 17p deletion, 9 patients (24%) had fludarabine-refractory CLL, and 9 (24%) had rituximab-refractory CLL. The median number of prior therapies was 2 (range: 1 to 5). A total of 18 patients who completed

combination therapy or discontinued prior to completion were evaluable for ORR. The ORR (CR/CRi + PR) was 78% (14 of 18 patients), with 7 (39%) patients achieving CR/CRi and 7 (39%) achieving PR. MRD was evaluated by local laboratory in 6 of 7 subjects with CR; 4 patients were MRD negative in the bone marrow. Of the 19 patients yet to complete combination therapy, 4 had confirmed PR, 9 have unconfirmed PR, and 6 were not yet evaluable for response.

2.3 Obinutuzumab (GA-101, Gazyva™)

2.3.1 Obinutuzumab Mechanism of Action

Obinutuzumab (GA-101, Gazyva™, formerly designated RO5072759) is a humanized and glycoengineered monoclonal antibody, derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering leading to the following characteristics):[17]

- High-affinity binding to CD20
- Type II binding to the CD20 epitope, leading to low complement-dependent cytotoxicity (CDC) related to the recognition of the CD20 epitope and the lack of CD20 localization into lipid rafts after binding of the monoclonal antibody to CD20
- Compared with the chimeric Type I anti-CD20 antibody rituximab, increased antibody–dependent cell–mediated cytotoxicity (ADCC) related to an improved binding of obinutuzumab to the different allotypes of FcγRIIIa expressed by natural killer (NK) cells
- Compared with rituximab, increased direct cell death induction related to an elbow hinge amino exchange of the Fab region and Type II binding of the CD20 epitope

Given the significantly greater ADCC and direct cell-death induction, it is possible that obinutuzumab may have greater efficacy than rituximab, particularly in the 80–85% of patients who are carriers of the FcγRIIIa low-affinity receptor polymorphism (FF/FV genotype), as such patients may have decreased overall survival (OS) compared with patients with the high-affinity (V/V) polymorphism who demonstrate improved survival following therapy with chemotherapy plus either rituximab or I^{131} tositumomab(.[18]

2.3.2 Obinutuzumab Nonclinical Toxicology

The nonclinical toxicology of obinutuzumab has been evaluated in repeat-dose studies in cynomolgus monkeys given weekly IV (30-minute infusion) up to 26 weeks in duration, and weekly SC injections for 4 weeks in duration. The high dose of 50 mg/kg in the 26-week study resulted in a steady-state AUC_{0-24hr} ($AUC_{0-24hrss}$) exposure of

341,000 μg • h/mL that is approximately 61-fold above that of the clinical exposure of 5584 μg • h/mL.

Consistent with expected pharmacological activity, obinutuzumab caused marked decreases in B cells with corresponding lymphoid depletion in spleen and lymph nodes. Circulating CD40 + mature B cells began to reverse after several months without treatment, and maximally reversed to 7%−152% of baseline by 37 weeks. In addition, transient decreases in NK cells were observed; this finding is consistent with the pharmacological effect of FcγRIIIa binding. Suspected opportunistic infections in as many as three unscheduled deaths were considered a possible secondary result of B-cell depletion.

Obinutuzumab was immunogenic in the cynomolgus monkey, which led to reduced systemic exposures in several animals and abrogation of the pharmacological activity. Hypersensitivity reactions were noted that included systemic inflammation and infiltrates consistent with immune-complex mediated hypersensitivity reactions such as arteritis/periarteritis, glomerulonephritis, and serosal/adventitial inflammation, and led to unscheduled termination in 6 animals.

Both the clinical intravenous (IV) formulation of obinutuzumab and the SC formulation were locally well tolerated across studies. No effects were present in male and female reproductive parameters included in the 26-week IV dose study. No obinutuzumab-related effects were observed on central nervous system, respiratory, or cardiovascular function.

In vitro assays using undiluted human whole blood measured significant increases in cytokine secretion caused by obinutuzumab, indicating that obinutuzumab has an increased propensity to trigger first infusion-related cytokine release in patients.

See the obinutuzumab Investigator's Brochure for details on the nonclinical studies.

2.3.3 Obinutuzumab Nonclinical Efficacy

Obinutuzumab has demonstrated in vivo efficacy superior to rituximab in various human lymphoma xenograft models. Both antibodies were tested in human SUDHL-4 cells (DLBCL model) subcutaneously injected in severe combined immunodeficient (SCID) beige mice. Rituximab administration was started when tumors were established and rapidly growing. Results showed that rituximab at 10 mg/kg inhibited tumor growth compared with rituximab at 1 mg/kg; however, increasing the rituximab dose to 30 mg/kg did not result in increased efficacy. In contrast, obinutuzumab showed a dose-dependent increase in efficacy in the range of 1 to 30 mg/kg. Results showed

complete tumor regression in all animals and lasting tumor eradication in 9 of 10 animals at the highest dose of 30 mg/kg and in 1 of 10 animals at a dose of 10 mg/kg.

Additional studies have also shown similar results, with obinutuzumab treatment controlling tumor growth, whereas vehicle- and rituximab-treated tumors were not controlled.[17]

See the obinutuzumab Investigator's Brochure for details on the nonclinical studies.

2.3.4 Overall Obinutuzumab Clinical Experience

See the most recent version of the obinutuzumab Investigator's Brochure for details of the clinical studies

2.3.4.1 Clinical Efficacy

In the monotherapy setting, no complete responses were observed among 38 patients with relapsed CLL. However, in study BO20999, 62% of patients in phase I and 15% of patients in phase II had a partial response at the end of treatment.

In the chemotherapy combination study BO21004/CLL11 (Stage 1a: obinutuzumab (G) + chlorambucil (Clb) vs Clb), 60%of patients in the Clb arm and 22% of patients in the GClb arm experienced a progression-free survival (PFS) event (death or disease progression). The addition of obinutuzumab to the Clb regimen significantly prolonged PFS when compared to Clb alone ($p < 0.0001$, log-rank test). The risk of having a PFS event (progression or death, whichever occurred first) as assessed by the investigator was statistically significantly decreased for patients treated with GClb (stratified HR 0.14, 95% CI [0.09;0.21]). The Kaplan − Meier estimated median PFS was 10.9 months in the Clb arm and 23.0 months in the GClb arm.

In Stage 2 (GClb vs Rituximab (R) + Clb), PFS as assessed by the investigator showed clinically meaningful and statistically significant benefit of GClb over RClb (HR 0.39, 95% CI [0.31;0.49], $p < 0.0001$, log-rank test).

2.3.4.2 Clinical Safety

As of the safety data cut-off date of July 02, 2013, obinutuzumab has been administered to 1979 patients with CLL or NHL in clinical trials, from doses of 50 mg to 2000 mg in monotherapy or in combination with chemotherapy. Overall, the safety of obinutuzumab as single agent or as combination therapy with chemotherapy was manageable.

The most frequent causes of death were disease progression and AEs describing

infectious diseases. This is consistent with the study population and disease being treated. The incidence of fatal events was similar across all ongoing trials. Of particular interest, the incidence of infusion-related reactions (IRRs) was observed consistently in all obinutuzumab trials; the highest incidence of IRRs was at the first infusion with the incidence decreasing rapidly with subsequent infusions. The incidence and severity of IRRs appeared to be higher in CLL than in NHL patients in the monotherapy trials.

One immunosuppressed and heavily pre-treated patient with DLBCL transformation of a FL experienced fatal progressive multifocal leukoencephalopathy (PML) approximately 2 years after the last dose of 1000 mg obinutuzumab. The investigator assessed the event of PML as related to obinutuzumab.

In the Stage 2 analysis of study BO21004/CLL11 (GClb vs RClb), a higher incidence of thrombocytopenia (all grades) was observed during the first cycle in patients with CLL treated with GClb, compared to patients treated with RClb. In addition, the occurrence of all grade hemorrhagic events was balanced between the treatment arms; however, the four fatal hemorrhagic events in the GClb arm occurred during the first cycle of treatment whereas the three fatal hemorrhagic events in the RClb arm occurred more than a year after treatment initiation. When thrombocytopenia was evaluated by cycle (Cycle 1 vs Cycle 2 onwards), it was noted that the incidence of all grade thrombocytopenia (11% GClb vs 3% RClb) and Grade 3/4 thrombocytopenia (8% GClb vs 2% RClb) was higher in the GClb arm than in the RClb arm during the first cycle. There were no Grade 5 events of thrombocytopenia in this study. Beyond Cycle 1, the incidence of all grade thrombocytopenia (7% GClb vs 5% RClb) and Grade 3/4 thrombocytopenia (4% GClb vs 2% RClb) were similar between the treatment arms.

2.3.5 Obinutuzumab Pharmacokinetics and Pharmacodynamics

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

number of obinutuzumab administrations during the first cycle of treatment may be expected to reduce the number of CD20-positive tumor cells, thus minimizing the impact of the time varying clearance pathway on obinutuzumab exposure.

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

2.4 Ibrutinib (PCI-32765, Imbruvica™)

Ibrutinib (PCI-32765, Imbruvica™) is a first-in-class, orally-administered, covalently-binding small molecule inhibitor of Bruton's tyrosine kinase (BTK) currently under development for the treatment of B-cell malignancies. Ibrutinib is approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with CLL/SLL and mantle cell lymphoma (MCL) who have received at least one prior therapy and currently under investigation in various Phase 3 studies, including MCL and CLL/SLL and other B cell malignancies.

Ibrutinib is a small-molecule inhibitor of BTK. Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro. In patients with recurrent B-cell lymphoma > 90% occupancy of the BTK active site in peripheral blood mononuclear cells was observed up to 24 hours after ibrutinib doses of ≥ 2.5 mg/kg/day (≥ 175 mg/day for average weight of 70 kg).

2.4.1 Clinical Pharmacokinetics

Ibrutinib is absorbed after oral administration with a median T_{max} of 1 to 2 hours. Ibrutinib exposure increases with doses up to 840 mg. The steady-state AUC observed in patients at 560 mg is (mean ± standard deviation) 953 ± 705 ng·h/mL. Administration with food increases ibrutinib exposure approximately 2-fold compared with administration after overnight fasting. Reversible binding of ibrutinib to human plasma protein in vitro was 97.3% with no concentration dependence in the range of 50 to 1000 ng/mL. The apparent volume of distribution at steady state ($V_{d,ss}$ /F) is approximately 10000 L.

Metabolism is the main route of elimination for ibrutinib. It is metabolized to several metabolites primarily by cytochrome P450, CYP3A, and to a minor extent by CYP2D6. The active metabolite, PCI-45227, is a dihydrodiol metabolite with inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. The range of the mean metabolite to parent ratio for PCI-45227 at steady-state is 1 to 2.8. Apparent clearance (CL/F) is approximately 1000 L/h. The half-life of ibrutinib is 4 to 6 hours. Ibrutinib, mainly in the form of metabolites, is eliminated primarily via feces. After a single oral administration of radiolabeled [^{14} C]-ibrutinib in healthy subjects, approximately 90% of radioactivity was excreted within 168 hours, with the majority (80%) excreted in the feces and less than 10% accounted for in urine. Unchanged ibrutinib accounted for approximately 1% of the radiolabeled excretion product in feces and none in urine, with the remainder of the dose being metabolites.

Ibrutinib is not significantly cleared renally; urinary excretion of metabolites is < 10% of the dose. Creatinine clearance > 25 mL/min had no influence on the exposure to ibrutinib. There are no data in patients with severe renal impairment (CLcr < 25 mL/min) or in patients on dialysis. Ibrutinib is metabolized in the liver. No clinical trials have been completed in subjects with impaired hepatic function. Preliminary PK data from an ongoing trial in subjects with hepatic impairment indicate that ibrutinib exposure is approximately 6-fold higher in subjects (N=3) with moderate hepatic impairment (Child-Pugh B) compared with mean exposures observed in healthy volunteer trials.

In a sequential design trial of 18 healthy volunteers, a single dose of 120 mg of ibrutinib was administered alone on Day 1 and a single dose of 40 mg of ibrutinib administered on Day 7 in combination with 400 mg of ketoconazole (given daily on Days 4 – 9). Ketoconazole increased ibrutinib dose-normalized C_{max} and AUC 29-fold and 24-fold, respectively. Simulations using physiologically-based pharmacokinetic (PBPK) models suggested that moderate CYP3A inhibitors (diltiazem and erythromycin) may increase the AUC of ibrutinib 6 to 9-fold in fasted condition.

Preliminary PK data from an ongoing dedicated drug interaction trial and simulations using PBPK indicate that rifampin (a strong CYP3A inducer) can decrease ibrutinib C_{max} and AUC by more than 10-fold. Simulations using PBPK suggested that a moderate CYP3A inducer (efavirenz) may decrease the AUC of ibrutinib up to 3-fold.

In vitro studies indicated that ibrutinib (I/Ki < 0.07 using mean C_{max} at 560 mg) and PCI-45227 (I/Ki < 0.03) are unlikely to be inhibitors of any major CYPs at clinical doses. Both ibrutinib and the PCI-45227 are weak inducers of CYP450 isoenzymes *in vitro*.

In vitro studies indicated that ibrutinib is not a substrate of p-glycoprotein (P-gp). Systemic ibrutinib is unlikely to be an inhibitor of P-gp at clinical doses ($[I]_1$ /Ki < 0.1). However, it may have an effect on P-gp substrates in the GI tract due to higher local

concentrations after an oral dose. Co-administration of oral narrow therapeutic index P-gp substrates (e.g., digoxin) with ibrutinib may increase their blood concentration.

2.4.2 Clinical Experience with Ibrutinib in CLL

Clinical data supporting the efficacy and safety of ibrutinib for the treatment of CLL, both treatment-naïve and relapsed/refractory, have recently been published.[19, 20] A Phase 1b/2, open-label, multicenter study in subjects with treatment naïve or relapsed/refractory CLL/SLL enrolled 117 subjects into 1 of 5 treatment groups, each receiving 1 of 2 fixed dose levels (420 mg per day or 840 mg per day) of ibrutinib.
Relapsed/Refractory Disease

Toxicity during long-term administration was modest, and most adverse events were grade 1 or 2 severity. The most common adverse events were diarrhea, fatigue, and upper respiratory tract infection, and most adverse events resolved without the need for a suspension of treatment. The most common adverse events of grade 3 or higher were pneumonia (in 10 patients [12%]) and dehydration (in 5 patients [6%]). Infections of grade 3 or higher occurred most frequently early in the course of therapy. The average rate of infection was 7.1 per 100 patient-months during the first 6 months and 2.6 per 100 patient-months thereafter. IgG and IgM levels remained relatively stable throughout treatment. Grade 3 or 4 hematologic toxic effects were infrequent; 5 patients (6%) had anemia, 13 patients (15%) had neutropenia, and 5 patients (6%) had thrombocytopenia. Bleeding events that were grade 3 or higher in severity occurred in 4 patients. A total of 8 patients died within 30 days after receiving the last dose of ibrutinib: 3 deaths were from pneumonia, 1 was from the systemic inflammatory response syndrome, 1 was from sarcoma, and 3 were related to CLL progression.

Treatment-naïve Patients

As part of this same study, a 31 patient symptomatic, untreated cohort of older (age >64 years) patients were enrolled. Toxicity was modest allowing long-term administration with an overall response rate of 71% (55% PR, 3% nPR, 13% CR). An additional, 13% achieved a PR with lymphocytosis. Estimated PFS and OS at 24 months was 96% and 97% respectively. Toxicity was mainly of mild-to-moderate severity (grade 1—2). 21 (68%) patients had diarrhea (grade 1 in 14 [45%] patients, grade 2 in three [10%] patients, and grade 3 in four [13%] patients). 15 (48%) patients developed nausea (grade 1 in 12 [39%] patients and grade 2 in three [10%] patients). Ten (32%) patients developed fatigue (grade 1 in five [16%] patients, grade 2 in four [13%] patients, and grade 3 in one [3%] patient). Three (10%) patients developed grade 3 infections, although no grade 4 or 5 infections occurred. One patient developed grade 3 neutropenia, and one developed grade 4 thrombocytopenia.

Anti-CD20 Antibody Therapy in Combination with Ibrutinib

Ibrutinib has also been administered in combination with anti-CD20 monoclonal antibody therapy in an effort to improve the overall and complete response rate. Our group undertook a phase Ib/II study of ibrutinib in combination with ofatumumab.[21] Patients with relapsed/refractory CLL/SLL were treated with 420 mg ibrutinib daily in 28-day cycles until disease progression. Ofatumumab was added using the licensed dose and schedule. 24 patients with either CLL/SLL/PLL were enrolled (median age 66 years, median 3 prior therapies, 63% having bulky disease (>5 cm), 42% del(17p13.1), 38% having Rai stage III/IV disease). No grade $\geq$3 infusion reactions, neutropenia, or thrombocytopenia were observed. The majority of adverse events were grade 1 and 2 with grade 3/4 events including anemia (11%), and pneumonia (11%). All 24 CLL/SLL/PLL patients achieved PR (100% ORR) within 6 cycles. With median follow-up of 6.5 months (range: 5.3-10.2), 23 CLL/SLL/PLL patients remained on study and 1 CLL/SLL patient went to transplant in PR. Burger, et al. have more recently reported preliminary results of the phase 2 combination of rituximab and ibrutinib in high-risk CLL, including patients with treatment-naïve disease. Thirty-nine patients were evaluable for response assessment per 2008 IWCLL guidelines. Thirty-four (87%) achieved partial remission, and three (8%) complete remission, accounting for an ORR of 95%. One CR was negative for MRD by flow cytometry. The ORR in the 20 patients with del17p or *TP53* mutation was 90% (16 PR, 2 CR). While both combinations resulted in more rapid clearance of peripheral blood lymphocytosis, randomized studies will be necessary to ascertain whether the combination will result in significantly higher complete response rates versus ibrutinib alone.[22]

2.5 Rationale for Combination Therapy

While the combination of a CD20 antibody with ibrutinib will likely improve early response by resolving peripheral lymphocytosis, the impact on MRD-negative CR is expected to be modest. Further, responses achieved after ibrutinib monotherapy appear to require long-term, continuous therapy. Additionally, despite durable responses achieved with this oral agent in patients with genetically low- or intermediate-risk disease, relapses continue to be observed in genetically high-risk patients most at risk for death from CLL. Genetically, work with the XID BTK mouse model demonstrated that over-expression of bcl-2 could rescue normal B-cells from enhanced apoptosis. This provides rationale for this combination in CLL where BTK is known to be a driving kinase similar to normal B-cells and bcl-2 over-expression is almost uniform. Studies from our laboratory have also shown that blood lymphocytes from patients with extended lymphocytosis after ibrutinib therapy are very sensitive to venetoclax.

