Oregon Health & Science University
OHSU Knight Cancer Institute
IRB Protocol #: 16140

Title: *A Phase I/II study of Syk inhibitor entospletinib (GS-9973) in combination with obinutuzumab in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and B-cell malignancies*

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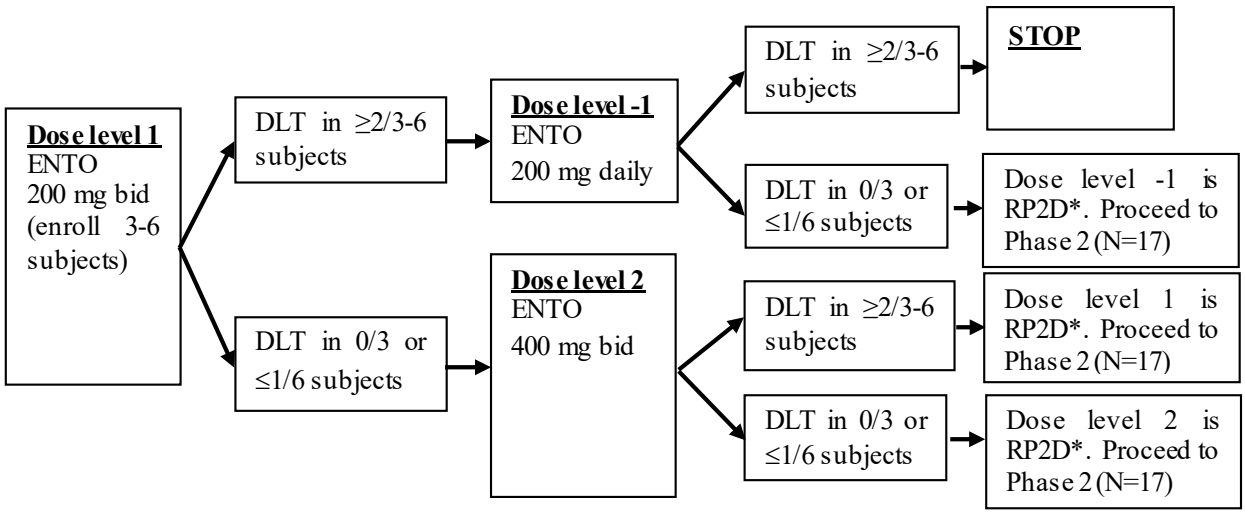
STUDY SCHEMA

Dose Level	Entospletinib (Cycles 1-12)	Obinutuzumab (Cycles 1-6) IV
-1*	200 mg daily	C1D1 – 100 mg; C1D2 – 900 mg C1D8 & 15 – 1000 mg C2-6 – 1000 mg on day 1
1	200 mg BID	
2	400 mg BID	

*Dose Level -1 will be studied only if more than one patient develops a DLT in Dose Level 1

Decision tree based on DLT's with cycle 1

(follow the Storer D 3+3 Phase I design; enroll between 3 and 6 subjects per dose level)



* The study will go back to the Phase I stage if 2 or more out of the first six subjects (including those treated in the Phase I) receiving the currently identified MTD experience DLT.

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1.0 STUDY OBJECTIVES

1.1 Primary Objective

1.1.1 Phase 1 (dose escalation):

To evaluate the safety and tolerability of entospletinib administered in combination with obinutuzumab in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and non-Hodgkin lymphoma (NHL), and identify the dose for phase 2 expansion

1.1.2 Phase 2:

To evaluate the efficacy of entospletinib in combination with obinutuzumab in patients with relapsed or refractory CLL/SLL, as measured by CR rate

1.2 Secondary objectives

Secondary endpoints of phase 2 portion of study are the following:

- Objective response rate (ORR, defined as complete remission, complete response with incomplete marrow recovery, partial remission and nodular partial response)
- Event free survival defined as the interval between the date of first study treatment and the date of objective signs of disease recurrence, subsequent anti-leukemic therapy, or death, whichever is first reported
- Safety and tolerability of entospletinib in combination with obinutuzumab by AEs

1.3 Exploratory objectives

- Peripheral blood B-cell depletion and recovery
- Pharmacodynamics effects of *in vivo* administration of entospletinib on NFκB activation and expression of anti-apoptotic proteins in CLL cells.
- Association of established biomarkers (chromosomal abnormalities, immunoglobulin heavy chain [*IGHV*] mutational status, p53 mutational status) with response (ORR and EFS) to ENTO in combination with obinutuzumab in patients with relapsed/refractory CLL