Based upon this data, we seek to investigate a novel combination of obinutuzumab, ibrutinib, and venetoclax. The combination is rational based upon 1) independent mechanisms of apoptosis induced by these three very active agents; 2) sensitivity of

ibrutinib treated persistent lymphocytosis cells to venetoclax; and 3) previously published data showing bcl-2 rescues B-lymphocytes from apoptosis induced by PH domain mutation/activity resulting in loss of BTK in XID mouse.

In this study, therapy is sequenced, first with obinutuzumab followed by ibrutinib and then venetoclax, in order to limit the influence of ibrutinib on NK-cell mediated ADCC (important for obinutuzumab activity) and to cytoreduce prior to initiating venetoclax, thereby limiting the risks for tumor lysis. The overall goal is to produce high rates of MRD-negative CR, thereby permitting discontinuation of CLL therapy.

2.6 Rationale for Dose Selection

Obinutuzumab

Obinutuzumab will be administered at the FDA approved dose and schedule except that an additional 2 cycles will be administered, in order to provide 6 cycles of therapy with all three agents. After a comprehensive review of all safety, efficacy, and PK data obtained in Phase I/II studies, an obinutuzumab dose of 1000 mg for all infusions was chosen as the dose most likely to be well tolerated and efficacious in a majority of patients regardless of their initial tumor burden. Obinutuzumab will be administered at 1000 mg weekly for 3 weeks followed by monthly (every 4 weeks) doses in the subsequent 7 cycles. In order to rapidly achieve and maintain adequate obinutuzumab exposure levels, schedule in obinutuzumab will be infused on Days 1, 8, and 15 of the first cycle followed by every 4-week dosing.

Venetoclax

Venetoclax dosing for this study was based on experience from ongoing Phase I/II studies with both single-agent venetoclax (M12-175) and combination therapy with obinutuzumab (GP28331) in relapsed and refractory CLL patients. These studies have established a step-up schedule over the first weeks of drug administration to reduce the risk for TLS. Starting doses of 20 mg QD for the first week, followed by 50 mg QD during the second week, with subsequent weekly dose increases (100 → 200 → 400 mg QD) have been well-tolerated. If safety data from ongoing trials become available to support a different venetoclax dosing regimen from that described below in Section 5.4, the protocol may be amended. Venetoclax therapy is planned to continue for 12 cycles (Cycles 3 through 14).

Ibrutinib

Ibrutinib will be administered at the FDA approved dose and schedule for relapsed CLL: 420 mg QD. At this dose, there is >95% occupancy of the BTK protein at 24-hours, resulting in sustained disease control in the majority (>70%) of relapsed and refractory CLL patients treated. Completed and ongoing Phase I/II studies have demonstrated that this dose can be safely combined with anti-CD20 monoclonal antibody therapy at standard doses of those agents. Ibrutinib therapy is planned to continue for 13 cycles

(Cycles 2 through 14), or longer at the discretion of the treating investigator.

Rationale for Assessment of SARS-CoV-2 Specific Follow-up

The success of this combination study and others with venetoclax and ibrutinib combination therapy has resulted in significant interest in this combination. Indeed, two NCTN phase 3 studies testing this three drug combination in older (≥70 years, NCT03737981) and younger (< 70 years, NCT03701282) are underway. Recognition that this regimen promotes short and long-term innate and potential adaptive immune defects (particularly humoral), long-term infection and secondary malignancies represent a concern for this treatment approach. The recent pandemic with SARS-CoV-2 has accentuated this concern, as cancer patients, particularly those who are elderly would be expected to have a higher morbidity, mortality, and potential difficulty in clearing virus if adaptive immune function is compromised. To date, we are aware of only one patient with relapsed CLL on this trial who had definite SARS-CoV-2 infection while continuing on ibrutnib post combination therapy. This patient had an extended course of moderate disease (>8 weeks) that required treatment with convalescent serum to clear active virus. As part of this amendment, we seek to asses prospectively by means of a 3 month questionnaire, serial 6 month blood draws for evidence of T-cell and humoral response (that can be done locally and sent to OSU), and collection of records from hospitalization (if this occurs) for covid-19 related illness and complications arising from this. Patients will be contacted and re-consented for participation in this long-term follow up assessment of all those on trial in treatment or long-term follow up. If a SARS-CoV-2 vaccine becomes commercially available, these patients will be assessed for humoral and cellular response to this as part of standard of care monitoring and data will be collected for this.

3 PATIENT SELECTION

3.1 Eligibility Criteria

1. Diagnosis of Chronic Lymphocytic Leukemia (CLL) meeting criteria established in the World Health Organization (WHO) classification of hematologic disorders.

2. Age ≥18 years

3. Eastern Cooperative Oncology Group (ECOG) performance status ≤1

4. Relapsed or refractory CLL patients must meet the following requirements:
   - Received at least 1 prior therapy
   - Require treatment in the opinion of the investigator
   - Relapsed patients must have developed progressive disease following a response to a prior therapy
   - Refractory patients must have failed to respond or relapsed within 6 months to the last prior therapy

5. Treatment-naïve CLL patients must meet the following requirements (Phase II only):

- Symptomatic disease as defined by IWCLL 2008 criteria.[3]
- Received no prior chemotherapy, immunotherapy, or targeted therapy for the treatment of CLL with the exceptions of palliative loco-regional radiotherapy and corticosteroids for symptom control.

6. Adequate bone marrow independent of growth factor support at screening unless clearly due to marrow involvement by CLL/SLL and/or disease-related immune thrombocytopenia:
   - Hemoglobin ≥8 g/dL
   - Absolute neutrophil count (ANC) ≥1000/mm^3
   - Platelets ≥40,000/mm^3

7. Adequate renal function, hepatic function, and coagulation studies at screening:
   - PT/PTT ≤1.5 x ULN
   - Total bilirubin ≤1.5 x ULN (excepting Gilbert's syndrome)
   - AST and ALT ≤2.5 × ULN
   - Serum creatinine <2.0 mg/dL

     OR

     Creatinine clearance (Cockcroft) ≥50 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal[†]

8. Female patients must be surgically sterile, post-menopausal (for at least 1 year), or have negative results from a pregnancy test performed as follows:
   - At screening, on a serum sample obtained within 14 days prior to the first study drug administration, and
   - Prior to dosing, on a urine sample obtained on Day 1 of treatment if it has been >7 days since obtaining the serum pregnancy test result

9. All female patients not surgically sterile or post-menopausal (for at least 1 year) and non-vasectomized male patients must practice at least one of the following methods of birth control:
   - Total abstinence from sexual intercourse (minimum one complete menstrual cycle)
   - A vasectomized partner
   - Hormonal contraceptives for at least 2 months prior to Day 1 of treatment
   - Double-barrier method

[†] Calculated creatinine clearance ≥ 50 mL/min using 24-hour creatinine clearance or modified Cockcroft-Gault equation (using ideal body mass [IBM] instead of mass):

$$eCCr = \frac{(140 - Age) \bullet IBM\ (kg) \bullet [0.85 \text{ if female}]}{72 \bullet \text{serum creatinine (mg/dL)}}$$

10. Non-vasectomized male patients must practice at least one of the following methods of birth control throughout the duration of study participation and for at least 3 months after study treatment:
    - A partner who is surgically sterile or postmenopausal (for at least 1 year) or who is taking hormonal contraceptives (oral, parenteral, vaginal ring, or transdermal) for at least 3 months prior to study drug administration
    - Total abstinence from sexual intercourse
    - Double-barrier method (condom, diaphragm or cervical cup with spermicidal, contraceptive sponge, jellies, or cream)

11. Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

1. Patients who have had chemotherapy, immunotherapy, radiotherapy, or investigational therapy within 28 days prior to entering the study or those who have not recovered from adverse events due to agents administered more than 28 days earlier. Steroids for control of disease related symptoms are permitted.

2. Patients who are receiving any other investigational agents.

3. Uncontrolled autoimmune hemolytic anemia or thrombocytopenia.

4. Active Richter's transformation.

5. Known active involvement of the central nervous system by lymphoma or leukemia.

6. Patients who require warfarin anticoagulation or who have received warfarin or equivalent Vitamin K antagonists ≤7 days prior to treatment Day 1. Patients may be eligible if able to be taken off warfarin and started on an alternative anticoagulant.

7. Received potent CYP3A4 inhibitors (such as ketoconazole or clarithromycin) within 7 days prior to the first dose of study treatment. (See **Appendix B**)

8. Received potent CYP3A4 inducers (such as rifampin, carbamazepine, phenytoin, St. John's wort) within 7 days prior to the first dose of study treatment. (See **Appendix B**)

9. Consumed grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruit within 3 days prior to the first dose of study treatment.

10. History of a prior significant toxicity, other than thrombocytopenia, from another Bcl-2 family protein inhibitor.

11. Known cysteine-481 BTK mutation or CLL refractory to or progressed during ibrutinib or other Cys-481 binding BTK inhibitor treatment.

12. Known infection with the HIV virus.

13. A cardiovascular disability status of New York Heart Association Class ≥ 2, defined as cardiac disease in which patients are comfortable at rest but ordinary physical activity results in fatigue, palpitations, dyspnea, or angina pain.

14. Positive hepatitis serology:
    - HBV: Patients with positive serology for Hepatitis B defined as positivity for HBsAg or anti-HBc. Patients who are positive for anti-HBc may be considered for inclusion in the study on a case-by-case basis if they are hepatitis B viral DNA negative and are willing to undergo ongoing HBV DNA testing by real-time PCR. Patients with positive serology may be referred to a hepatologist or gastroenterologist for appropriate monitoring and management.
      - Patients with positive hepatitis B surface antigen (HBSAg) consistent with prior vaccination to HBV (i.e., anti-HBs+, anti-HBc-) may participate.
      - Patients suspected to have false positive serologic studies because of IV immunoglobulin administration are potentially eligible after negative PCR studies for viral DNA/RNA and discussion with the principal investigator.
    - Hepatitis C (HCV): Patients with positive hepatitis C serology unless HCV RNA is confirmed negative and *may* be considered for inclusion in the study on a case-by-case basis (e.g., patients with negative viral load after HCV-specific treatment).

15. History of severe (defined as Grade 4 and/or requiring permanent discontinuation of prior antibody therapy) allergic or anaphylactic reactions to human, humanized, chimeric, or murine monoclonal antibodies.

16. A female patient who is pregnant or breast-feeding.

17. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

18. History of other active malignancies other than CLL within the past 3 years prior to study entry, with the exception of:
    - Adequately treated in situ carcinoma or the cervix uteri or breast
    - Basal cell or localized squamous cell carcinoma of the skin
    - Previous malignancy confirmed and surgically resected (or treated with other modalities) with curative intent or without relapse for ≥ 2 years.

19. Vaccination with a live vaccine <28 days prior to the start of treatment.

20. Inability to swallow capsules or tablets, or disease significantly affecting gastrointestinal function and/or inhibiting small intestine absorption (malabsorption syndrome, resection of the small bowel, poorly controlled inflammatory bowel disease, etc.)

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4 REGISTRATION PROCEDURES

4.1 Informed Consent

The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts. Human protection committee approval of this protocol and a consent form is required. Written informed consent will be obtained by a co-investigator or a specific designee previously approved by the OSU Institutional Review Board (IRB), using forms approved by the IRB.

Patients who are being re-consented after an amendment to the protocol and informed consent document may be consented by phone.

4.2 Registration Procedures

The study will be conducted at The Ohio State University (OSU). Dr. Kerry Rogers, the principal investigator/scientific protocol chairman will coordinate protocol management. Patients will undergo an initial assessment to determine eligibility and to determine baseline disease status prior to study enrollment. Patients will be registered through the database of the OSU Clinical Trials Office (CTO) and provide written informed consent. All patients for whom questions arise relative to eligibility for the study should be discussed with the principal investigator prior to entry onto the study.

To ensure timely communication of treatment tolerance, the progress of each patient will be discussed with the principal investigator on a monthly basis with any adverse events being promptly communicated to the principal investigator by the treating physician or designee to ensure safe treatment of other patients in the study.

5 TREATMENT PLAN

5.1 Overview

This phase Ib/II study will evaluate the combination of obinutuzumab, venetoclax, and ibrutinib for the treatment of chronic lymphocytic leukemia. The agents will be given in sequence in order to limit the influence of ibrutinib on NK-cell mediated ADCC (important for obinutuzumab activity) and to cytoreduce prior to initiating venetoclax, thereby limiting the risks for tumor lysis. Venetoclax will be dose escalated in a phase 1b trial treating relapsed and refractory CLL before proceeding to a phase II trial of the combination enrolling 2 separate cohorts of previously untreated and relapsed/refractory patients.

The protocol was amended to enrollment of a 3rd phase II cohort of previously untreated patients (Cohort 3). This cohort will be treated in the same manner as the prior phase II cohorts (Cohorts 1 &2) which the exception that they will NOT be allowed to continue ibrutinib past the end of Cycle 14. Cohort 3 subject will also have additional testing to determine changes in disease volume with treatment including CT scans, bone marrow biopsy, and lymph node biopsy if feasible. There will also be additional laboratory correlative testing on samples from these subjects to examine changes in disease biology with treatment.

The treatment plan is summarized in **Table 1** below. Instructions for administration of the individual agents, including dose escalation of venetoclax during Cycle 3, are described in **Section 5.2** through **Section 5.7**. Procedures for prophylaxis and treatment of tumor lysis syndrome (TLS) during Cycle 3 dose escalation of venetoclax are detailed in **Appendix D**.

Table 1: Treatment Plan Overview

	Cycle 1	Cycle 2	Cycle 3	Cycles 4-8	Cycles 9-14
Obinutuzumab	X	X	X	X	
Ibrutinib*		X	X	X	X
Venetoclax			Intra-patient dose ramp-up to cohort dose (**Section 5.4**)	X	X

Cycle length = 28 days (except Cycle 3, which varies during Phase 1b)
Planned duration of therapy = 14 cycles (approximately 1 year)
[*]Ibrutinib may be continued past Cycle 14 if deemed by the treating investigator to be in the best interested of the individual patient. Patients enrolled in Cohort 3 will <u>not</u> be allowed to continue ibrutinib past cycle 14.

5.2 Obinutuzumab

Obinutuzumab administration will commence on an outpatient basis during Cycle 1. Obinutuzumab will be administered by IV infusion as an absolute (flat) dose of 1000 mg. Obinutuzumab will be administered in a single day, with the exception of the first dose, which is given over two consecutive days (split dose) in Cycle 1 to limit the risk for infusion reactions: 100 mg on Day 1 and 900 mg on Day 2. Prophylactic medications and drug administration instructions are detailed below.

5.2.1 Schedule of Obinutuzumab Administration

Obinutuzumab is administered on a weekly basis for the first 3 weeks of treatment (Cycle 1: D1/2, D8, D15) and then every 4 weeks thereafter for 7 additional doses.

5.2.2 Prophylaxis for Infusion Related Reactions

All obinutuzumab infusions should be administered after premedication with oral acetaminophen (e.g.,1000 mg) and an antihistamine such as diphenhydramine (50 mg), 30−60 minutes prior to starting each infusion (unless contraindicated).

For the first dose of obinutuzumab, premedication with corticosteroids (e.g., 100 mg IV prednisolone or equivalent) is mandatory for all patients and must be administered at least 1 hour prior to the 100 mg dose on Day 1 and the 900 mg dose on Day 2. An equivalent dose of dexamethasone (20 mg) or methylprednisolone (80 mg) is permitted, but hydrocortisone should not be used.

For subsequent infusions, corticosteroid premedication should be given:

- To patients who experienced a Grade 3 IRR with the previous infusion
- To patients with lymphocyte counts > 25×10^9/L
- At the investigator's discretion.

For patients who do not experience Grade ≥ 2 infusion-related symptoms with their previous infusion (i.e., do not receive medication to treat the reaction symptoms and do not experience infusion interruption), premedication for subsequent infusions may be omitted at the investigator's discretion.

5.2.3 *Obinutuzumab Administration*

During the initial infusion of obinutuzumab, obtain vital signs pre-infusion, then every 15 minutes for 90 minutes, then every 30 minutes until the end of infusion, and then every 60 minutes until the infusion line is removed. If obinutuzumab is well tolerated without significant infusion-related symptoms, vital signs for subsequent infusions can be obtained every 30 minutes until the infusion line is removed.

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

Hypotension may be expected with infusions; therefore, withholding of antihypertensive treatment should be considered for 12 hours prior to the obinutuzumab infusions, throughout the obinutuzumab infusions, and for the first hour after obinutuzumab infusions.

Patients with pre-existing cardiac and/or pulmonary conditions or who have had a prior clinically significant cardiopulmonary AE with rituximab should be monitored particularly carefully throughout the infusion and post-infusion period. Patients with prior clinically significant cardiac disease are excluded per eligibility criteria.

5.2.4 *First Infusion of Obinutuzumab*

The first obinutuzumab infusion will be administered as a split infusion with 100 mg on Day 1 (administered as an IV infusion at 25 mg/hour over 4 hours) and 900 mg on Day 2 (administered at the initial rate of 50 mg/hour). See **Section 8.1.3**, **Table 9** below for additional details.

If a hypersensitivity or IRR develops, the infusion should be temporarily interrupted or slowed down and concomitant medication may be administered if deemed appropriate by the investigator. Upon resolution of symptoms, the infusion will resume at one-half the previous rate (the rate being used at the time that the hypersensitivity or IRR occurred) and infusion rate escalation may resume at the increments and intervals described above.

See **Appendix C** for the suggested management of IRRs.

5.2.5 *Subsequent Infusions of Obinutuzumab*

See **Section 8.1.2**, **Table 9** below.

If the patient's previous infusion of obinutuzumab was well tolerated (defined by an absence of Grade 2 IRRs during a final infusion rate of ≥ 100 mg/hour), subsequent infusions will be administered at an initial rate of 100 mg/hour and increased by 100 mg/hour increments at 30-minute intervals, as tolerated, to a maximum rate of 400 mg/hour. If a hypersensitivity or IRR develops, the infusion should be temporarily interrupted or slowed down and concomitant medication may be administered if deemed appropriate by the investigator. Upon resolution of symptoms, the infusion will resume at one-half the previous rate (the rate being used at the time that the hypersensitivity or IRR occurred) and infusion rate escalation may resume at the increments and intervals described above. If the previous infusion rate was not well tolerated as defined above, instructions for the first infusion rate will be used.

Administration of the dose of obinutuzumab may be split on 2 consecutive days if there is concern for IRRs (e.g., in those patients with a high tumor burden or prior infusion reaction) or if the obinutuzumab dose cannot be administered in 1 day.

See **Appendix C** for the suggested management of IRRs.

5.3 Ibrutinib

Ibrutinib treatment will be administered continuously beginning Cycle 2 Day 1.

On days when ibrutinib is taken with other study drugs, the order of administration will be venetoclax (within 30 minutes after eating the first meal of the day) → ibrutinib → obinutuzumab.

The starting dose will be 420 mg (3 x 140 mg capsules) daily. Ibrutinib will be administered orally once daily with 8 ounces of water. The capsules should be swallowed intact, and subjects should not attempt to open the capsules or dissolve them in water. Each dose of ibrutinib should be taken at approximately the same time every day. Study patients will self-administer ibrutinib by mouth QD.

If a patient misses a dose of ibrutinib, the patient should take it as soon as he or she remembers that day up to 6 hours past the scheduled time. If more than 6 hours past the scheduled time, the dose should not be taken. Missed doses will not be made-up.

A patient drug administration diary will be used to aid in study drug administration

compliance. Patients will be instructed to record the date and time (to the nearest minute) they take their daily dose in the patient drug administration diary. Each patient's medication calendar from the previous cycle will be reviewed to assess compliance.

5.4 Venetoclax

5.4.1 *Venetoclax Administration*

Venetoclax is manufactured by AbbVie, Inc and will be supplied as oral tablets of 10 mg (16 tablets/bottle), 50 mg (8 tablets/bottle), and 100 mg (32 tablets/bottle). Venetoclax will be administered orally once daily (QD), continuously, beginning Cycle 3 Day 1. Each dose of venetoclax should be taken with approximately 240 mL of water within 30 minutes after the completion of breakfast or first meal of the day. Study patients will self-administer venetoclax tablets by mouth QD.

On days when venetoclax is taken with other study drugs, the order of administration will be venetoclax (within 30 minutes after eating the first meal of the day) → ibrutinib → obinutuzumab.

In cases where a dose of venetoclax is missed or forgotten, the patient should take the dose as soon as possible, *ensuring that the dose is taken with food within 8 hours of the missed dose. Otherwise, the dose should not be taken.* Patients will be instructed to record the date and time (to the nearest minute) they take their daily dose in the patient drug administration diary.

5.4.2 *Risk Classification for Initiation of Venetoclax Treatment*

TLS is a risk for patients with CLL who are treated with high cell-killing agents. Clinical data from CLL patients treated to date with venetoclax suggest that patients with baseline lymph nodes ≥10 cm diameter are at a greater risk for TLS than those with baseline lymph nodes <10 cm. In addition, the data showed that creatinine clearance of <80 mL/min at screening was a secondary risk factor for TLS. A detailed description of risk factors for developing tumor lysis following treatment with venetoclax is available in the venetoclax Investigator's Brochure. The section below describes the management of patients throughout dosing based on their risk factors for developing TLS identified upon study entry. On the basis of the data review performed by the manufacturer, the following are three TLS risk categories identified:

TLS low-risk: the presence of all measurable lymph nodes with the largest diameter <5 cm by radiographic assessment AND absolute lymphocyte counts <25 x 10^9/L.

TLS medium-risk: the presence of all measurable lymph nodes with the largest diameter ≥ 5 cm and <10 cm by radiologic assessment OR absolute lymphocyte count ≥25 X 10^9/L.

TLS high-risk: the presence of any lymph node with the largest diameter ≥10 cm by radiologic assessment OR the presence of BOTH an absolute lymphocyte count >25 x 10^9/L AND a measurable lymph node with the largest diameter >5 cm by radiologic assessment.

All patients enrolling in the study will be assessed at screening and categorized in a TLS risk category as described above. However, because patients may have experienced significant tumor de-bulking after treatment with obinutuzumab and ibrutinib before starting venetoclax in Cycle 3, enrolled patients may undergo CT re-staging prior to beginning Cycle 3 at the discretion of their treating physician. TLS risk may then be then re-classified according to the above scheme.

Patients classified as TLS high risk at screening and/or immediately prior to beginning Cycle 3 due to a measurable lymph node with the largest diameter ≥ 10 cm by radiologic assessment OR the presence of BOTH an absolute lymphocyte count >25 x 10^9/L AND a measurable lymph node with the largest diameter >5 cm by radiologic assessment may have a re-evaluation of their TLS risk category. Based on those results, one of the following two options may be implemented:

- If the patient's ALC decreases to < 25 × 10^9/L and/or the measurable lymph node to < 5 cm by radiologic assessment, the patient may be categorized as TLS medium/low- risk and follow the management guidelines for the TLS medium/low risk category for subsequent dose increases (to 100, 200, 400 mg) of venetoclax during the intra-patient dose escalation

- If the patient's ALC remains ≥ 25 x 10^9/L and lymph node > 5 cm OR only lymph node > 10 cm by radiologic assessment the patient will remain in the TLS high risk category and continues to follow management guidelines for TLS high risk patients for subsequent dose increases of venetoclax during the Ramp-Up Period.

Similar reassessment of the patient's TLS risk category can occur prior to each subsequent dose increase.

Treatment setting and other details of TLS prophylaxis and monitoring depend upon TLS risk assessment. Details are presented in the following sections and summarized below in **Table 2**.

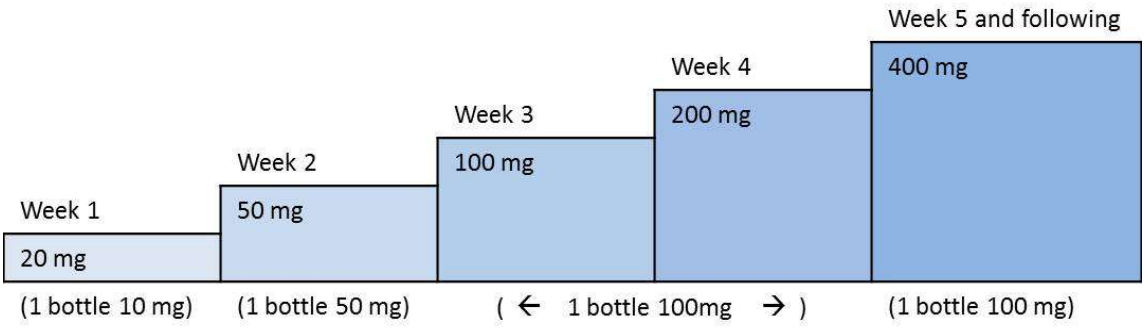
5.4.3 *Venetoclax Dosing Schedule: Overview and General Considerations*

To mitigate the risk for TLS, a lead-in period of up to 5 weeks (see **Table 2**) will be employed with a step-wise intra-patient dose ramp up. All patients will begin treatment with an initial dose of 20 mg venetoclax on Week 1 Day 1 of Cycle 3. If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7.

All patients will then receive a dose of 50 mg venetoclax once daily to be administered beginning Week 2 Day 1 of Cycle 3. After a week at 50 mg, dose escalation will proceed with weekly dose increments → 100 mg → 200 mg → 400 mg as tolerated or until the assigned cohort dose (phase 1b; see cohort dose escalation plan in **Section 5.5** below) or phase 2 combination dose is reached.

If no significant findings occur within 24 hours at dose ramp up, the study drug will be continued at the same dose from Days 2 through 7. If there is indication of lab or clinical TLS the study drug dose will be held or decreased to the previous dose till resolution of all findings. TLS management will be implemented as appropriate.

Figure 1. Venetoclax Intra-patient Dose Ramp Up Schematic



Any patient who, at any dose, develops clinically significant electrolyte abnormalities must have his or her subsequent venetoclax dose held until the electrolyte abnormalities resolve. Patients who develop electrolyte abnormalities should undergo

aggressive management and further monitoring per **Appendix D: Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome**.

Any time during the ramp-up period, if venetoclax was held for 7 days or less, the patient may resume venetoclax at the same dose level or at one lower dose level as determined by the investigator based on a risk assessment (including tumor burden status). Dose must be resumed at one lower dose level if dose held more than 7 days with the exception of initial dose level of 20 mg (400 mg → 200 mg, 200 mg → 100 mg, 100 mg →50 mg, 50 mg →20 mg). All patients must receive the intended dose for at least 7 days before increasing to the next ramp-up dose.

5.4.4 *First Dose of Venetoclax at 20 mg and at 50 mg*

All patients, irrespective of their TLS risk category, must receive the following TLS prophylaxis measures prior to the initiation of the first dose*s* of venetoclax:

- Administration of an oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to dose and continued until the first week of venetoclax is completed
- Oral hydration consisting of fluid intake of approximately 1.5−2 L/day starting at least 48 hours prior to the start of treatment and continued for at least 24 hours after the first dose
- Whole blood potassium, serum chemistry, and hematology laboratory samples must be drawn anytime within 72 hours prior to first dose and electrolyte values should be reviewed and not demonstrate any clinically significant abnormalities prior to the first dose of venetoclax. If clinically significant laboratory abnormalities are observed in this baseline laboratory assessment, first dose of venetoclax must be delayed until resolution and management per the protocol **Appendix D: Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome**, must be initiated. If needed, patient should receive additional prophylactic treatment prior to the initiation of dosing.

Additional TLS prophylaxis and monitoring procedures are tailored to the individual TLS risk category as follows.

5.4.4.1 *Initial Dosing of Venetoclax (20 mg, 50 mg):* ***Low Risk***

Low-risk patients will receive their initial doses of 20 and 50 mg as outpatients.

- For patients unable to maintain oral hydration at 1.5-2 L/day starting at least 48 hours prior to the start of treatment, IV hydration in the outpatient setting on the day of dosing during the clinic stay is recommended in order to assure that this full amount of hydration is achieved. For patients for whom volume

overload is considered a significant risk, hospitalization should be considered.
- Whole blood potassium, serum chemistries and vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose), 8 and 24 hours after dosing time points. Laboratory samples should be sent and analyzed immediately.
- For patients in whom the laboratory values required to be done within 72 hours prior to the first dose were in fact obtained within 24 hours before dosing and were within normal limits, results from "before dosing" laboratory values are not required to be available prior to initiating venetoclax treatment but rather will serve only as a baseline for post-dosing laboratory results comparisons.
- The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.
- Furthermore, the investigator or sub-investigator must review the 24-hour laboratory results prior to dosing on the next day.
- Additional laboratory assessments may be performed per investigator discretion.

5.4.4.2 *Initial Dosing of Venetoclax (20 mg, 50 mg):* ***Medium Risk***

Medium-risk patients who have creatinine clearance ≥80 mL/min will receive their initial doses of 20 and 50 mg as outpatients.

- Patients with creatinine clearance < 80 mL/min and/or who have higher tumor burden (defined per the discretion of the investigator) may be handled as high-risk patients (see the High Risk section for details of hydration, laboratory, etc.).
- In addition to oral hydration stated above, IV hydration (1.5−2 L) will be given in the outpatient setting during the clinic stay. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.
- Whole blood potassium, serum chemistry, and vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose), 8 and 24 hours after dosing time points. Laboratory samples should be sent and analyzed immediately.

For patients in whom the laboratory values required to be done within 72 hours prior to the first dose were in fact obtained within 24 hours before dosing and were within normal limits, results from "before dosing" laboratory values are not required to be available prior to initiating venetoclax treatment, but rather will serve only as a baseline for post-dosing laboratory results comparisons.

The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.

Furthermore, the investigator or sub-investigator must review the 24-hour laboratory results prior to dosing on the next day.

Additional laboratory assessments may be performed per investigator discretion.

5.4.4.3 *Initial Dosing of Venetoclax (20 mg, 50 mg):* ***High Risk***

High-risk patients will be hospitalized to receive their initial doses of 20 and 50 mg. Hospitalization will begin the evening prior to each initial dose of venetoclax and continue for 24 hours after.

- Upon admission, serum chemistry and hematology laboratory samples should be drawn and IV hydration should be started with a target of approximately 2–3 L per day or as clinically appropriate.
- Rasburicase may be administered per institutional guidelines as prophylaxis prior to the first dose of venetoclax for high-risk patients with high uric acid levels at pre-dose (above the local laboratory ULN or Cairo-Bishop threshold of 476 µmol/L). For patients with a contraindication to rasburicase (i.e., glucose-6-phosphate dehydrogenase deficiency), the TLS risk-mitigation plan must be reviewed with the Principal Investigator.
- Nephrology (or acute dialysis service) consultation should be considered on admission (per institutional standards or based on investigator discretion) for hospitalized patients to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.
- Whole blood potassium, serum chemistry, and vital signs will be performed before dosing and at 4, 8, 12, and 24 hours after dosing. These samples are to be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator or sub-investigator. The 24-hour post-dose laboratory results must be reviewed by the investigator or sub-investigator before the patient leaves the hospital or receives any additional study drug. Additional laboratory assessments may be performed per investigator discretion.

5.4.5 *Subsequent Dosing of Venetoclax (100, 200, and 400 mg doses)*

All patients, irrespective of their risk category, must receive the following TLS prophylaxis measures prior to subsequent dose increases of venetoclax:

- Continued administration of an oral uric acid reducer as indicated above.
- Oral hydration consisting of fluid intake of approximately 1.5–2 L/day starting at least 48 hours prior to dosing. IV hydration is encouraged at subsequent dose increases for patients unable to maintain such oral hydration. IV hydration in the outpatient setting on the day of dosing during the clinic stay is recommended in order to assure this full amount of hydration is achieved. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.

- Whole blood potassium, serum chemistry, and hematology laboratory samples must be drawn within 72 hours prior to dose and electrolyte values should be reviewed and not demonstrate any clinically significant abnormalities prior to each dose increase of venetoclax, or the patient should receive additional prophylactic treatment prior to dosing. If clinically significant laboratory abnormalities are observed in this laboratory assessment, dose of venetoclax must be delayed until resolution, and management per the protocol **Appendix D: Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome**, must be initiated. If needed, patient should receive additional prophylactic treatment prior to the initiation of dosing.

Additional TLS prophylaxis and monitoring procedures are tailored to the individual TLS risk category as follows.

5.4.5.1 *Subsequent Dosing of Venetoclax (100, 200, and 400 mg doses):* ***Low Risk***

Low-risk patients will receive the subsequent dose increases (100, 200, and 400 mg) as outpatients.

- Whole blood potassium, serum chemistry, and vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose) and at 8 and 24 hours after dosing time points. Laboratory samples should be sent and analyzed immediately.
- For patients in whom the laboratory values required to be done within 72 hours prior to the first dose were in fact obtained within 24 hours before dosing and were within normal limits, results from "before dosing" laboratory values are not required to be available prior to initiating venetoclax treatment but rather will serve only as a baseline for post-dosing laboratory results comparisons.
- The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.
- Furthermore, the investigator or sub-investigator must review the 24-hour laboratory results prior to dosing on the next day. Additional laboratory assessments may be performed per investigator discretion.

5.4.5.2 *Subsequent Dosing of Venetoclax (100, 200, and 400 mg doses):* ***Medium Risk***

Medium-risk patients who have creatinine clearance ≥ 80 mL/min will receive their subsequent dose increases as outpatient. Patients with creatinine clearance < 80 mL/min and/or who have high tumor burden (defined per the discretion of the investigator) may be hospitalized.

- For patients who receive this subsequent dose increases as outpatient, serum chemistry, hematology, and vital signs will be performed before dosing (defined

as up to 4 hours before venetoclax dose) and 8 and 24 hours after dosing time points. Laboratory samples should be sent and analyzed immediately.
- For patients in whom the laboratory values required to be done within 72 hours prior to the first dose were in fact obtained within 24 hours before dosing and were within normal limits, results from "before dosing" laboratory values are not required to be available prior to initiating venetoclax treatment but rather will serve only as a baseline for post-dosing laboratory results comparisons.
- The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.
- Furthermore, the investigator or sub-investigator must review the 24-hour laboratory results prior to dosing on the next day.
- Additional laboratory assessments may be performed per investigator discretion.

For patients hospitalized during subsequent dose increases:

- Whole blood potassium, serum chemistry, and vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose) and 4, 8, 12, and 24 hours after dosing. These samples are to be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator or sub-investigator. The 24-hour after dosing laboratory results must be reviewed by the investigator or sub-investigator before the patient leaves the hospital or receives any additional study drug.
- IV hydration should be started with a target of approximately 2−3 L per day or as clinically appropriate for patients who are hospitalized.