2.0 BACKGROUND

2.1 Study Disease – Non-Hodgkin lymphoma (NHL) and CLL

Non-Hodgkin lymphomas (NHL) are a heterogeneous group of malignancies arising from lymphoid tissue, with varied clinical and biological features. In 2008, there were an estimated 356,000 new cases of NHL and 192,000 deaths from NHL worldwide. NHL is the 8th most commonly diagnosed cancer in men and the 11th in women. Over 90% of NHL are B-cell type. B-cell NHL arise from the accumulation of monoclonal B lymphocytes in lymph nodes and often in organs such as blood, bone marrow, spleen, and liver. This group includes histopathologic varieties such as FL (follicular lymphoma), MZL (marginal zone lymphoma), MCL (mantle cell lymphoma), CLL/SLL, LPL (lymphoplasmacytic lymphoma), and DLBCL (diffuse large B-cell lymphoma). These disorders are characterized by lymphadenopathy, cytopenias, and sometimes induce life-threatening organ dysfunction. Patients may also have constitutional symptoms (fevers, night sweats, and/or weight loss) and fatigue. DLBCL is the most common type of NHL accounting for 30-40% all new diagnoses, whereas FL and MCL account for approximately 20-25% and 6-10% of new lymphomas, respectively.

Few patients with B-cell malignancies are cured with available therapies. The 3-year PFS is only 40% with activated B-cell (ABC) DLBCL compared to 74% with germinal center type (GC)-DLBCL. For patients refractory to primary therapy or who relapse and are not transplant candidates, few therapeutic options exist. For patients with the indolent NHL (FL, MZL, CLL/SLL, and LPL) the goal of first and subsequent

line therapies is to induce tumor regression and delay tumor progression in order to control disease-related complications and potentially extend life. Patients who require treatment are commonly given chemotherapeutic and/or immunotherapeutic agents. Although patients with indolent NHL and CLL can achieve durable remissions with front-line combination therapies, most patients will eventually experience disease relapse.

While considered a B-cell NHL, CLL is the most common leukemia in the Western Hemisphere. It is estimated that 15,720 men and women will be diagnosed with and 4,600 patients will die from CLL and its complications in 2016 [1]. The median age of a patient with CLL at diagnosis is 72 years, and 2/3 of cases are diagnosed among those aged 65 and older. Age adjusted incidence of CLL is estimated at 3.9/100,000 people, increasing to 22.3/100,000 among greater than 65 year olds and an estimated under-reporting of 10 to 30% of cases [2, 3]. Therapy of CLL has undergone significant evolution in the past two decades resulting in an improved survival of patients with this disease [4]. Alkylating agents and glucocorticoids were first used in treatment of CLL in the 1950's [5, 6]. Purine analogues (cladribine, fludarabine and pentastatin) were introduced in the 1980's. Development of rituximab and its subsequent FDA approval for treatment of NHL in 1997 introduced highly efficacious chemo-immunotherapy regimens which to this day remain the standard approach to initial therapy of younger fit patients with CLL [7]. FCR (fludarabine, cyclophosphamide, rituximab) leads to an overall response rate (ORR) of ~90% and a complete response rate (CR) of 30-72% when administered to previously untreated patients with CLL [7, 8]. Unfortunately, despite these improvements, the disease ultimately becomes resistant to standard chemo-immunotherapy approaches and therefore development of agents with novel mechanisms of action is imperative.

It has recently been recognized the survival of CLL cells is strongly dependent on the soluble mediators present in the lymph node and bone marrow microenvironment. Targeted therapies which disrupt signaling through the B-cell receptor (BCR)-associated kinases (BCRi) have been introduced in the clinic. Those therapies, in addition to direct cytotoxic effects, lead to partial disruption of the support niche, inducing cell egress into circulation, where they apoptose. Ibrutinib, a small molecule inhibitor of Bruton tyrosine kinase (BTK), and idelalisib, an inhibitor of phosphoinotiside-3 kinase δ (PI-3Kδ), have received FDA approval and are now a standard of care for both previously untreated (ibrutinib) and relapsed/refractory (ibrutinib, idelalisib) CLL [9]. Ibrutinib exhibited a remarkable single drug activity inducing responses in 71% of patients with relapsed/refractory CLL in a pivotal Phase Ib/II study [9]. However, complete responses were rare, and disease persisted in the lymph nodes and bone marrow despite daily administration of the drug. Most worrisomely, patients who progress on ibrutinib (~20% after 2 years of therapy) rapidly succumb to disease, with an estimated survival between 1 and 3 months [10-12]. Acquired resistance to ibrutinib due to mutations in BTK and phospholipase-Cγ (PLCγ) has now been documented in CLL as well as other B-cell malignancies [10, 13]. Still, such mutations do not account for all patterns of resistance and functional studies have already begun identifying additional mechanisms of resistance to BCRi's. Finally, FDA approved BCRi's are less efficacious, especially as single agents, in other lymphomas (FL, DLBCL, MCL), where responses are less common and are short-lived.