5.4.5.3 *Subsequent Dosing of Venetoclax (100, 200, and 400 mg doses):* ***High Risk***

High-risk patients with creatinine clearance of ≥ 80 mL/min will receive the subsequent dose increases as outpatients. Patients with creatinine clearance < 80 mL/min and/or high tumor burden (defined per the discretion of the investigator) may be hospitalized. Hospitalization will begin the evening prior to the dose of venetoclax and continuing for 24 hours after.

- IV hydration (1.5−2 L) will be given in the outpatient setting during the clinic stay. For patients who are hospitalized, IV hydration should be started with a target of approximately 2−3 L per day or as clinically appropriate.
- For patients not hospitalized, whole blood potassium, serum chemistries, hematology, and vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose) and 8 and 24 hours after dosing time points. Laboratory samples should be sent and analyzed immediately.
- For patients in whom the laboratory values required to be done within 72 hours prior to the first dose were in fact obtained within 24 hours before dosing and were within normal limits, results from "before dosing" laboratory values are not

required to be available prior to initiating venetoclax treatment, but rather will serve only as a baseline for post-dosing laboratory results comparisons.

- The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.
- Furthermore, the investigator or sub-investigator must review the 24-hour laboratory results prior to dosing on the next day.

For patients hospitalized during subsequent dose increases:

- Whole blood potassium, serum chemistry, and vital signs will be performed before dosing (defined as up to 4 hours before venetoclax dose) and 4, 8, 12, and 24 hours after dosing. These samples are to be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator or sub-investigator. The 24-hour after dosing laboratory results must be reviewed by the investigator or sub-investigator before the patient leaves the hospital or receives any additional study drug.
- IV hydration should be started with a target of approximately 2−3 L per day or as clinically appropriate for patients who are hospitalized.
- Additional laboratory assessments may be performed per investigator discretion.

Table 2. Summary of TLS Prophylaxis and Monitoring Measures

TLS Risk Category	Day 1 of Dose Level	Prophylaxis Medication	Hospitalization	Hydration [a]	Laboratory Assessments [b, e, f]
TLS low-risk	20, 50, 100, 200, 400 mg	Oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to dose and continued until the first week of therapy with venetoclax is completed.	No	Oral hydration of 1.5–2 L/day beginning at least 48 hours prior to dose and continuing for at least 24 hours after dose.	Chemistry and Hematology within 72 hours prior to dose, before dosing (defined as up to 4 hours before venetoclax dose), 8 and 24 hours after dosing timepoints. The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day. The investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.
TLS medium-risk	20 and 50 mg	Oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to dose and continued until the first week of therapy with venetoclax is completed.	No [c,d]	Oral hydration of 1.5–2 L/day beginning at least 48 hours prior to dose and continuing for at least 24 hours after dose. In addition to oral hydration, IV hydration (1.5–2 L) will be given in the outpatient setting during the clinic stay.	Chemistry and Hematology within 72 hours prior to dose, before dosing (defined as up to 4 hours before venetoclax dose), 8 and 24 hours after dosing timepoints. The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day. The investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.
	100, 200, 400 mg	Continue oral uric acid reducer as above.		Oral hydration of 1.5–2 L/day beginning at least 48 hours prior to dose and continuing for at least 24 hours after dose.	

TLS Risk Category	Day 1 of Dose Level	Prophylaxis Medication	Hospitalization	Hydration [a]	Laboratory Assessments [b, e, f]
TLS high-risk	20 and 50 mg	Oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to dose and continued until the first week of combination therapy with venetoclax is completed. Rasburicase must be administered per institutional standards/institutional guidelines as prophylaxis prior to the first dose of venetoclax for high-risk patients with high uric acid levels at pre-dose (above the local laboratory ULN or Cairo-Bishop threshold of 476 µmol/L). For patients with a contraindication to rasburicase (i.e., glucose 6 phosphate dehydrogenase deficiency), the TLS risk-mitigation plan must be reviewed with the Principal Investigator.	Yes [d]	Oral hydration of 1.5–2 L/day beginning at least 48 hours prior to dose and continuing for at least 24 hours after dose. Upon hospital admission, IV hydration should be started with a target of approximately 2–3 L per day or as clinically appropriate.	Chemistry and Hematology within 72 hours prior to dose, before dosing (defined as up to 4 hours before venetoclax dose), 4, 8, 12 and 24 hours after dosing timepoints. Samples are to be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator or subinvestigator. The 24-hour after dosing laboratory results must be reviewed by the investigator or subinvestigator before the patient leaves the hospital or receives any additional study drug
	100, 200, 400 mg	Continue oral uric acid reducer as above	No [c,d]	Oral hydration of 1.5–2 L/day beginning at least 48 hours prior to dose and continuing for at least 24 hours after dose. In addition to oral hydration, IV hydration (1.5–2L) will be given in the outpatient setting during the clinic stay.	Chemistry and Hematology within 72 hours prior to dose, before dosing (defined as up to 4 hours before venetoclax dose), 8 and 24 hours after dosing timepoints. The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day. The investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

Table 2 Legend

[a] For patients unable to maintain oral hydration at 1.5–2 L/day starting at least 48 hours prior to the start of treatment, IV hydration in the outpatient setting on the day of dosing during the clinic stay is recommended (unless being hospitalized) in order to assure that this full amount of hydration is achieved. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.

[b] Results from pre-dose laboratory values are not required to be available prior to initiating venetoclax treatment provided laboratory values obtained within 24 hours before dosing were within normal limits. For laboratory samples drawn on days on study treatment, "before dosing" laboratory samples should be drawn within 0–4 hours before the dose. Other laboratory samples occurring on the same day should be obtained within a ± 15-minute window of any exact scheduled time. Any laboratory tests occurring at time intervals greater than or equal to 24 hours after dose should be obtained within a ± 2 hour window of the scheduled time.

[c] Patients with creatinine clearance < 80 mL/min and/or who have higher tumor burden (defined per the discretion of the investigator) may be handled as TLS high-risk patients.

[d] Nephrology (or acute dialysis service) consultation should be considered on admission (per institutional standards or based on investigator discretion) for hospitalized patients to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.

[e] Any patient who, at any dose, develops clinically significant electrolyte abnormalities must have subsequent venetoclax dose held until the electrolyte abnormalities resolve. Patients who develop electrolyte abnormalities should undergo aggressive management and further monitoring per **Appendix D**. Any time during the ramp-up period, if venetoclax was held for 7 days or less, the patient may resume venetoclax at the same dose level or at one lower dose level as determined by the investigator based on a risk assessment (including tumor burden status). Dose must be resumed at one lower dose level if dose held more than 7 days with the exception of initial dose level of 20 mg (400 mg → 200 mg, 200mg → 100 mg, 100 mg → 50 mg, 50 mg→ 20 mg).

[f] Because an elevated white blood cell counts can confound accurate measurement of serum potassium values, concurrent whole blood potassium levels will be obtained. In instances where whole blood and serum values are incongruent, whole blood values will be used for decision-making purposes.

5.5 Cohort Dose Escalation Plan (Phase 1b only)

A standard 3 x 3 phase 1 study rule-based design will be used in the phase 1b dose assessment portion of the study. Target doses of venetoclax for the dose escalation are listed for each cohort in **Table 3** below.

Table 3. Venetoclax Dose Escalation Schedule

Cohort	Target Dose Venetoclax	Planned Weekly Intrapatient Ramp Up
1	100 mg daily	20 mg → 50 mg → 100 mg
2	200 mg daily	20 mg → 50 mg → 100 mg → 200 mg
3	400 mg daily	20 mg → 50 mg → 100 mg → 200 mg → 400 mg

Patients will be enrolled and sequentially assigned to the appropriate dosing cohort. Enrollment may be staggered to allow patients to start the ramp up period of venetoclax for the next cohort prior to the completion of the DLT observation period for the previous cohort. However, no patients will escalate to a higher target dose until all patients have completed the DLT observation period from the previous cohort.

5.6 Definition of Dose-Limiting Toxicity (Phase 1b only)

The DLT observation period is defined ad Cycle 3 day 1 until completion of Cycle 3 for each dose cohort and will require that patients receive the obinutuzumab infusion and at least 80% of venetoclax and ibrutinib doses during that cycle. A patient will be considered unevaluable for dose escalation decisions and an additional patient will be enrolled on the same dose cohort in the following three cases: 1) a patient goes off-study for any reason prior to beginning Cycle 3, 2) a patient does not complete the DLT observation period in Cycle 3 due to infusional toxicity attributable to obinutuzumab alone, or 3) a patient does not complete the DLT observation period in Cycle 3 due to reasons other than toxicity (e.g. progression).

Any of the following events that are attributed as having a reasonable possibility of being related to the administration of venetoclax, ibrutinib, and/or obinutuzumab and which cannot be attributed by the investigator to a clearly identifiable cause such as tumor progression, concurrent illness, or concomitant medication, will be considered a DLT:

- Grade 4 neutropenia (that was not present at screening) lasting more than 7 days. The first occurrence of neutropenia may be treated with G-CSF and as long as the neutropenia resolves within 7 days it will not be considered a DLT.
- Grade 3 or Grade 4 febrile neutropenia (regardless of duration)

- Grade 4 thrombocytopenia (or reduction of $>$ 50% for those patients with thrombocytopenia at baseline) resulting in bleeding, or that does not improve to Grade $\leq$ 2 (or to $\geq$ 80% of the baseline value, whichever is lower) by Cycle 4 Day 1 without platelet transfusion.
- Clinically significant TLS that requires active intervention (events must be clinically significant, i.e., decrease in calculated creatinine clearance, cardiac arrhythmias, sudden death, or seizures) or clinically significant laboratory TLS (i.e., events that require active intervention such as re-hospitalization for monitoring/medical intervention or dose interruption of venetoclax).
- Grade 4 infusion-related reaction IRR to obinutuzumab beyond Cycle 1 despite appropriate premedication and administration rate (defined as an infusion-related toxicity occurring during or within 24 hours after completing an infusion of obinutuzumab)
- All other Grades ≥3 adverse events will be considered a DLT with the following exceptions:
  - Grade 3 obinutuzumab IRR that is reversible with treatment and does not require a dose delay of >24 hours is not considered a DLT.
  - Grade 3 neutropenia without fever
  - Grade 3 thrombocytopenia that does not result in bleeding
  - Grades ≥ 3 lymphopenia and/or leukopenia
  - Grade ≥ 3 nausea, vomiting and/or diarrhea despite the use of optimal anti-emetic or anti-diarrheal therapy or lasts ≥3 days.
- Any toxicity that results in >7 day delay of Cycle 4 Day 1

Any DLT will require an interruption and possible discontinuation of venetoclax, ibrutinib, and/or obinutuzumab. If only one of the agents (venetoclax, ibrutinib, or obinutuzumab) is clearly associated with the toxicity in question, that agent must be interrupted but the patient may continue on treatment with the other agents. If all agents are suspected or if causality is unknown, treatment with venetoclax, ibrutinib, and/or obinutuzumab will be interrupted. If the toxicity severity decreases to Grade $\leq$ 2 or to baseline within 4 weeks, then venetoclax, ibrutinib, and/or obinutuzumab may be reintroduced at the same starting dose or at a reduced starting dose. This decision will be made in consultation with the Principal Investigator. If a DLT does not resolve after 4 weeks of suspended study treatment, the patient must be permanently discontinued from study treatment.

Detailed management and dose modifications associated with the above adverse events are outlined in Section 6 below.

5.7 Dose Escalation Rules (Phase 1b only)

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above.

Table 4: Dose Escalation Rules

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

5.8 Selection of Dose for Phase 2 Study Cohorts

The selection of the dose of venetoclax to be used in the Phase 2 study cohorts will be made after completion of the DLT observation period for all patients in the dose-finding cohorts. The data from the dose-finding portion will be reviewed, and the selection of a venetoclax dose will be based on the observed DLTs and MTD determined in the dose findings stage, as well as the overall safety and tolerability profile.

Independent of the DLT assessment during Cycle 3 that will inform the dose escalation of venetoclax, further safety monitoring will be applied in parallel, applicable to the first 6 patients who complete Cycle 2 of therapy with ibrutinib and obinutuzumab. If 2 or more of these 6 patients experience a toxicity that could be considered dose limiting during Cycle 2, the dose escalation of venetoclax will continue as planned but at a lower dose of ibrutinib and the same dose of obinutuzumab. If, as anticipated, 1 or 0 patients in the first 6 patients experience toxicity that could be considered dose limiting during Cycle 2, formal monitoring of toxicities due to the ibrutinib and obinutuzumab combination without venetoclax will be discontinued for the remainder of the phase Ib study. Lastly, if the highest dose level proposed for venetoclax is not safely achieved in relapsed/refractory patients, cohorts of treatment-naïve patients may be assessed for

safety prior to advancing to the phase II portion of the study.

5.8.1 Further Venetoclax Dose Ramp-Up after Phase 2 Dose Established (Phase Ib only)

After a recommended phase 2 dose of venetoclax is established, Phase 1b patients treated at lower dose levels of venetoclax may be considered for further ramp-up to the established phase 2 dose at the discretion of their treating physician. In these cases, dose ramp-up would begin with day 1 of the next scheduled cycle and would follow the dose ramp-up schedule (including required laboratory monitoring) specified in protocol Section 5.4 above.

5.9 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of both ibrutinib and venetoclax with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. **Appendix B** presents guidelines for identifying medications/substances that could potentially interact with the study agent(s). See also **Section 3.2**, **items 7-9** regarding specific eligibility exclusions for patients taking CYP3A4 active agents.

5.9.1 Anticoagulants and Antiplatelet Agents

Laboratory studies have shown that, *in vitro*, ibrutinib can prevent platelets from aggregating normally. The clinical significance of this finding is unknown at this time. While serious bleeding has been uncommon in patients treated to date, it is possible that treatment with the study drug could increase the risk of bruising or bleeding, particularly in subjects receiving oral anticoagulants.

Subjects receiving antiplatelet agents in conjunction with ibrutinib should be observed closely for any signs of bleeding or bruising, and ibrutinib should be withheld in the event of any bleeding events.

Co-administration of ibrutinib and warfarin is absolutely contraindicated (see Appendix B). Subjects requiring the initiation of anticoagulation with warfarin or other coumarin agent during the course of the study should be instructed to immediately stop taking ibrutinib and be permanently discontinued from protocol therapy.

5.9.2 Colony Stimulating Factors

Colony stimulating factors including filgrastim (G-CSF; Neupogen) and peg-filgrastim

(peg-GCSF; Neulasta) may be employed for primary and secondary prophylaxis according to American Society of Clinical Oncology (ASCO) Guidelines. Their use must be documented within the medical record and recorded on the study flow sheets.

5.9.3 Corticosteroids

Use of corticosteroids for management of disease-related symptoms or management of unrelated chronic medical illnesses (e.g. COPD exacerbation) will be allowed at doses equivalent to ≤20 mg prednisone daily. Short-term use of higher doses for management of unrelated medical illnesses will be allowed, but is strongly discouraged. Any such use should be carefully documented on the study flow sheets.

5.9.4 Anti-Emetics

Prophylactic antiemetic therapy and other anti-emetic therapy will be given at the discretion of the treating physician, but should not routinely include corticosteroids.

5.9.5 Antimicrobial Prophylaxis

Patients may receive anti-infective prophylaxis for varicella zoster virus (VZV), herpes simplex virus (HSV) and pneumocystis pneumonia (PCP) at the discretion of the physician. Prophylactic antibiotic administration is left to the discretion of the treating physician but is strongly encouraged for neutropenic patients.

5.9.6 Perioperative/Periprocedural Management

Consider the benefit-risk of withholding ibrutinib for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding. The decision to withhold ibrutinib and the duration should be individualized for the specific patient and procedure.

5.10 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for up to 14 cycles (approximately 1 year) or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s) as defined in **Section 6** below,
- Patient decides to withdraw from the study, or

- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

Patients will be allowed to continue ibrutinib past cycle 14 if none of the above criteria apply. Except in Cohort 3 where ibrutinib must be discontinued at the end of cycle 14. Patients will stop ibrutinib and venetoclax at the end of cycle 14 even if the C14D21-28 assessments are not completed.

5.11 Duration of Follow Up

All patients, including those discontinuing for unacceptable adverse events, will be followed for safety and disease assessments until initiation of alternative CLL therapy, disease progression, death, or until at least 90 days after the last patient is completes study combination treatment. Patients taking ibrutinib per physician discretion in follow-up (after completion of the 14 cycles of planned combination therapy) are not considered on alternative therapy. All patients will be followed for survival until their death, withdrawal from the study, or study closure.

Provision for Remote Follow Up

Patients who have completed treatment through end of treatment restaging may be eligible for remote follow-up.

To be eligible for remote follow-up subjects must:

- Be unable or unwilling to return to OSU for post-therapy follow-up
- Have the agreement of the treating investigator and principal investigator that they are appropriate to participate for remote follow-up
- Have resolution of all study treatment related toxicity to grade <3
- Establish care with a local oncologist and be seen every 3 months (+/- 2 weeks) for the first two years after treatment and then every 6 months (+/- 4 weeks) thereafter
- Be willing to participate in remote follow up
- Be willing to be contacted by study personnel by phone

Patients who continue ibrutinib after cycle 14 will be eligible for remote follow-up if the above criteria are met with the stipulation that they return to OSU at least annually. For patients in remote follow-up survival, progressive disease, any new CLL therapy, and laboratory values for absolute neutrophil count, absolute lymphocyte count, hemoglobin, and platelet count will be captured. Any patient in remote follow-up coming to OSU for a visit will have a regular study follow-up visit.
After June 1st of 2020 all patients in follow up will also have data collected regarding their history of COVID-19 illness, outcome, testing for SARS-CoV-2 (PCR, antibody, or any other

test), and vaccination (along with response to this with commercial testing when available). Patients in follow up at OSU or in remote follow-up may also submit peripheral blood samples every 6 months for assessment of humoral and cellular response to COV-SARS-2 or vaccine to this. This is optional and not mandatory for participation in follow-up. Details for peripheral blood testing is outlined in **Section 9.5**.

5.12 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in **Section 5.10** applies. The reason for study removal and the date the patient was removed must be documented in the case report form.

5.13 Provision for Survival Follow Up

Patients who experience disease progression should be entered into survival follow up. If the patient wasin remote follow up prior to disease progression, they will continue be contacted by phone or e-mail as frequently as every 6 months to determine if they are alive. Those who are to be followed at the Ohio State University can be contacted in person, by phone, or have their records reviewed to determine if they are alive.

Patients previously removed from the study due to progressive disease will be re-contacted and enter survival follow up if they are agreeable. They may be contacted by phone or e-mail if previously following remotely and not following at Ohio State. If the patient is following at Ohio State they may also be contacted in person.

6 DOSING DELAYS/DOSE MODIFICATIONS

<u>This section only applies to patients taking study treatment through cycle 14. All subsequent ibrutinib treatment will be managed at the discretion of the treating investigator.</u>

Patients who experience Grade 3 or 4 toxicities may have their treatment delayed for monitoring of resolution or improvement of toxicity. A dose delay of up to 4 weeks is permitted to allow recovery of toxicities to Grade ≤1 or baseline level. If treatment is delayed for more than 4 weeks, the patient will be withdrawn from study treatment. Patients discontinuing study therapy for reasons other than progressive disease should remain on the study and continue to have disease assessments per protocol.

Patients who experience Grade 3 or 4 toxicity that can be clearly attributed to obinutuzumab, venetoclax, and/or ibrutinib may continue treatment with the other agents while the causative agent is delayed until resolution of toxicity. In cases where Grade 3 or 4 toxicity cannot be attributed to a specific study drug, all suspect study drugs should be stopped regardless of attribution of toxicity until the toxicity is resolved.

Guidelines for dose delays (**Section 6.1**) and dose modifications (**Section 6.2**) of the respective agents are detailed below.

6.1 Dosing Delays

6.1.1 Dosing Delays for Hematological Toxicities

There is a potential for significant lymphopenia in this study. If clinically indicated, anti-infective prophylaxis should be implemented at the investigator's discretion, including appropriate prophylaxis for viral, fungal, bacterial, or Pneumocystis infections. Potential for drug-drug interactions should be considered (for instance, many anti-fungals are excluded and other commonly used agents may be cautionary or prohibited due to drug-drug interactions).

Table 5: Dose Delay Instructions for Hematological Toxicity

Toxicity Grade *	Action to be Taken
Platelets	
Grade 1 or 2	No dose delay mandated.
Grade 3 or 4	▪ If there is a Grade 3–4 thrombocytopenia (for those patients with a normal baseline platelet count) OR a platelet count decrease of >50% (for those patients with thrombocytopenia at baseline), treatment (venetoclax, obinutuzumab, and/or ibrutinib) must be delayed for up to 4 weeks. ▪ If thrombocytopenia does not resolve to Grade ≤ 2 or baseline after 3 weeks, all treatment must be discontinued. ▪ If toxicity recurs, the dose of venetoclax and/or ibrutinib should be modified as detailed in **Section 6.2** below. ▪ Treatment cannot be delayed for more than 4 weeks. ▪ No more than three dose delays and/or two dose reductions are allowed.
Neutrophils	
Grades 1–3	No dose delay mandated.
Grade 4	▪ If there is a Grade 4 neutropenia, treatment (venetoclax, obinutuzumab, and/or ibrutinib) must be delayed for up to 4 weeks. ▪ If Grade 4 neutropenia persists for >1 week or is complicated by fever or infection, GCSF support should be given until recovery. ▪ If neutropenia does not resolve to Grade ≤ 2 or baseline after 3 weeks despite growth factor support, all treatment must be discontinued. ▪ Treatment cannot be delayed for more than 4 weeks. ▪ If toxicity recurs, the dose of venetoclax and/or ibrutinib should be modified as detailed in **Section 6.2** below. ▪ No more than three dose delays and/or two dose reductions are allowed.

* Per NCI-WG CLL grading scale (see **Appendix F**).

6.1.2 Dosing Delays for Non-hematological Toxicities

Table 6: Dose Delay Instructions for Non-Hematological Toxicity

Toxicity Grade	Action to be Taken
Grades 3–4	▪ If there is a Grade 3-4 toxicity, treatment (venetoclax, obinutuzumab, and/or ibrutinib) must be delayed for up to 4 weeks. ▪ If toxicity does not resolve to Grade ≤ 2 or baseline after 3 weeks, all treatment must be discontinued. ▪ Treatment cannot be delayed for more than 4 weeks. The sponsor should be consulted prior to the resumption of dosing. ▪ If toxicity recurs, the dose of venetoclax and/or ibrutinib should be modified as detailed in **Section 6.2** below. ▪ No more than three dose delays and/or two dose reductions are allowed.
Grades 1–2	No dose delay

6.2 Dose Modification Guidelines

6.2.1 Dose Modifications for Obinutuzumab

There will be no dose reductions of obinutuzumab (1000 mg). Patients who experience Grade 3 or 4 toxicities may have their doses of obinutuzumab delayed for monitoring of resolution or improvement of toxicity according to guidelines detailed in **Section 6.1** above.

6.2.2 Dose Modifications for Venetoclax

After recovery from recurrent Grade 3 or 4 non-hematologic toxicity, Grade 3 or 4 thrombocytopenia, or Grade 4 neutropenia possibly or likely attributable to venetoclax, therapy is resumed at a reduced dose as outlined in the table below. No more than three dose delays and/or two dose reductions are permitted before the patient must discontinue venetoclax.

Table 7: Dose Modifications for Venetoclax

Venetoclax Dose	Reduced Dose
400 mg	200 mg
200 mg	100 mg
100 mg	50 mg
50 mg	Re-challenge at 50mg*

*Subjects who do not tolerate 50 mg will discontinue venetoclax

6.2.3 Dose Modifications for Ibrutinib

After recovery from recurrent Grade 3 or 4 non-hematologic toxicity, Grade 3 or 4 thrombocytopenia, or Grade 4 neutropenia possibly or likely attributable to ibrutinib, therapy is resumed at a reduced dose as outlined in the table below. No more than three dose delays and/or two dose reductions are permitted before the patient must discontinue ibrutinib.

Table 8: Dose Modifications for Ibrutinib

Ibrutinib Dose	Reduced Dose
420 mg	280 mg
280 mg	140mg

7 REPORTING OF ADVERSE EVENTS

7.1 Assessment of Safety

Safety assessments will consist of monitoring and reporting AEs and SAEs, including all events of death, and any study specific issues of concern.

7.1.1 Adverse Events

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

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with obinutuzumab, ibrutinib, or venetoclax that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

- All AEs should be reported on the Adverse Event CRF using correct medical terminology/concepts.
- Avoid colloquialisms and abbreviations.
- Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

7.1.2 Serious Adverse Events

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

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

7.2 Methods and Timing for Assessing and Recording Safety Variables

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

7.2.1 Adverse Event Reporting Period

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

7.2.2 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its

duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

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

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

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

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

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

7.3 Procedures for Eliciting, Recording, and Reporting Adverse Events

7.3.1 Eliciting Adverse Events

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

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

7.3.2 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations. Only treatment emergent AEs (those

with onset date after the start of C1D1's infusion) and AEs with grade changes from baseline will be recorded in the EDC.

7.3.2.1 *Diagnosis versus Signs and Symptoms*

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

7.3.2.2 *Deaths*

All deaths that occur during the protocol-specified AE reporting period (see **Section 7.2.1**), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

7.3.2.3 *Preexisting Medical Conditions*

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

7.3.2.4 *Hospitalizations for Medical or Surgical Procedures*

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

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

7.3.2.5 *Pregnancy*

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

7.3.2.6 *Post-Study Adverse Events*

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

7.3.2.7 *Safety Reconciliation*

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

7.3.2.8 *Adverse Events of Special Interest (AESIs)*

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

The following AEs are considered of special interest and must be reported to the Sponsor expeditiously (see **Section 7.3.3** for reporting instructions) irrespective of regulatory seriousness criteria:

Adverse Events of Special Interest which require reporting within 24 hours of awareness:

- Grade 4 thrombocytopenia
- Grade > 3 neutropenia
- Grade = or > 3 IRR
- Grade = or > 3 tumor lysis syndrome
- Grade > 3 infection
- Grade > 3 hemorrhage
- Grade ≥3 elevations in AST, ALT, or serum bilirubin, OR cases of elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice
- Suspected transmission of an infectious agent by the study drug, as defined below: Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

7.3.3 Adverse Event Reporting

The adverse event reporting timelines for this study are outlined in the SDEA separately. Should a discrepancy arise between the timelines stated in protocol and SDEA, the SDEA should take precedent.

Investigators must report all SAEs to Genentech within the timelines described below. The completed MedWatch/case report should be faxed immediately upon completion

To:
GENENTECH/ROCHE
welwyn.pds-pc@roche.com
Fax : +44 1707 377 967 *or* +44 1707 373 779 *or* +44 1707 373 793 *or* +44 1707 390 959

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

SAE, Pregnancy, and AESI reports whether related or unrelated to obinutuzumab or venetoclax will be transmitted to Genentech within 24 hours of the Awareness Date.

Additional reporting requirements to Genentech include the following:

- Any reports of pregnancy following the start of administration with the obinutuzumab or venetoclax and within the follow-up period (for female patients within 18 months after the last dose of obinutuzumab or venetoclax in the female partner of a male patient within three months of completing therapy) will be transmitted to Genentech within 24 hours of the Awareness Date.
- All non-serious *obinutuzumab and venetoclax* AEs originating from the study will be forwarded Genentech *quarterly (every 3 months)*

Note: Investigators will also report events to the OSU IRB as required.

MedWatch 3500A Reporting Guidelines

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

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

Follow-Up Information

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

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e., D.O.B. initial, patient number), protocol description and number, if assigned, brief AE description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report).

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and AE was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.
MedWatch 3500A (Mandatory Reporting) form is available at
http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm

7.3.4 Additional Reporting Requirements for IND

Studies conducted under an Investigator's IND requires additional reporting to the FDA in accordance with the guidance set forth in 21 CFR § 600.80.

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

7 Calendar Day Telephone or Fax Report
The Investigator is required to notify the FDA of any fatal or life-threatening AE that is unexpected and assessed by the investigator to be possibly related to the use of study drug. An unexpected AE is one that is not already described in the ibrutinib package insert or the Obinutuzumab and/or venetoclax Investigator Brochures. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

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

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

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

Contact Information for IND Safety Reports

FDA fax number for IND safety reports:
Fax: 1 (301)-796-9845

All written IND safety reports submitted to the FDA by the investigator must also be submitted to the following:

Genentech/Roche

us_drug.safety@gene.com

ga101-gsur@gene.com

Site's IRB: OSU IRB Submit (**http://orrp.osu.edu/irb/**)

For questions related to safety reporting, please contact Genentech/Roche Drug Safety: welwyn.contact_line_rce@roche.com

7.3.5 IND Annual Reports

Copies of all IND annual reports submitted to the FDA by the Sponsor-Investigator should be sent to:

contact_line.drug_safety@roche.com

and

Genentech Clinical Operations
Fax (866) 706-3927 or ga101-gsur@gene.com

7.3.6 Product Quality Complaints

Any product quality complaints related to obinutuzumab or venetoclax must be reported to Genentech. A product complaint is 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.

All complaints must be submitted within 15 calendar days on Medwatch forms.

- Product quality complaints associated with an adverse event will be reported by e-mail or fax to: usds_aereporting-d@gene.com OR 650-238-6067
- Product quality complaints NOT associated with an adverse event will be reported to: PC Hotline Number: (800) 334-0290

7.4 Data and Safety Monitoring

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of data and patient safety at their regular Disease Group meetings (at least monthly) and the

discussion will be documented in minutes. The PI of the trial will review toxicities and responses of the trial where applicable at these disease center meetings and determine if the risk/benefit ratio of the trial changes. Frequency and severity of adverse events will be reviewed by the PI and compared to what is known about the agent/device from other sources; including published literature, scientific meetings and discussions with sponsors, to determine if the trial should be terminated before completion. Serious adverse events and responses will also be reviewed by the OSUCCC Data and Safety Monitoring Committee (DSMC). The PI will also submit a progress report (biannually for Phase II and quarterly for Phase I) that will be reviewed by the committee per the DSMC plan. All reportable Serious Adverse Events (SAE) will be reported to the IRB of record as per the policies of the IRB.

7.5 Study Close-Out

The Clinical Study Report (final study report) should be sent to Genentech. Copies of the report should be mailed to the assigned Clinical Operations as follows:

Clin Ops Email: ga101-gsur@gene.com
Fax: 866-706-3927

8 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in **Section 7.1**.

8.1 Obinutuzumab (GA-101, GAZYVA™)

Obinutuzumab used in this study will be supplied by Genentech.

8.1.1 Formulation

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

8.1.2 Storage and Preparation

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

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

One vial may be used to prepare both the 100-mg dose (equals 4 mL) and 900-mg dose (equals 36 mL) following the directions below. If both bags are prepared at the same time, the reconstitution/dilution has to take place in a controlled and validated aseptic conditions. Subsequently store the 900-mg bag for a maximum of 24 hours at 2°C−8°C and administer the next day.

To prepare a 100-mg dose: The final drug concentration of a 100-mg dose should be in the range of 0.4 mg/mL to 4.0 mg/mL. Using a 250-mL infusion bag containing 0.9%

NaCl, withdraw and discard 4 mL of the sodium chloride. Withdraw 4 mL of obinutuzumab from a single glass vial and inject it into the infusion bag (discard any unused portion of obinutuzumab left in the vial unless reconstitution/dilution has taken place in controlled and validated aseptic conditions). Gently invert the infusion bag to mix the solution. Do not shake.

To prepare a 900-mg dose: The final drug concentration of a 900-mg dose should be in the range of 0.4 mg/mL to 4.0 mg/mL. Using a 250-mL infusion bag containing 0.9% NaCl, withdraw and discard 36 mL of the sodium chloride. Withdraw 36 mL of obinutuzumab from a single glass vial and inject it into the infusion bag (discard any unused portion of obinutuzumab left in the vial unless reconstitution/dilution has taken place in controlled and validated aseptic conditions). Gently invert the infusion bag to mix the solution. Do not shake.

To prepare a 1000-mg dose: The final drug concentration of a 1000-mg dose should be 4 mg/mL. Using a 250-mL infusion bag containing 0.9% NaCl, withdraw and discard 40 mL of the NaCl. Withdraw 40 mL of obinutuzumab from a single glass vial and inject it into the infusion bag (discard any unused portion of obinutuzumab left in the vial). Gently invert the infusion bag to mix the solution. Do not shake.

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

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

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

8.1.3 Dosage and Administration

Obinutuzumab will be administered by IV infusion as an absolute (flat) dose of 1000 mg. Obinutuzumab will be administered in a single day, with the exception of the first administration when patients will receive their first dose of obinutuzumab over two consecutive days (split dose) in Cycle 1: 100 mg on Day 1 and 900 mg on Day 2.

During the initial infusion of obinutuzumab, obtain vital signs pre-infusion, then every 15 minutes for 90 minutes, then every 30 minutes until the end of infusion, and then every 60 minutes until the infusion line is removed. If obinutuzumab is well tolerated without significant infusion-related symptoms, vital signs for subsequent infusions can be obtained every 30 minutes until the infusion line is removed.

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

Hypotension may be expected with infusions; therefore, withholding of antihypertensive treatment should be considered for 12 hours prior to the obinutuzumab infusions, throughout the obinutuzumab infusions, and for the first hour after obinutuzumab infusions.

Patients with pre-existing cardiac and/or pulmonary conditions or who have had a prior clinically significant cardiopulmonary AE with rituximab should be monitored particularly carefully throughout the infusion and post-infusion period. Patients with prior clinically significant cardiac disease are excluded per eligibility criteria.

See **Appendix C** for the management of IRRs.

Prophylaxis for IRRs

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

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

- IV glucocorticoid: dexamethasone (20 mg) or methylprednisolone (80 mg) administered at least one hour prior to obinutuzumab infusion. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.
- An oral acetaminophen (1000 mg) and an antihistamine such as diphenhydramine (50 mg) administered at least 30 minutes before starting each obinutuzumab infusion.

Cycle 1, Days 8 and 15 and Cycles 2-8, Day 1:

- All patients require pre-medication with oral acetaminophen (1000 mg) administered at least 30 minutes before starting each obinutuzumab infusion.
- Patients who experience an IRR (Grade 1 or more) with the previous infusion will require pre-medication with an antihistamine such as diphenhydramine (50 mg) administered at least 30 minutes before starting each subsequent obinutuzumab infusion.

- Patients who experience a Grade 3 IRR with the previous infusion or who have lymphocyte counts of $\geq 25 \times 10^9$/L prior to the next treatment will require pre medication with IV glucocorticoid: dexamethasone (20 mg) or methylprednisolone (80 mg) administered at least one hour prior to obinutuzumab infusion. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.

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

Obinutuzumab Dosing
The first 1000 mg of obinutuzumab will be administered over 2 days. During Cycle 1, Day 1, 100 mg will be administered. On the following day (Cycle 1, Day 2), 900 mg will be administered (see Table XX).