The only curative approach in CLL and indolent lymphomas currently involves allogeneic stem cell transplantation. This approach is associated with substantial morbidity and mortality in this older group of patients. As such, most patients are not eligible for transplant. Stem cell transplant recipients with CLL who experience a relapse have limited therapeutic options and an overall survival of 35 months; outcomes are worse in patients who do not have evidence of graft-versus-host disease [14]. Thus, novel combination therapy approaches are needed to induce deep and durable responses.

2.2. Study Agent (entospletinib, GS-9973)

Entospletinib (ENTO) is a potent and highly selective inhibitor of spleen tyrosine kinase (SYK) that is being developed by Gilead Sciences for oral administration in the treatment of hematologic malignancies and chronic graft versus host disease.

Studies have suggested a role for the dysregulation of SYK in B-cell malignancies. SYK is expressed in B-cells and is essentially involved in multiple signal transduction pathways downstream of the BCR. SYK trans-autophosphorylates and activates effector molecules such as PLCγ, PI-3K, and mitogen-activated protein kinase (MAPK), and their associated signaling pathways, to induce B-cell proliferation, survival, differentiation, and apoptosis. In B-cell malignancies, including CLL, the BCR can deliver antigen-independent signals that have also been postulated to require SYK activity. Therefore, inhibition of BCR-mediated SYK activity is an attractive therapeutic target, which could inhibit the proliferation and survival of malignant B cells. Preclinical evidence suggests that SYK inhibition may have independent benefit from BTK inhibition in B-cell malignancies.

2.2.1. Nonclinical Pharmacology - entospletinib

Entospletinib is an adenosine triphosphate (ATP) competitive inhibitor of SYK with an EC_{50} of 8.5±3.6 nM. Entospletinib binds in the ATP pocket of the SYK active site and disrupts the kinase activity of the enzyme. Kinase selectivity profiling showed a >14-fold selectivity of entospletinib for SYK versus 359 non-mutant kinases and no significant binding (< 50%) to 67 ion channels, transporters, and receptors screened at 1 μM entospletinib. No significant off-target or adverse pharmacological effects of clinical relevance were noted in preclinical evaluations.

Entospletinib was evaluated in a battery of safety pharmacology studies. The IC_{50} for the inhibitory effect of entospletinib on human ether-à-go-go-related gene (hERG) potassium current *in vitro* was estimated to be >1 μM. In dogs, entospletinib caused small increases in heart rates at doses ≥ 15 mg/kg, but had no effects on electrocardiograms (ECGs) or blood pressure at up to 150 mg/kg, the highest dose evaluated. Because entospletinib is 97.3% protein bound in human plasma and the total plasma concentration of entospletinib is in the 1 to 3 μM range, with a corresponding range of free entospletinib of 27 to 81 nM, it is unlikely that a clinically relevant effect on QT interval would occur.

No entospletinib-related effects were noted on neurological or respiratory function in rats at doses up to 1000 mg/kg.

2.2.2. Nonclinical Absorption, Distribution, Metabolism and Elimination

High bioavailability of entospletinib was observed in nonclinical studies. Consistent with this finding, entospletinib showed high permeability across Caco-2 monolayers and low potential for efflux. Despite high plasma protein binding, entospletinib had a moderate volume of distribution, close to that of total body water. The systemic clearance was low in rats, moderate in dogs, and moderate to high in monkeys.
Single-day dose escalation of entospletinib administered orally to rats, dogs, and monkeys showed a less than dose proportional increase in entospletinib systemic exposure in all species over the dose ranges tested.