Table 9: Obinutuzumab Dosing Schedule

Cycle and Day of Administration		Dose of Obinutuzumab	Rate of Infusion (in the Absence of Infusion Reactions/ Hypersensitivity during Previous Infusions)
Cycle 1	Day 1	100 mg	Administer at 25 mg/hour over 4 hours. Do not increase the infusion rate.
	Day 2	900 mg	Administer at 50 mg/hour. The rate of the infusion can be escalated in increments of 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour.
	Day 8	1000 mg	Infusions can be started at a rate of 100 mg/hour and increased by 100 mg/hour increments every 30 minutes to a maximum of 400 mg/hour.
	Day 15	1000 mg	
Cycles 2–8	Day 1	1000 mg	

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

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

See **Appendix C** for additional details regarding the management of IRRs.

8.2 Venetoclax (GDC-0199, ABT-199)

Venetoclax used in this study will be supplied by Genentech.

8.2.1 Formulation

Venetoclax is manufactured by AbbVie, Inc and will be supplied as oral tablets of 10 mg (16 tablets/bottle), 50 mg (8 tablets/bottle), and 100 mg (32 tablets/bottle).

The venetoclax tablets will be packaged in high-density polyethylene (HDPE) plastic bottles to accommodate the study design. Each bottle will be labeled per local regulatory requirements. A desiccant canister may be included in the bottle. The tablets must be stored at 15°C to 25°C (59°F to 77°F) and protected from light and moisture. If supplied with a desiccant, desiccant canister should be returned to the bottle directly after each tablet removal.

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

8.2.2 Dosage, Administration, and Storage

Study patients will self-administer venetoclax tablets by mouth QD. Each dose of venetoclax will be taken with approximately 240 mL of water within 30 minutes after the completion of breakfast.

If vomiting occurs within 15 minutes of taking venetoclax and all expelled tablets are still intact, another dose may be given and the second dose noted in the drug log. 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, ensuring that the dose is taken within 8 hours of the missed dose with food. Otherwise, the dose should not be taken.

8.3 Ibrutinib (PCI-32765, Imbruvica™)

Ibrutinib used in this study will be prescribed from commercial supply.

8.3.1 Formulation

Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK). It is a white to off-white solid with the empirical formula C25H24N6O2 and a molecular weight 440.50. Ibrutinib is freely soluble in dimethyl sulfoxide, soluble in methanol and practically insoluble in water. The chemical name for ibrutinib is 1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1Hpyrazolo[3,4 d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one.

Ibrutinib capsules for oral administration are supplied as white opaque capsules that contain 140 mg ibrutinib as the active ingredient. Each capsule also contains the following inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate. The capsule shell contains gelatin, titanium dioxide and black ink. Each white opaque capsule is marked with "ibr 140 mg" in black ink.

8.3.2 Dosage, Administration, and Storage

Administer ibrutinib orally once daily at approximately the same time each day. Swallow the capsules whole with water. Do not open, break, or chew the capsules.

If a dose of ibrutinib is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra capsules of ibrutinib should not be taken to make up for the missed dose.

The white opaque 140 mg capsules marked with "ibr 140 mg" in black ink are available in white HDPE bottles with a child-resistant closure:

- 90 capsules per bottle: NDC 57962-140-09
- 120 capsules per bottle: NDC 57962-140-12

Store bottles at room temperature 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F to 86°F). Retain in original package.

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Pharmacodynamic and Cytokine Assessment

Blood samples will be collected and used for pharmacodynamic testing. Samples will be collected at screening, pre-dose on Cycle 1 Day 1, pre-dose on Cycle 2 Day 1, pre-dose on Day 1 of Cycles 3-6, 9, and 12, anytime on end-of-treatment week 4, follow up months 3, 6, and 9. Samples will also be collected at any time when bone marrow biopsy is performed. Pharmacodynamic samples required will include 2 x 8.5-mL ACD yellow top tubes and 2 x 6-mL potassium EDTA [lavender-top vacutainer] from peripheral blood and 8.5-mL ACD yellow top tube from bone marrow aspirate drawn at

baseline and at response assessment. These will be delivered to the Clinical Trials Processing Laboratory (CTPL). Whole blood tubes will be forwarded directly to the Byrd lab. EDTA tubes will be spun according to the CTPL's Plasma and Serum Preparation SOP. Four plasma aliquots will be obtained. Cryovials should be labeled with the following information: protocol number, subject ID, collection timepoint and date and time of collection. Plasma will be stored at -70C and sent in batches to the Byrd Lab.

For serial samples collected we will examine for a) baseline and change in known down-stream Btk targets or signaling pathways; b) spontaneous apoptosis and proliferation; c) expression of bcl-2 family member proteins and BH3 priming studies; d) soluble chemokine expression; cytokine expression (plasma); exosome content change and e) in select subjects, serial global phosphoproteomic and mutational studies assessing markers of disease resistance.

On bone marrow samples we will culture fibroblasts for mutational and SNP studies. Subjects relapsing during this treatment will be examined for baseline characteristics and will potentially be subjected to extensive molecular characterization to determine the reason for drug resistance. Potential molecular characterization will include modulation of specific drug targets (BTK, CD20, and BCL2 and other targets). If a nodal biopsy is performed then excess fresh or paraffin derived material from this may be used for these studies.

Excess material obtained from this study may be used for additional studies related to mechanism action and toxicity of ibrutinib, obinutuzumab, venetoclax or biology of CLL. These samples may be shared with other investigators working collaboratively with OSU.

9.2 Immunologic Assessment

In addition to the immunologic studies examining immunoglobulin levels and immune cell numbers that are typically monitored over time to determine the need for immunologic supplementation of immunoglobulin or prophylactic anti-viral and PCP therapy, we will perform studies to assess if ibrutinib allows activation of NK cells as measured by cytokine production of TNF-α, IFN-γ, IL-6, degranulation (CD107a) ex vivo at baseline and prior to cycle 2 of therapy. In addition, we will assess for in vivo serial cytokine production (TNF-α, IFN-γ, and IL-6), CD69 expression and CD107a degranulation.

For immunologic studies we will collect 2 x 8.5-mL ACD yellow top tubes, 1 x 10-mL Heparin green top tube, and 1 x 6-mL potassium EDTA [lavender-top vacutainer] from peripheral blood at Screening, pre-dose, 1 hour post-start of obinutuzumab infusion, and 4 hours post-start of infusion on Cycle 2 Day 1.

The ACD yellow top tubes and heparin green top tube will be forwarded directly to the Byrd Lab as whole blood. The EDTA tube will be spun according to the CTPL's Plasma and Serum Preparation SOP. Two plasma aliquots will be obtained. Cryovials should be labeled with the following information: protocol number, subject ID, collection timepoint and date and time of collection. Plasma will be stored at -70C and sent in batches to the Byrd Lab.

9.3 Health related quality of life and emotional distress assessment

During screening, sociodemographic information (e.g., age, race, marital status) and reports of recent (last year) stressful events will be obtained. The assessment will consist of measures of emotional distress, depressive symptoms, and quality of life. Quality of life measures will be administered during screening or C1D1, and on C1D15, C2D1, C3D1, C3D15, C6D1 and C12D1. [See **Appendix H**].

Measures:

Cognition – General Concerns (PROMIS)

The PROMIS version 1.0 short-form subscale of cognitive concerns contains 8 items. It targets self-assessments of poor cognitive functioning such as (e.g., "My thinking has been slow", "I have had trouble concentrating"). Items are rated on a 5-point scale ranging from "never" to "very often". Items are summed to create a total score, with higher scores indicating more perceived cognitive difficulties.

NIH Toolbox Auditory Verbal Learning Test (Rey)

This instrument is a measure of immediate recall, in which the participant is presented with a list of 15 unrelated words via audio recording and is asked to recall as many as he/she can. This process is repeated twice more, and the score is equal to the total number of words recalled across all three trials. The test takes approximately 3 minutes to administer.

Controlled Oral Word Association Test (COWAT)

This instrument is a measure of verbal fluency (Patterson, 2011). Verbal fluency is a cognitive function that facilitates information retrieval from memory. Successful retrieval requires executive control over cognitive process such as selective attention, mental set shifting, internal response generation, and self-monitoring. This test takes approximately 3 minutes to administer.

9.4 Additional Assessments for Cohort 3

In addition to the above testing, subjects in Cohort 3 may have analysis performed on blood, marrow, and tissues samples. This includes detailed genomic, biochemical, and epigenetic assessment of the residual tumor cells and microenvironment persisting at end of therapy for comparison to baseline tumor features. Detailed assessment of the cellular and innate immune cell numbers at serial time points may be performed as well.

Whole genome sequencing may be performed. No genes known to cause a hereditary disease will be specifically tested. Since whole genome sequencing may be done it is a possibility that a gene known to cause a hereditary disease will be incidentally discovered. The genetic testing is done to compare germline sequences to tumor (CLL) sequences to look for genetic changes that are responsible for resistance to the CLL treatment being studied in the clinical trial. Since we may perform germline sequencing it is possible we will uncover a genetic change responsible for an inherited disease or that has health implications for the subject. If any clinically actionable mutations are identified, the subject's provider will be informed of these results who can determine if the subject should be referred for clinical confirmatory genetic testing and genetic counseling. There is no plan to inform participants of new development in CLL treatment beyond what is standard through discussions with their treating physician.

Lymph Node Specimen Collection and Processing

Lymph node samples will be collected and the available tissue will be first sent to the clinical lab. Any remaining tissue will be used for research purposes. Samples will be collected in sterile saline. Lymph node samples in sterile saline will be delivered to the Experimental Hematology Laboratory (Byrd Lab) for additional processing, storage, and analysis.

9.5 Sample Collection for Testing of Immune Function and Exposure to SARS-CoV-2

For patients in follow-up after completing cycle 14 of treatment additional blood samples may be collected to better understand the longer term effects of this regimen on the immune system and also how this may impact illness from and response to SARS-CoV-2. These are optional blood samples and will not be mandatory for any patient in the study. For patients who have this optional sample collected at OSU they will be delivered to the Experimental Hematology Laboratory (Byrd Lab). These will be collected every 6 months. For patients in remote follow-up blood may be collected at other sites and shipped to the Experimental Hematology Laboratory.

Testing on these samples may include assays for immune senescence, number and type of immune cells, immune functional assays, tests to detect or to antibodies or to quantitate antibodies, PCR or other testing for SARS-CoV-2, and/or any of the testing specified above for this protocol.

Peripheral blood will be collected by venipuncture. A total of 2 x 8.5-mL ACD yellow top tubes will be collected. These will be shipped overnight at room temperature without additional processing prior to shipment.

Samples will be shipped to:

Experimental Hematology Laboratory (EHL)
410 W 12th Avenue Room 417
4th Floor CCC Building
Columbus, OH 43210

Phone (614) 292-8824

All samples must be labeled with the date of collection, subject initials, subject birth date, and study number (OSU 14266). Once samples arrive in the laboratory this information will be dissociated from the samples and they will be stored and tracked in a de-identified manner as with other samples in the study.

9.6 Samples at Time of Disease Progression

To better understand mechanisms of resistance to ibrutinib and venetoclax samples will be collected at time of disease progression after treatment. This will be collected at their next visit to OSU, even if they have already started subsequent treatment for CLL. These samples will be analyzed with the same techniques outlined in **Section 9.4**, which may include genetic testing.

Peripheral blood will be collected by venipuncture. A total of 5 x 8.5-mL ACD yellow top tubes and 2 x 6 mL EDTA lavender top tubes will be collected. If a bone marrow biopsy is performed one 8.5-mL ACD yellow top tube of bone marrow aspirate will also be collected. These will be delivered to the Experimental Hematology Lab (EHL) for processing where cells will be viably cryopreserved for batch analysis according to current laboratory procedures.

10 STUDY CALENDAR

	Screening	Obinutuzumab					Obinutuzumab + Ibrutinib				Obinutuzumab + Ibrutinib + Venetoclax														EOT[A]	FU[B]
											Venetoclax Dose Escalation															
Cycle		1					2				3							4,5	6	7, 8	9	10 ,11	12	13, 14		
Day[C]		**1**	**2**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**2**	**8**	**9**	**15**	**(22)**	**(29)**	**1**	**1**	**1**	**1**	**1**	**1**	**1**		
HOSPITALIZATION[D]											(X)		(X)		(X)	(X)	(X)									
TREATMENT[AA]																										
Obinutuzumab		x	x	x	x		x				x							x	x	x						
Ibrutinib							x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x^{x}		
Venetoclax											x	x	x	x	x	x	x	x	x	x	x	x	x	x		
INVESTIGATIONS																										
Informed Consent	x																									
Medical History	x																									
Concomitant Medications	x	x	x	x	x		x				x	x	x	x	x	(X)	(X)	x	x	x	x	x	x	x^{z}	x	x
Adverse Events	x	x	x	x	x		x				x	x	x	x	x	(X)	(X)	x	x	x	x	x	x	x^{z}	x	x^{B}
ECOG Performance Status	x	x					x				x							x	x	x	x	x	x	x^{z}	x	x
Physical Examination[E, AA]	x	x					x				x		x		x	(X)	(X)	x	x	x	x	x	x	x^{z}	x	x
Vital Signs[F, AA]	x	x	x	x	x		x				x	x	x	x	x	(X)	(X)	x	x	x	x	x	x	x^{z}	x	x
MUGA/Echocardiogram	x																									
12-Lead ECG	x																									
Bone Marrow Biopsy	x^{G}																				$x^{H, BB}$			$x^{H, AA}$	$x^{H, AA}$	$x^{J, AA}$
CT (or MRI) Scans[I]	x										x^{I}										x^{BB}			$x^{I, AA}$	x^{AA}	$x^{J, AA}$
LABORATORY ASSESSMENTS[AA]																										
Hematology[K]	x	x	x	x	x	x^{v}	x	x^{v}	x^{v}	x^{v}	x	x	x	x	x	(X)	(X)	x	x	x	x	x	x	x^{z}	x	x
Serum Chemistries[L]	x	x	x	x	x	x^{v}	x	x^{v}	x^{v}	x^{v}	x^{M}	x^{M}	x^{M}	x^{M}	x^{M}	$(X)^{M}$	$(X)^{M}$	x	x	x	x	x	x	x^{z}	x	x

	Screening	Obinutuzumab					Obinutuzumab + Ibrutinib				Obinutuzumab + Ibrutinib + Venetoclax													EOT[A]	FU[B]
											Venetoclax Dose Escalation														
Cycle		1					2				3							4, 5	6	7, 8	9[BB]	10, 11	12	13, 14[Z]		
Day[C, AA]		1	2	8	15	22	1	8	15	22	1	2	8	9	15	(22)	(29)	1	1	1	1	1	1	1		
Serum Pregnancy Test[N]	X																									
HBV and HCV screening[O]	X																									
Urinalysis	X																									
Quantitative immunoglobulins	X																	X	X	X	X[BB]				X	X
CORRELATIVE LABORATORY STUDIES																										
CLL Prognostic Factors[P]	X																									
β2 microglobulin	X																				X[BB]				X	
B-, T-, and NK-cells (flow)[Q]	X						X				X							X[Q]			X[BB]				X	X
MRD Peripheral Blood (flow)	X																				X[BB]			X[Z]	X	
MRD Bone Marrow (flow)																					X[BB]			X[Y, Z]	X	
PD sample (bone marrow)[R]	X																				X[BB]			X[Y, Z]	X	
PD and cytokines (blood)[S]	X	X					X				X							X	X		X[BB]		X	X[Y, Z]	X	X
Immunologic Assessment[T]	X						X																			
HRQoL Surveys[U]	X	X			X		X				X				X				X					X		
Lymph Node Biopsy																								X[W]		
Disease Progression Sample[CC]																										X[CC]

EOT = End of Treatment; FU = Follow-up; MRD = minimal residual disease; (X) = visit may be required depending upon risk group and/or assigned venetoclax dose level (see **Section 5.4)**; PD = pharmacodynamics; HRQoL = Health Related Quality of Life

[A] Patients are seen 4 weeks after the last dose of study drug, regardless of the reason for discontinuation. Patients completing all planned therapy should also return 8 weeks (±7 days) after the last dose of study drug for response assessment. Due to the COVID-19 pandemic some patients will not be able to return 8 weeks after

completing C14D28 of study treatment. For these patients who are unable to return for this assessment, the EOT response assessment with CT or MRI imaging, bone marrow biopsy, and blood tests will be done any time more than 8 weeks after Cycle 14 Day 28 that it is safe and feasible to perform this assessment. This will be considered as their EOT assessment and duration from C14D28 to this assessment will be recorded. For patients discontinuing before completion of planned therapy, all listed EOT studies are required except peripheral blood flow for MRD, CT/MRI scans, and bone marrow biopsy, which are only obtained from patients completing Cycle 14. For patients who continued on ibrutinib after completion of Cycle 14, response assessment will be done as planned 8 weeks (±7 days) after completion of Cycle 14. These patients will be followed in the same manner as patients who discontinue ibrutinib.

[B] After end of treatment, patients are followed every 3 months for 2 years then every 6 months until disease progression, initiation of another CLL therapy, death, or end of study, whichever comes first. All follow up visits will have a +/- 2 week window for patients on 3 month follow up and +/- 4 weeks for patients on 6 month follow up. As per **Section 5.11** patients who are in remote follow up will have local visits at the same time points as outlined in **Section 5.11** with the same widows. Patients are required to have annual visits at the study site if they remain on ibrutinib. After June 1st, 2020 patients who are in follow up may have peripheral blood collected for additional immunological assays as outlined in **Section 9.5**. This is optional and patients who choose not to have blood collected will still participate in follow-up. Adverse events will be recorded in follow-up as per Section 7.2.1. After 30 days of completing treatment those patients not on study treatment will only have SAEs related to study treatment recorded. This is for both in person and remote follow-up. Any patient continuing on ibrutinib will have all AEs recorded as they are on active study treatment are will not be considered to have ended treatment for the purposes of AE recording. Patients who experience disease progression will move to survival follow-up and should be contacted every 6 months; see sec. 5.13 for details.