Entospletinib showed good metabolic stability with human hepatic material in vitro. Therefore, clearance through metabolism in humans is expected to be low. The primary routes of metabolism of entospletinib involved oxidative opening of the morpholine ring as well as further oxidation or conjugation. In vitro data indicates entospletinib is primarily metabolized by CYP2C9 and to a lesser extent by CYP3A and CYP1A2. Metabolism followed by biliary excretion is likely the major route of elimination of entospletinib and its metabolites, as < 5% of the radiolabeled dose administered orally to rats was recovered in urine.

Entospletinib is an inhibitor of UGT1A1 and may transiently inhibit UGT1A1 activity in vivo at the expected clinical concentrations. Entospletinib is also an inhibitor of the uptake transporters OATP1B1 and OATP1B3 as well as the efflux transporters P-gp and BCRP with an IC_{50} value of approximately 2 µM for each of these transporters. Entospletinib may affect the activity of these transporters in vivo at the expected clinical concentrations and could transiently affect the disposition of other drugs, although high plasma protein binding (> 97%) may mitigate some of the potential drug-drug interactions at clinically relevant doses.

2.2.3. Nonclinical Toxicology

Entospletinib was well tolerated in single-dose studies at doses of 1000 mg/kg in dogs, and cynomolgus monkeys. In repeat-dose studies in rats, entospletinib was well tolerated for 14 days at doses of 1000 mg/kg/day and for 4 weeks at 50 mg/kg/day. In dogs, entospletinib was well tolerated for 7 days at 50 mg/kg/day and for 4 weeks at 10 mg/kg/day. In cynomolgus monkeys, entospletinib was well tolerated for 13 weeks at 100 mg/kg/day, which was the highest dose tested as dosing higher than that did not increase exposure. In rabbits, it was tolerated for 7 days at 300 mg/kg/day.

The target organ(s) of toxicity identified in rats was the duodenum (enteropathy), and in rabbits and dogs were predominantly the gastrointestinal tract (hemorrhage and/or inflammation) and lymphoid organs. No target organs were identified in the cynomolgus monkeys. Additional organs potentially affected in individual dogs at higher doses included gallbladder, pancreas (rabbits and dogs), urinary bladder, and epididymis. Gastrointestinal tract toxicity in rats, rabbits, and dogs was associated with decreased food consumption and/or decreased body weight or body weight gain. However, decreased food consumption and body weight changes, in rabbits and dogs also occurred at doses lower than those which showed histological evidence of gastrointestinal toxicity.

Increases in total and/or indirect bilirubin in rats, rabbits, and dogs were observed at ≥ 30 mg/kg/day and may have been due to the inhibition of the enzyme UGT1A1. As no histological evidence of hepatobiliary toxicity was noted concurrently with bilirubin increases in entospletinib-treated rats or dogs, and entospletinib levels above the IC50 for UGT1A1 were achieved in serum, this seems a plausible mechanism for the noted increases in bilirubin.

Hemorrhage and/or sinus erythrocytosis in lymph nodes with decreases in red cell mass in individual animals was noted in rabbits and dogs, but not in rats or cynomolgus monkeys. Although the mechanism for these changes is not clear, rodents with SYK deficiency or SYK-deficient bone marrow have been associated with hemorrhage, the latter in the presence of normal bleeding times, suggesting normal platelet function [15]. No evidence of altered coagulation parameters were noted at any dose level in the entospletinib nonclinical studies and no biologically relevant effects were noted in an in vitro study of platelet aggregation. Other inhibitors of SYK have been found to have no effect on platelet function at efficacious dose levels in patients with rheumatoid arthritis (RA) as determined by ex vivo assays, and similarly, SYK inhibition has not been found to affect bleeding time in rodents [16].

Adverse effects on lymphoid tissues including spleen, lymph nodes, and/or the thymus were noted in rabbits and dogs, but not in rats or cynomolgus monkeys despite higher exposures achieved. Recently, published data demonstrated that species-specific lymphoid changes can occur in dogs, but not in rats, cynomolgus monkeys, or humans treated with small molecule kinase inhibitors that inhibit pathways that overlap with SYK signaling pathways [17]. Lymphoid toxicity also occurs in dogs treated with p38α MAPK inhibitors, but not in rats or cynomolgus monkeys despite higher exposure levels achieved in these species. There has been no evidence of significant immune-toxicity in clinical trials with p38α MAPK inhibitors. The relevance of the findings in rabbits and dogs to humans is unknown.

Entospletinib was negative in bacterial mutation, in vitro chromosomal aberration, and rat micronucleus assays and is considered non-genotoxic. Dose-range finding embryo-fetal developmental toxicity studies have been completed in rats and rabbits. Maternal toxicity was demonstrated by dose-dependent decreases in the body weight gains of the dams. Dose-dependent developmental findings included increased incidence of early and late fetal resorptions at 500 mg/kg/day (rat only) and reduced fetal weights (500 and ≥ 15 mg/kg/day; rats and rabbits, respectively) which correlated with the maternal toxicity.

2.2.4. Clinical Trials

Entospletinib has been administered to 540 subjects (328 healthy subjects, 7 subjects with rheumatoid arthritis, 76 subjects with CLL, and 155 subjects with NHL) in 11 Phase 1 and Phase 2 clinical studies. Single agent efficacy has been demonstrated with entospletinib in subjects with relapsed or refractory hematologic malignancies (CLL/SLL, MCL, DLBCL, FL, LPL, or MZL). PFS rates are 70.1% (95% CI: 51.3%, 82.7%) at 24 weeks for subjects with CLL (n=41) and 50.2% (95% CI: 29.3%, 67.9%) at 24 weeks in subjects with FL (n=41). The most common AEs (observed in ≥ 15% of subjects) in hematology patients receiving entospletinib alone (n = 186) include fatigue (52.5%), nausea (43.3%), diarrhea (40.8%), decreased appetite (27.1%), constipation (23.8%); cough (22.5.0%), dizziness (19.6%), pyrexia (18.8%), vomiting (18.3%), headache (17.9%), dyspnea (16.7%), insomnia (15.8%), dehydration (15.0%), and upper respiratory infection (15.0%). Thirty four subjects (14.2%) reported an AE of rash.

Entospletinib is expected to produce *asymptomatic and transient elevations of indirect bilirubin* due to inhibition of UGT1A1. In studies of subjects with hematologic malignancies, 9 of 252 subjects had elevations of direct bilirubin with the onset of elevation ranging from Day 8 to 85, except for 1 subject at Day 169. Bilirubin elevations were generally self-limited and did not result in discontinuation of entospletinib.

In a phase 2, open label study evaluating the efficacy, safety, tolerability, and pharmacodynamics of the combination of entospletinib and idelalisib administered twice daily over multiple 28 day cycles to subjects with relapsed or refractory lymphoid malignancies, pneumonitis was reported in 12 of 66 subjects (18.2%), leading to the discontinuation of further evaluation of this combination [18]. All subjects were to receive treatment with entospletinib and idelalisib twice daily under fasted conditions and the study allowed intra-subject dose escalations every 2 weeks. Of the 12 pneumonitis AEs, 11 (91.7%) were SAEs, 7 were Grade 3, 2 were Grade 4, and 2 were Grade 5. The protocol was amended to allow a subset of subjects to receive monotherapy with entospletinib after a 14 to 28 day washout period with no subsequent cases of pneumonitis reported. Pneumonitis has *not* been identified as a risk with entospletinib monotherapy.

2.3. Obinutuzumab (GA101, Gazyva™)

Obinutuzumab (GA101, RO5072759, Gazyva®, Gazyvaro®) is a humanized glycoengineered type II anti-CD20 monoclonal antibody (mAb) being developed by Genentech for the treatment of various hematologic malignancies. Obinutuzumab (Gazyva®) was approved in the U.S. on 1 November 2013 for use in combination with chlorambucil for the treatment of patients with previously untreated CLL. In Europe, obinutuzumab (Gazyvaro®) was approved on 25 July 2014 for use in combination with chlorambucil for the treatment of adult patients with previously untreated CLL and comorbidities making them unsuitable for full-dose fludarabine-based therapy.

Obinutuzumab is also undergoing Phase III evaluation in NHL in combination with chemotherapy.

2.3.1. Structure and Mechanism of Action of Obinutuzumab

Obinutuzumab is characterized by high-affinity binding to a CD20 epitope that is different from the epitope targeted by rituximab, which is currently the widely used anti-CD20 monoclonal antibody [19, 20]. Obinutuzumab was derived by humanization of the parental B-Ly1 mouse antibody and subsequent

glycoengineering leading to the following characteristics: high affinity binding to the CD20 antigen, high antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP); low complement-dependent cytotoxicity (CDC) activity; and high direct cell death induction. Nonclinical studies with obinutuzumab in comparison with rituximab show significantly greater ADCC and ADCP, increased direct cell–death induction, and low CDC. Superior efficacy to rituximab has been demonstrated in various human lymphoma xenograft models [19, 21].