[C] Starting Cycle 1 Day 1, all treatment visits will have a ±1 day window through the end of Cycle 8. Starting Cycle 9, visits will have a ±7 day window. All follow up visits will have a +/- 2 week window for patients on 3mo follow up and +/- 4 weeks for patients on 6mo follow up.

[D] See **Section 5.4**. Hospital admission prior to beginning venetoclax treatment is mandatory for high-risk and some medium-risk patients during the first two weeks of treatment (20 mg, 50 mg doses). Hospitalization for subsequent dose escalations and/or patients in other risk groups is at the discretion of the treating physician in consultation with the principle investigator. Note that patients with high risk at baseline may be re-categorized prior to starting treatment if their peripheral lymphocyte count and largest nodal mass have been reduced to sizes compatible with medium- or low-risk status. See **Section 5.4.2** for additional details.

[E] Complete physical examination, including measured height, is obtained at screening. Targeted physical examination is sufficient at all subsequent time points. Weight, bi-dimensional lymph node measurements (bilateral cervical, supraclavicular, axillary, and inguinal), and measurement of liver and spleen (centimeters below the costal margin) should be recorded at all time points.

[F] Vital signs are recorded at each visit. Additional vital sign monitoring during obinutuzumab infusions are described in protocol **Section 5.2** and **Section 8.1**.

[G] Bone marrow biopsy and aspirate is obtained from all participants at baseline unless results are available from a biopsy performed no more than 6 months prior to starting protocol therapy and absent intervening anti-CLL treatment.

[H] Repeat bone marrow biopsy and aspirate is obtained for response assessment at Cycle 9 (±7 days) and 8 weeks (±7 days) after completing combination therapy (i.e., after completing Cycle 14). Repeat bone marrow biopsy should also be performed 8 weeks after any non-scheduled response assessment meeting criteria for CR. For patients in Cohort 3 a repeat bone marrow biopsy will be obtained on C14D28 or up to 7 days prior. Patients may not discontinued study treatment until bone marrow biopsy is performed, except for patients who cannot undergo this assessment due to the COVID-19 pandemic. In cases where the C14D28 assessment is omitted for safety reasons during the pandemic patients will still discontinue ibrutinib and venetoclax after C14D28.

[I] CT scans of the chest, abdomen, and pelvis (or MRI if CT contraindicated) with IV and oral contrast within 2 weeks prior to starting treatment (baseline) at C9D1 (±7 days) (first response assessment), and 8 weeks (±7 days) after completing therapy (final response assessment). At the discretion of the treating physician, CT restaging can be performed prior to Cycle 3 to reassess TLS risk parameters prior to beginning treatment with venetoclax (See protocol **Section 5.4.2**). CT scans can also be performed after any non-scheduled response assessment meeting criteria for PR or CR. For patients in Cohort 3 CT scans (or MRI if CT contraindicated) must be performed prior to Cycle 3. This can occur up to 7 days prior to C3D1. Patients in Cohort 3 will also have CT scans (or MRI if contraindicated) on C14D28 (±7 days).

[J] Repeat bone marrow biopsy and contrast-enhanced CT studies are encouraged at the time of suspected disease progression in the absence of clinically overt progression.

[K] Includes complete blood cell count and white blood cell differential. PT/PTT is drawn at screening only.

[L] Includes whole blood potassium (Cycle 3 only) and serum measures of sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, magnesium, phosphorus, total bilirubin (direct bilirubin only if total is elevated), total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, LDH, and uric acid.

[M] Laboratory monitoring during any inpatient venetoclax dose initiation and/or escalation is outlined in protocol **Section 5.4**. For venetoclax dose initiation and/or escalation occurring in the outpatient setting, repeat serum chemistries outlined in footnote “L” above are obtained at 8 and 24 hours post venetoclax dose (except bilirubin, protein, albumin, ALT/AST, alkaline phosphatase) as further described in protocol **Section 5.4**.

[N] Required of all women of reproductive potential within 7 days of initial study treatment.

[O] Minimum HBsAg, IgG anti-HBcAb, and Hep C Ab serology required.

[P] Includes blood for IGVH mutational status,*TP53* mutation status, and interphase FISH CLL panel.

[Q] Peripheral blood immunophenotyping is sent as standard of care at screening, at the beginning of each cycle during initiation of combination therapy (Day 1 of Cycles 2, 3, and 4), at each response assessment (Cycle 9 Day 1, EOT), and during surveillance for disease recurrence/progression (each visit during follow-up; see "B" above for time points).

[R] Instructions for collection of bone marrow samples for PD assessments and cytokine assessment are described in **Section 9.1**.

[S] Instructions for collection of peripheral blood samples for PD assessments and cytokine assessment are described in **Section 9.1**.

[T] Instructions for collection of peripheral blood for immunological studies are described in **Section 9.2**.

[U] Schedule for Health Related Quality of Life Instrument administration is described in **Section 9.3**. HRQoL instruments are detailed in **Appendix G**. Patients enrolled in Cohort 3 will not have HRQoL performed.

[V] Hematology and Serum Chemistry labs may be draw locally. If drawn locally labs must be reviewed by the treating investigator and entered into the medical record of the subject.

[W] Core lymph node biopsy for standard pathology and research samples will be obtained on C14D28 (or up to 7 days prior) if a suitable lymph node is identified on imaging. This may be core or excisional. Patient may not stop study treatment until lymph node biopsy is obtained if one is feasible. In cases where the C14D28 assessment is omitted for safety reasons during the COVID-19 pandemic patients will still discontinue ibrutinib and venetoclax after C14D28, even if the lymph node biopsy is not performed. The treating investigator will determine if a lymph node biopsy is feasible. If a biopsy is felt to be an unreasonable risk to the patient biopsy will not be obtained.

[X] All patients in Cohort 3 must discontinue ibrutinib and venetoclax after C14D28 once repeat imaging, bone marrow biopsy, and lymph node biopsy (if feasible) are obtained. In cases where the C14D28 assessment is omitted for safety reasons during the COVID-19 pandemic patients will still discontinue ibrutinib and venetoclax after C14D28, even if the C14D28 studies were not performed. In these cases the studies will be omitted. Patients in other cohorts are allow to continue ibrutinib after C14D28 at the discretion of the treating investigator.

[Y] Samples will be obtained for studies described in **Section 9.4.**

[Z] For Cohort 3 there will a study visit scheduled between C14D21 and C14D28 for clinic and laboratory assessment. During the COVID-19 pandemic patients who cannot safely addend a study visit and cannot have the imaging, blood, bone marrow biopsy, or lymph node biopsy will have these studies omitted. The clinic visit for C14D28 may also be omitted if felt appropriate by the treating investigator. Patients will discontinued ibrutinib and venetoclax after C14D28 and will not have these studies performed for this time point.

[AA] During the COVID-19 pandemic visits to the study site ma y not be safe or feasible. During this time there is an increased risk to patients of contracting SARS-CoV-2. As CLL is associated with a higher rate of major infections it is assumed that CLL patients are at risk for severe COVID-19 infection. Therefore it is in their interest to omit some study procedures that must be performed on site, rather than putting them at risk by requiring them to attend study visits. In cases where it is not safe or feasible for them to addend clinic visits these visits may be conducted remotely by telemedicine utilizing either a video or telephone format. Laboratory studies may be omitted for up to 3 consecutive months if the treating investigator feels this is safe and appropriate. Local testing may be substituted for testing done at OSU for all clinically reportable tests (not research assays). In cases where patients meet criteria for continued treatment the study oral medications will be shipped to the patient directly. Obinutuzumab infusions that cannot be safely administered due to the COVID-19 pandemic will be omitted and will not be administered locally or made up.

[BB] For patients who are not able to undergo the CT or MRI imaging, bone marrow biopsy, or research laboratory testing occurring on Cycle 9 Day 1 due to safety concerns during the COVID-19 pandemic these assessments will be omitted and not made up at a later date.

[CC] Patients who experience disease progression will have a research sample collected from the peripheral blood and bone marrow, if a bone marrow biopsy is performed. This will be collected at their next visit to OSU, even if they have already started subsequent treatment for CLL. Samples will be processed as outlined in **Section 9.6**. Patients in remote follow up do not have to return for sample collection, however if they do choose to return, a sample will be collected at their next visit.

11 MEASUREMENT OF EFFECT

For disease assessments, response will be assessed by the investigator based on analysis of clinical laboratory tests (hematology laboratory values), complete physical examination, CT scans of involved anatomic regions (or MRI if CT is medically contraindicated), and bone marrow aspirate and biopsy (including measurement of MRD by 4-color flow cytometry). Subjects will be evaluated against the 2008 Modified IWCLL NCI-WG Criteria for Tumor Response with the addition of CT (or MRI) imaging.[3]

At Screening, all measurable disease must be documented by laboratory testing (hematologic status), physical examination, CT (or MRI) imaging, and bone marrow. During the study, subjects will be assessed on a continuous basis at each visit by a physical examination and laboratory testing. When a response (PR or CR) is determined by clinical criteria at any time during the study, a CT scan or MRI can be performed at least 8 weeks (± 7 days) later for confirmation. For determination of CR, both the CT scan and bone marrow are required to be negative. If the scans confirm a CR, then a BM biopsy is required for confirmation of the CR.

Mandatory restaging with assessment of response will occur at the conclusion of combination therapy (within 1 week prior to beginning Cycle 9) and again 8 weeks (±7 days) after 14 cycles of therapy. All patients will undergo restaging of measurable disease by CT (or MRI) imaging, bone marrow aspirate and biopsy, and assessment of MRD by 4-color flow cytometry (peripheral blood and bone marrow) at these time points.

If a subject exhibits clinical signs of possible disease progression (i.e., increased or de novo enlargement of liver, spleen or lymph nodes on physical examination) without an increase in lymphocytes meeting PD criteria, then additional assessments including contrast-enhanced CT scan (or MRI) and/or bone marrow should be performed ≥ 2 weeks subsequent to confirm or rule out PD.

11.1 Definitions

Measurable disease. Measurable sites of disease are defined as lymph nodes, lymph node masses, or extranodal sites of lymphoma/leukemia. Each measurable site of disease must be greater than 1.5 cm in diameter. Bi-dimensional measurements of palpable and or imaging identified lesions are recorded

Treatment-related lymphocytosis Treatment-related lymphocytosis is defined as an elevation in blood lymphocyte count of >50% compared to baseline. Subjects with treatment-related lymphocytosis should remain on study treatment in the absence of treatment-limiting toxicity or in the absence of meeting other criteria for progressive disease. In this particular setting, it will not be considered PD as recommended by the updated iwCLL guidelines.[3]

11.2 Criteria for Response Assessment: Summary

Parameter	CR	PR	PD
Group A			
Lymphadenopathy[a]	None > 1.5 cm	Decrease ≥50%	increase ≥50%
Hepatomegaly	None	Decrease ≥50%	increase ≥50%
Splenomegaly	None	Decrease ≥50%	increase ≥50%
Blood lymphocytes	<4000/µl	Decrease ≥50% from baseline	increase ≥50% over baseline[c]
Marrow[b]	Normocellular, <30% lymphocytes, no B lymphoid nodules. Hypocellular defines CRi	50% reduction in marrow infiltrates or B lymphoid nodules	
Group B			
Platelet count	≥100,000/µl	>100,000/µl or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL
Hemoglobin	>11 g/dl	>11g/dl or increase ≥50% over baseline	Decrease of >2g/dl from baseline secondary to CLL
Neutrophils[b]	>1500/µl	>1500/µl or increase ≥50% over baseline	

[a] Sum of the products of multiple lymph nodes (as evaluated by clinical palpation)
[b] This parameter is not relevant for the PD category.
[c] Subjects with treatment-related lymphocytosis should remain on study treatment in the absence of other criteria for progressive disease.
Note: Group A defines the tumor load and Group B defines the function of the hematopoietic system
CR: all of the criteria need to be met and patients have to lack disease related constitutional symptoms
PR: at least 2 of the above criteria from Group A plus 1 of the criteria from Group B must be met
SD : the absence of PD and the failure to achieve a PR
PD: at least 1 of the above criteria from Group A or B are met
Cross reference: Hallek 2008[3]

11.3 Complete Response (CR)

CR requires all of the following criteria:

- Peripheral blood lymphocytes (evaluated by blood and differential count) below 4 × 10^9/L (4000/µL)
- Absence of lymphadenopathy (nodes > 15 mm in longest diameter or any extra nodal disease) by physical examination and CT scan
- No hepatomegaly or splenomegaly by physical examination (as determined by measurement below the relevant costal margin)
- Absence of disease or constitutional symptoms (B symptoms: unexplained fevers > 38°C or 100.4°F, drenching night sweats, > 10% body mass weight loss in the preceding 6 months)
- Blood counts above the following laboratory values:
  Neutrophils > 1.5 × 10^9/L [1500/µL] (without the need for exogenous growth factors)
  Platelets > 100 × 10^9/L [100,000/µL] (without the need for platelet transfusion or exogenous growth factors)
  Hemoglobin > 110 g/L [11 g/dL] (without the need for blood transfusions or exogenous erythropoietin)
- Bone marrow at least normocellular for age, < 30 % of nucleated cells being lymphocytes. Lymphoid nodules should be absent. Bone marrow aspirate and biopsy should be performed at least 8 weeks after CR/CRi has been achieved. If the bone marrow is hypocellular, a repeat determination should be made in 4 weeks or when peripheral blood counts have recovered. A marrow biopsy should be compared to a pre-treatment marrow if available. Subjects who are otherwise in a complete remission, but bone marrow nodules can be identified histologically should be considered to be nodular PR (nPR). Immunohistochemistry should be performed to define whether these nodules are composed of primarily T cells or lymphocytes other than CLL cells, or CLL cells.

11.4 Complete Response with Incomplete Marrow Recovery (CRi)

Subjects who fulfill the criteria for CR (including bone marrow) but who have persistent cytopenias (anemia or thrombocytopenia or neutropenia) apparently unrelated to CLL but related to drug toxicity will be considered CRi. The marrow evaluation described above should be performed with scrutiny and not show any clonal infiltrate.

11.5 Minimal Residual Disease

Assessments of minimal residual disease (MRD) will be used in patients classified as CR to further evaluate their status as disease-free and if this further impacts their ability to remain progression-free and alive. MRD will be determined by high sensitivity 4 color

flow cytometric analysis of the bone marrow using validated panels. A sample will be classified as positive if 50 or more lymphocytes (out of 500,000 total leukocyte events) are positive for CD5, CD19, CD43, and CD45 bright, and negative for CD10, CD79b, and CD81. Dr. Gerard Lozanski at OSU will perform these studies.

11.6 Partial Response (PR)

To be considered a PR at least 2 of the following must be met:

- ≥ 50% decrease in peripheral blood lymphocyte count from the pretreatment baseline value.
- ≥ 50% reduction in lymphadenopathy.
- ≥ 50% reduction in the size of the liver and/or spleen (if abnormal prior to therapy).

In addition at least **one** of the following criteria must be met:

- Neutrophils >1,500/µL or ≥ 50% improvement over baseline.
- Platelets > l00,000/µL or ≥ 50% improvement over baseline.
- Hemoglobin > 11.0 g/dL or ≥ 50% improvement over baseline without transfusions or exogenous growth factors.

11.7 Progressive Disease (PD)

Progressive disease is characterized by at least one of the following:

- Appearance of any new lesion, such as enlarged lymph nodes (> 1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates. An increase by 50% or more in greatest determined diameter of any previous site.
- An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.
- An increase in the number of blood lymphocytes by 50% or more with at least 5,000 B lymphocytes per microliter not meeting criteria for treatment-related lymphocytosis. The increase should be assessed against the best response while on study.
- Transformation to a more aggressive histology (e.g., Richter's Syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy. For subjects experiencing disease progression due to Richter's Syndrome while on study, supplemental data may be collected.
- Occurrence of cytopenias (neutropenia, anemia or thrombocytopenia) attributable to CLL.

12 STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

This phase Ib/II study will be conducted in two sequential parts. Patients enrolled on the phase Ib portion will not be included in the analysis of the phase II portion. As part of the phase Ib portion, we will first assess safety and tolerability of this combination using a traditional 3 + 3 design until the MTD or highest dose is established. Once safety is established, the regimen will be formally assessed for efficacy using a single-stage phase II clinical trial design, in each of two unique cohorts: previously untreated and relapsed/refractory disease.

A standard 3 + 3 dose-escalation design will be implemented in the phase Ib portion of the study and will include CLL patients with relapsed or refractory disease. We will require ≤1 DLT in 3-6 patients at each dose level during dose escalation and ≤ 1 DLT in 6 patients at the MTD to be deemed safe (please see Section 5.7 for details). The DLT observation period will be defined during Cycle 3 and will require that patients receive the obinutuzumab infusion and at least 80% of venetoclax and ibrutinib doses during that cycle. A patient will be considered inevaluable for dose escalation decisions and an additional patient will be enrolled on the same dose cohort in the following three cases: 1) a patient goes off-study for any reason prior to beginning Cycle 3, 2) a patient does not complete the DLT observation period in Cycle 3 due to infusional toxicity attributable to obinutuzumab alone, or 3) a patient does not complete the DLT observation period in Cycle 3 due to reasons other than toxicity (e.g. progression).