2.3.2. Clinical Experience with Obinutuzumab

Obinutuzumab is approved for use in combination with chlorambucil in previously untreated CLL on the basis of data from the Phase III study BO21004/CLL11 [22]. Obinutuzumab is also undergoing Phase III evaluation in NHL in combination with chemotherapy.
For the most up-to-date information on obinutuzumab, please refer to the current version of the Investigator's Brochure.

2.3.2.1. Clinical Pharmacology

The clinical pharmacology properties of obinutuzumab have been characterized in a number of clinical studies in patients with CLL or NHL. These studies include two Phase I/II monotherapy studies (BO20999 and BO21003); two Phase I monotherapy studies in Japanese patients with NHL (JO21900) and Chinese patients with FL, DLBCL, or CLL (YP25623); two Phase Ib combination studies (BO21000 and GAO4779g); two Phase II studies (a combination Study GAO4915g and a monotherapy Study GAO4768g at 1000 mg and 2000 mg); and two Phase III combination studies (BO21004/CLL11 and GAO4753g). A serum sampling scheme for the quantitation of obinutuzumab was undertaken in these studies to enable population PK analysis, which demonstrated that a two-compartment PK model comprising both a linear clearance pathway and a non-linear time-varying clearance pathway adequately described serum obinutuzumab concentration data. The initial clearance of obinutuzumab was $> 2 \times$ higher than the steady-state clearance, which is consistent with a decrease in the time-varying clearance component, which is high at the start of treatment and declines with repeated cycles of obinutuzumab treatment. The time-varying clearance pathway is consistent with target-mediated drug disposition such that, at the start of treatment when there is a large quantity of CD20-positive cells, it binds obinutuzumab. With repeated dosing of obinutuzumab, the pool of CD20-positive cells is saturated, thereby reducing this component in clearance. The linear clearance pathway is consistent with catabolism of IgG antibodies and is therefore independent of CD20-positive cells. Analysis further supports the need to minimize the time-varying clearance component quickly and has led to the proposed dose and regimen of 1000 mg in both induction and extended treatment.

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

2.3.2.2. Clinical Experience of Obinutuzumab in Chronic Lymphocytic Leukemia

Study BO20999 (GAUGUIN; NCT00517530) (Phase I)
BO20999 was an open-label, multicenter, Phase I/II study to explore obinutuzumab safety and activity in relapsed/refractory NHL and CLL. Thirteen CLL patients have received obinutuzumab at doses with a range of 400–2000 mg (given as a flat dose) across four cohorts. There were no dose-limiting toxicities (DLTs) and no requirement for dose reductions. Infusion-related reactions (IRRs) occurred in all CLL patients and were characterized predominantly by National Cancer Institute Common Terminology Criteria

(NCI-CTC) Grade 1–2 toxicities: chills, nausea, vomiting, fever, pyrexia, hypertension, hypotension, dyspnea, and dizziness. Two patients experienced four NCI-CTC Grade 3 toxicities: sweats, flushing, asthenia, and hepatic cytolysis.

Although the safety profile appears otherwise similar between NHL and CLL, there was an increase in NCI-CTC v3.0 Grade 3–4 neutropenia noted in CLL patients, which were observed in 9 patients across the four dose levels administered. Five patients experienced NCI-CTC Grade 4 neutropenia and 4 patients experienced NCI-CTC Grade 3 neutropenia as the maximum severity. Of the 9 patients, 7 had one NCI-CTC Grade 3–4 event and 2 patients experienced more than one event. Granulocyte colony-stimulating factor (G-CSF) support was administered to 6 of the 9 patients, and these patients responded quickly to G-CSF support. For the 3 patients who did not receive G-CSF, neutrophil counts normalized spontaneously. Furthermore, it is important to note that these neutropenia events did not appear to be accompanied by a higher incidence of infections. No deaths were reported in Phase I of this study for CLL. As assessed by the International Workshop on CLL (IWCLL) criteria, the end-of-treatment response rate with obinutuzumab monotherapy was 62% (8 of 13 patients with partial response [PR]).