Independent of the DLT assessment during Cycle 3 that will inform the dose escalation of venetoclax, further safety monitoring will be applied in parallel, applicable to the first 6 patients who complete Cycle 2 of therapy with ibrutinib and obinutuzumab. If 2 or more of these 6 patients experience a toxicity that could be considered dose limiting during Cycle 2, the dose escalation of venetoclax will continue as planned but at a lower dose of ibrutinib and the same dose of obinutuzumab. If, as anticipated, 1 or 0 patients in the first 6 patients experience toxicity that could be considered dose limiting during Cycle 2, formal monitoring of toxicities due to the ibrutinib and obinutuzumab combination without venetoclax will be discontinued for the remainder of the phase Ib study. Lastly, if the highest dose level proposed for venetoclax is not safely achieved in relapsed/refractory patients, cohorts of treatment-naïve patients may be assessed for safety prior to advancing to the phase II portion of the study

Once safety of the combination has been established, an additional 50 patients (25 relapsed/refractory and 25 treatment-naïve) will be accrued under the phase II study to examine the efficacy of this combination regimen. In the phase II setting, all patients who receive at least one dose of any study drug will be evaluable for the primary endpoint, MRD- complete response (CR) at the assessment following Cycle 14 as defined

by the IWCLL 2008 criteria. Considering that MRD- CR has been observed in relapsed/refractory patients treated with venetoclax alone, albeit in a small proportion of patients, it is assumed that the combination regimen obinutuzumab + ibrutinib + venetoclax would be considered uninteresting in CLL patients with relapsed/refractory disease if the true MRD- CR rate is less than 10% (null) and that a true MRD- CR rate of 30% or more in this population would be of considerable interest (alternative). If 5 or more patients have a MRD- CR in 25 evaluable patients with relapsed/refractory CLL, then this will be considered sufficient evidence that the treatment combination warrants further testing in subsequent studies and in this group of patients. This design has 90% power with a one-sided alpha of 10%. Since little data exist regarding MRD- CR status with these agents in symptomatic, treatment-naïve CLL patients, the same study design and decision rule will be used in a second cohort of 25 evaluable patients with previously untreated CLL.

For some of the 25 treatment-naïve patients in Cohort 3 of the phase 2 portion of the study, the assessment for the primary endpoint at 2 months post end of treatment (EOT) might not be performed as scheduled due to the COVID-19 pandemic. For these patients, the assessment will be postponed to the earliest time point after 2 months post EOT when it is deemed safe to do so. To estimate the primary endpoint of MRD (-) CR rate in Cohort 3, we will include all responses assessed AT or AFTER 2 months post EOT in the calculation. For all assessments performed after 2 months, the responses and the corresponding time points when the responses are evaluated will be described in detail. If sample size allows, we will explore the possible relationship between when the response is assessed and the degree of response.

12.2 Analysis of Secondary Endpoints

Several secondary endpoints will be assessed. For all patients who receive at least one day of treatment, toxicities will be tabulated by type and grade using NCI-CTCAE Version 4.0 criteria, and displayed in summary form. Toxicities across the study will be reviewed as well as those experienced particularly during each of the first three cycles of treatment, since agents are sequentially added to the overall regimen during Cycles 1-3.

In addition, the number of cycles started/completed, number of patients who reach the target dose of venetoclax, number of patients requiring dose reductions, and the reason for going off treatment may be summarized. Overall response rate with a 95% CI will be reported for all evaluable patients in the phase II setting, within and potentially across cohorts, assuming a binomial distribution. Progression-free survival defined as the time from first treatment date until the date of progression or death, whichever occurs first, will be summarized by the Kaplan-Meier method for each of the phase II cohorts. In addition, baseline prognostic factors, serial assessment of target modulation by ibrutinib, cytokine measurement with infusion of obinutuzumab, free and exosome pharmacology of obinutuzumab, immune effector cell monitoring, studies of resistance

will be performed in conjunction with this phase Ib/II clinical trial. Quality of life measures will also be collected over time in this study. Analysis of these data will primarily be descriptive in nature, using various graphical displays to identify patterns and trends. Relationships between baseline prognostic factors and response may be screened and analyzed quantitatively using logistic regression and adjusting for disease cohort, particularly if a sufficient number of patients respond to this combination therapy. Immune response to SARS-CoV-2 will be analyzed in a descriptive manner using graphic displays to identify patterns and trends to inform ongoing phase 3 studies using this regimen.

12.3 Analysis plan to determine effect of patients continuing ibrutinib past Cycle 14

The original protocol was modified to allow patients to continue on single-agent ibrutinib treatment past Cycle 14. This was done as the treating investigators deemed this to be in the best interest of the individual patients. The response of the entire cohort will be described, and the response of those patients who continue with ibrutinib versus those who stop all treatment by cycle 14 will also be described separately to better understand the influence of continued treatment on response. As ibrutinib continuation may also influence PFS, a similar analysis will be performed for PFS as well.

13 RETENTION OF RECORDS

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

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APPENDIX A ECOG PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
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.

APPENDIX B SAMPLE LIST OF EXCLUDED AND CAUTIONARY MEDICATIONS

Excluded	**CYP3A Inducers – Weak/Moderate (Cautionary)**
warfarin (Coumadin)*	barbiturates
Biologic agents	efavirenz
Anticancer therapy	nevirapine
Other investigational agents+	oxcarbazepine
Steroid therapy for anti-neoplastic intent	rifapentine
	troglitazone
CYP3A Inhibitors (Excluded)	
atanazavir	**CYP2C8 Substrates# (Cautionary)**
clarithromycin	amiodarone
indinavir	amodiaquine
itraconazole	cerivastatin
fluvoxamine	chloroquine
ketoconazole	eltrombopag
nefazodone	lovastatin**
nelfinavir	pioglitazone
ritonavir	repaglinide
saquinavir	rosiglitazone
telithromycin	simvastatin**
voriconazole	
posaconazole	**CYP2C9 Substrates (Cautionary)**
	celecoxib
CYP3A Inducers – Potent (Excluded)	diclofenac
avasimibe	fluvastatin
carbamazepine	glipizide
mitotane	irbesartan
phenobarbital	losartan
phenytoin	phenytoin
rifabutin	sulfamethoxazole
rifampin	sulfinpyrazone
St. John's Wort	tolbutamide
	torsemide

* Warfarin is also a CYP2C9 substrate.

\+ Including targeted small molecule agents.

\# Only certain statins qualify as CYP2C8 substrates.

** Significant increase in AUC by coadministration of gemfibrozil, a potent CYP2C8 inhibitor. However, the involvement of CYP2C8 is unclear.

APPENDIX C MANAGEMENT OF OBINUTUZUMAB INFUSION-RELATED SYMPTOMS

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

[a] Refer to National Cancer Institute Common Terminology Criteria for Adverse Events v4.0, for the grading of symptoms.

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

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

APPENDIX D RECOMMENDATIONS FOR INITIAL MANAGEMENT OF ELECTROLYTE ABNORMALITIES DURING VENETOCLAX TREATMENT

First Dose of venetoclax or Dose Escalation

- Within the first 24 hours after either the first dose or dose increase, if any laboratory criteria below are met, the patient should be hospitalized for monitoring and the investigator notified. No additional venetoclax doses should be administered until resolution. A rapidly rising serum potassium level is a medical emergency.
- 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, paresthesias, mental status changes, confusion, and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour STAT.
- 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.
- Because an elevated white blood cell counts can confound accurate measurement of serum potassium values, concurrent whole blood potassium levels will be obtained. In instances where whole blood and serum values are incongruent, whole blood values will be used for decision-making purposes.

In addition to the recommendations in the table below, for patients with CLL/SLL receiving first dose of venetoclax:

- For potassium increase $\geq$ 0.5 mmol/L from baseline, or any value $>$ 5.0 mmol/L, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT and follow guideline.
- For phosphorus increase of $>$ 0.5 mg/dL AND $>$ 4.5 mg/dL, administer phosphate binder and recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT.

Abnormality	Management Recommendations
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT. 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 discretion of 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 STAT 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 × 1. • 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 STAT. • 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 STAT 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 × 1. • 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 STAT.
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/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 STAT.

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 predose 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 STAT. • 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) *OR* 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 STAT. • 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.
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 STAT. • 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 STAT.

IV=intravenous; ULN=upper limit of normal; WNL=within normal limits.

Ongoing Dosing of Venetoclax

Management of electrolyte changes from last value at intervals > 24 hours after either the first dose or dose increase (e.g., 48 or 72 hours) are as below. Note: If the patient is hospitalized, no additional venetoclax doses should be administered until resolution.

For potassium, admit patient for any increase ≥ 1.0 mmol/L (1.0 mEq/L), or any level > upper limit of normal.

- Refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose increase (table above).

If a smaller potassium increase is observed that does not meet the criteria for admission above, recheck potassium, phosphorus, uric acid, calcium, and creatinine in 24 hours and confirm no evidence of tumor lysis prior to further venetoclax dosing.

For uric acid, calcium, phosphorus, and creatinine, refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose increase (table above).

APPENDIX E CAIRO-Bishop Definition and Grading of Tumor Lysis Syndrome

From: Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol 2004;127:3-11.

Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome (LTLS)

Uric Acid	≥ 476 µmol/L (≥ 8.0 mg/dL) or 25% increase from baseline
Potassium	≥ 6.0 mmol/L (≥ 6.0 mEq/L) or 25% increase from baseline
Phosphorous	≥1.45 mmol/L (≥ 4.5 mg/dL) or 25 % increase from baseline
Calcium	≤ 1.75 mmol/L (≤ 7.0 mg/dL) or 25% decrease from baseline
Laboratory tumor lysis syndrome (LTLS) is defined as either a 25% change or level above or below normal, as defined above, for any two or more serum values of uric acid, potassium, phosphate, and calcium within 3 days before or 7 days after the initiation of chemotherapy. This assessment assumes that a patient has or will receive adequate hydration (± alkalization) and a hypouricemic agent(s).	

ULN = upper limit of normal.
*Not directly attributable to a therapeutic agent.

Cairo-Bishop Grading System for Tumor Lysis Syndrome

Grade	LTLS	Creatinine	Cardiac Arrhythmia	Seizure
0	-	≤ 1.5 × ULN	None	None
1	+	1.5 × ULN	Intervention not indicated	None
2	+	> 1.5 – 3.0 × ULN	Non-urgent medical intervention indicated	One brief generalized seizure; seizure(s) well controlled or infrequent; focal motor seizures not interfering with ADL
3	+	> 3.0 – 6.0 × ULN	Symptomatic and incompletely controlled medically or controlled with device	Seizure in which consciousness is altered; poorly controlled seizure disorder; breakthrough generalized seizures despite medical intervention
4	+	> 6.0 × ULN	Life-Threatening	Seizures of any kind that are prolonged, repetitive, or difficult to control
5	+	Death*	Death*	Death*

LTLS = laboratory tumor lysis syndrome; ULN = upper limit of normal; ADL = activities of daily living.
*Probably or definitely attributable to clinical TLS.

APPENDIX F NATIONAL CANCER INSTITUTE–SPONSORED WORKING GROUP HEMATOLOGIC ADVERSE EVENT GRADING SCALE FOR CHRONIC LYMPHOCYTIC LEUKEMIA FOR PATIENTS WITH BASELINE ABNORMAL HEMATOLOGIC LABORATORIES

Decrease in Platelets [a] or Hgb [b] from Pretreatment Value	Grade	ANC/μL [c] (nadir) ($\times 10^9$ cells/L)
No change–10%	0	$\geq$ 2000 ($\geq$ 2.00)
11%–24%	1	$\geq$ 1500 and $<$ 2000 ($\geq$ 1.5 and $<$ 2.0)
25%–49%	2	$\geq$ 1000 and $<$ 1500 ($\geq$ 1.0 and $<$ 1.5)
50%–74%	3	$\geq$ 500 and $<$ 1000 ($\geq$ 0.5 and $<$ 1.0)
$\geq$ 75%	4	$<$ 500 ($<$ 0.5)

Source: Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. Blood 2008;111:5446–56.

ANC = absolute neutrophil count; Hgb = hemoglobin; Grades: 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening.

[a] If, at any level of decrease, the platelet count is $< 20 \times 10^9$/L (20,000/μL), this will be considered a Grade 4 toxicity unless a severe or life-threatening decrease in the initial platelet count (e.g., 20×10^9/L [20,000/μL]), was present before treatment, in which case the patient is unevaluable for toxicity with regard to platelets.

[b] Baseline and subsequent Hgb determinations must be performed before any given infusion.

[c] If ANC was $< 1 \times 10^9$/L prior to therapy, the patient is unevaluable for toxicity in ANC.

APPENDIX G HEALTH RELATED QUALITY OF LIFE AND EMOTIONAL DISTRESS MEASUREMENT

Sociodemographic Information
Single items are used to assess age, race/ethnicity, marital status, education, occupation, work-related functioning, and income.

Stressful Life Events
The *Life Events* scale was adapted from the Women's Health Initiative study (Matthews et al., 1997). Participants will be asked to indicate if they had experienced any of five stressful life events during the previous year(death, financial difficulty, divorce or break-up of family member or friend, major conflict with children or grandchildren, robberies or accidents). Two scores are calculated: presence versus absence of each event (*0 =not occurred, 1 =occurred),* and the total number of events reported (range 0-5). Higher scores indicate more frequent life events and greater distress.

Health-Related Quality of Life
The *Medical Outcomes Study-Short Form* 12(SF-12; Ware, Kosinski, & Keller, 1996; Ware, Kosinski, Turner-Bowker, & Gandek, 2002) is used to assess health-related quality of life during the past *month.* The SF-12 assesses eight aspects of quality of life including physical functioning, role functioning physical, bodily pain, general health perceptions, vitality, social functioning, role functioning-emotional, and mental health. Higher scores reflect better quality of life.

The Brief Pain Inventory (BPI; Cleeland & Ryan, 1994) is a 7-item self-report measure of pain severity and daily functional interference. Higher scores indicate greater interference.

The Fatigue Symptom Inventory (FSI: Hann et al.., 1998) disruption index is a 7-item assessment of the impact of fatigue on quality of life on an 11-point Likert-type scale ranging from 0 = *no interference* to 10 = *extreme interference*; higher scores indicating greater interference.

The *Brief Illness Perception Questionnaire* (BIPQ; Broadbent et al., 2006) is a 9-item questionnaire to assess patients' perceptions of their illness. Questions are rated on an 11-item Likert scale from 0 (not at all) to extremely (10). The Medical Outcomes Study-Sleep Scale (MOS) is a 12-item measure of sleep quantity and quality (Hays et al., 2005).

Depressive Symptoms
The *Beck Depression Inventory- 2nd Edition* (BDI-11; Beck, Steer, & Brown, 1996) is a 21-item self-report instrument used to assess the severity of symptoms of depression. Respondents are asked to describe the way they have been feeling during the past *month* by rating each item (e.g., sadness, pessimism, loss of pleasure) on a scale from 0 to 3. Thus, possible scores are 0 (minimal depression) to 63 (high depression).
Complete remission of depressive symptoms is indicated by scores of 9 or less on the BDI. Partial remission is indicated by scores ranging from 10 to 16. No symptom remission is

indicated by scores of 17 or greater. Two additional items have been included (0.22 and 23) to assess current and past Dysthymic Disorder.

Emotional Distress

The Profile of Mood States- Short Form (POMS-SF; Shacham, 1983 *Journal of Personality Assessment;* Curran, Andrykowski, Studts, 1995, *Psychological Assessment)* is used to assess patient mood. The POMS is a 37-item self-report inventory asking the subject how (s)he has felt during the past *week,* yielding six mood subscales: Anxiety, Depression, Anger, Vigor, Fatigue, and Confusion. The Anxiety subscale scores can range from 0 to 24, the Depression from 0 to 32, the Anger from 0 to 28, the Vigor from 0 to 24, the Fatigue from 0 to 20, and the Confusion from 0 to 20. Higher scores on each subscale indicate greater levels of each type of mood.

The Impact of Events Scale (IES-R; Horowitz, Wilner, & Alvarez, 1979; Weiss & Marmar, 1996) is a 22-item standardized self-report questionnaire used to assess reactions to cancer diagnosis and treatment. Responses are rated on a 5-point scale; higher scores indicate greater distress.

Questionnaires assessing social support will be added to the battery of QOL questionnaires. Both constructs have been found to be robustly associated with physical health, in both healthy and medical populations.

Social Support

The *Social Network Index* (SNI; Berkman, 1977) is a 10-item measure of the number of an individual's social ties as well as his or her involvement within this network. The SNI is composed of 4 major components: marital status, number of close friends and relatives and frequency of monthly contact with these individuals, church group membership, and membership in other groups (social, vocational, child-related, service-oriented, other) with intimate contacts weighted more heavily than church affiliations and group memberships. Social Network scores range from 1 to 12 with higher scores representing greater social involvement.

The *Social Support- NIH Toolbox* scales (Cyranowksi, Zill, et al., 2013) of emotional support, instrumental support, and loneliness will be utilized to measure social support and loneliness in a 21-item measure. Questions are rated on a 5-point Likert scale from 0 (never) to 4 (Always). Higher scores indicate poorer social support and greater feelings of loneliness.

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APPENDIX H SAFETY REPORTING FAX COVERSHEET

Safety Reporting Fax Coversheet
Genentech Supported Research

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

Initial Report Date (DD/MON/YYYY)	____ / _____ /_____
Follow-up Report Date (DD/MON/YYYY)	____ / _____ /_____

Subject Initials (Please enter a dash if the patient has no middle name)	____ - ____ -____

SAE or Safety Reporting questions, contact Genentech/Roche Safety:

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PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

Page 1 of ___

APPENDIX I PATIENT MEDICATION ADMINISTRATION DIARY

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Study #:_____
Patient ID"_____

Patient Medication Calendar

Patient Name: _____ Day 1 of Cycle: _____

			VENETOCLAX	IBRUTINIB	Comments
Cycle Day	Day of Week	Date	Time/ # of capsules	Time/ # of capsules	
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
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25					
26					
27					
28					

You will stop taking pills out of your current study medication bottles on the last day of the cycle. At your return appointment on Day 1 of each new cycle, always wait until you receive your new bottles of study medication before taking your dose for that day. Be sure to bring this calendar, the pill bottles, and all remaining pills with you for your return appointment. Return them to the research coordinator. Sign below. Thank you

Patient's Signature_____

For Official Use Only

Medication Dispensed _____ Date Dispensed_____