Study BO20999 (GAUGUIN; NCT00517530) (Phase II)
Twenty patients with relapsed/refractory CLL have received 1000 mg of obinutuzumab. The most commonly reported adverse event (AE) during the treatment period was IRR, reported in 19 (95%) of 20 patients. Fifteen patients experienced Grade 3–4 AEs of whom 14 patients had treatment-related Grade 3–4 AEs (investigator assessment). Treatment-related Grade 3–4 AEs were IRR (6 patients), neutropenia (4 patients), lymphopenia (2 patients), thrombocytopenia (2 patients), and anemia, pure red cell aplasia, pancytopenia, febrile neutropenia, herpes zoster, and interstitial lung disease (1 patient each). Eleven serious adverse events (SAEs) in 9 patients were reported during treatment, 9 of which were assessed by the investigator as related to obinutuzumab: IRR (4 patients) and febrile neutropenia, pancytopenia, pure red cell aplasia, interstitial lung disease and pyrexia (1 patient each). Three patients withdrew from further study treatment after the first infusion due to IRR. One death has been reported during follow-up from colon cancer. The most common AE in follow-up was nasopharyngitis, reported in 2 patients. End-of-treatment response assessment showed that three patients (15%) achieved a clinical response.

Study BO21003 (GAUSS; NCT00576758) (Phase I)
BO21003 is an open-label, dose-escalating, multicenter Phase I/randomized Phase II study in patients with relapsed/refractory CD20+ malignant disease. In Study BO21003, 5 CLL patients have been administered obinutuzumab. The fifth patient withdrew at Cycle 1, Day 1 because of a Grade 4 IRR, which occurred minutes after the start of infusion in the setting of high tumor burden. Efficacy assessments are available for only the 4 patients who completed treatment (received 4 cycles of infusion). The end-of-treatment response in patients with CLL receiving obinutuzumab monotherapy in this study included 3 stable disease and 1 progressive disease.

Study GAO4768g / GAGE / NCT01414205 (Phase II)
GAO4768g is an open-label, randomized, multicenter, Phase II study evaluating the efficacy and safety of obinutuzumab administered at 1000 mg versus 2000 mg doses in patient with previously untreated CLL. The results of the GAGE study were recently presented at the 2014 annual meeting of the American Society of Clinical Oncology.

Eighty patients were randomized and stratified based on Rai stage and tumor mass.

For patients who received the 1000-mg doses, obinutuzumab was administered with three 1000-mg doses in the first 21-day cycle (the first 1000-mg dose was administered over 2 days: 100 mg administered on Day 1, 900 mg administered on Day 2; 1000 mg was administered on both Days 8 and 15). In the subsequent cycles (2–8), 1000 mg of obinutuzumab was administered on the first day of each cycle.

For patients who received the 2000-mg doses, obinutuzumab was administered as follows: 100 mg on Cycle 1, Day 1; 900 mg on Day 2; and 1000 mg on Day 3. On Days 8 and 15 of Cycle 1, 2000 mg was administered on each day. For Cycles 2–8, 2000 mg of obinutuzumab was administered on Day 1 of each cycle.

ORR was assessed at 2 months post-therapy according to the IWCLL criteria. The ORR for the 1000-mg and 2000-mg obinutuzumab treatment arms were 49% compared with 67%, respectively; 2-sided p = 0.0779. Complete response/complete remission with incomplete blood count recovery (CR/CRi) were achieved by 5% of patients (2/41) in the 1000-mg arm compared with 21% of patients (8/39) in the 2000-mg arm.

The most common Grade 3/4 AEs were neutropenia (11/40 patients [27.5%] in the 1000 mg arm and 12/38 patients 31.6% in the 2000 mg arm) and thrombocytopenia (6/40 patients [15%] in the 1000 mg arm and 5/38 patients [13.2%] in the 2000 mg arm). Grade 3/4 anemia was experienced by 6/38 patients (15%) in the 1000 mg arm and 2/38 patients 5.3% in the 2000 mg arm.

Study GAO4779g (GALTON; NCT01300247) (Phase II)
GAO4779g is an open-label, non-randomized, multicenter, Phase II study. In the GALTON study, 41 patients with untreated CLL were treated with obinutuzumab 1000 mg (100 mg IV on Day 1, 900 mg on Day 2, and 1000 mg on Days 8 and 15 of Cycle 1; 1000 mg on Day 1 in Cycles 2–8) and either fludarabine + cyclophosphamide (G-FC; 25/250 mg/m2 IV on Days 2–4 of Cycle 1, then on Days 1–3 of Cycles 2–6) or bendamustine G-B; 70 mg/m2 IV on Days 2–3 of Cycle 1, then on Days 1–2 of Cycles 2–6). Each cycle was 28 days long.

In the G-FC arm, 6/21 patients (29%) experienced an SAE, most frequently febrile neutropenia (14%); all other events were isolated events and were mostly infectious in nature (3 patients each had one serious infection; pneumonia, cellulitis and appendicitis). The incidence of AEs which lead to withdrawal of any treatment was 33% with 7/21 experiencing mostly hematological events (neutropenia [2 patients], pancytopenia [1 patient] and thrombocytopenia [1 patient]).

Seventeen of the 21 patients (81%) treated with G-FC experienced 39 related Grade 3-4 AEs, most frequently neutropenia (5 patients [23.8%]), followed by alanine transaminase increase (4 patients [19.0%]), IRRs (3 patients [14.3%]), febrile neutropenia (3 patients [14.3%]), thrombocytopenia (3 patients [14.3%]) and anemia (3 patients [14.3%]).

All patients experienced at least one AE, most frequently IRR (76.2%), nausea (76.2%), fatigue (57.1%), and constipation (47.6%).

Overall, obinutuzumab can be administered with FC, the combination is manageable. Hematologic events were the most frequent cause of treatment withdrawals of obinutuzumab or FC. IRR (all grade) occurred in 76% of patients. These events were managed with dose interruption and only one patient withdrew from obinutuzumab treatment for this reason.

In the G-benda arm, 11 patients (55.0%) experienced an SAE, most frequently IRRs (15%), febrile neutropenia (10%) and pyrexia (10%); all other events were isolated events. The incidence of AEs which led to withdrawal of treatment was 10% with 2/20 patients experiencing neutropenia.

Grade 3-4 AEs were experienced by 85% (17/20) of patients, most frequently neutropenia (50%), thrombocytopenia (15%), febrile neutropenia (10%) and erythema (10%).

All patients experienced at least one AE, most frequently IRR (70.0%), nausea (65.0%), diarrhea (50.0%), neutropenia (50.0%), and pyrexia (45.0%).

Overall, obinutuzumab can be administered with bendamustine, the combination is manageable. IRRs (all grade) occurred in 90% of patients. These events were managed with dose interruption and no patient withdrew from any treatment for this reason.

The ORR was 62% (CR, 2; CRi, 3; PR, 8) in patients who received G-FC and 90% (CR, 4; CRi, 5; PR, 9) in patients who received G-B, including 6 patients (G-FC, n=4; G-B, n=2) not evaluable due to inadequate response evaluation. Four patients in the G-FC arm (0 in G-B) had stable disease during and after therapy. No patient progressed during the study.

Study BO21004 (CLL11; NCT01010061) (Phase III)
This is an open-label, multicenter, three-arm randomized, Phase III study to compare the efficacy and safety of obinutuzumab + chlorambucil (GClb), rituximab + Clb (RClb), or Clb alone in previously untreated CLL patients with comorbidities. BO21004 enrolled 781 patients and an additional 6 patients during a safety run-in period before randomization.

This study included a safety run-in period before randomization. During the run-in period, 6 patients received obinutuzumab in combination with Clb for up to 6 cycles. All 6 patients have completed treatment and are in follow-up; the safety data for these patients are not reported but are consistent with the safety data of the randomized patients in this study. In Stage 1, patients were randomized in a 2:2:1 ratio to GClb (238 patients), RClb (233 patients) or to Clb alone (118 patients). In Stage 2, the randomization continued in a 1:1 ratio to GClb and RClb for an additional 190 patients; 663 patients (330 patients randomized to the RClb arm and 333 patients randomized to the GClb arm) were included in this Stage 2 analysis. The safety data from Stage 2 is presented in this section since all randomized patients who received obinutuzumab are included.

The incidence of death was 22.9% in the GClb arm and 28.0% in the RClb arm.

Fatal AEs occurred in 5.7% and 7.5% of patients in the GClb and RClb arms, respectively. The type and number of fatal AEs was balanced between the treatment arms with the exception of cardiac disorders which occurred in 6/321 patients (1.9%) RClb arm compared with 2/336 patients (0.6%) in the GClb arm. The incidence of SAEs in the GClb and RClb arms was 42.0% and 36.8% respectively, the incidence of Grade 3-4 AEs was 70.5% and 56.7% respectively, and the incidence of AEs leading to withdrawal of any study medication was 20.2% and 15.3%, respectively.

Imbalances between the treatment arms in AEs, SAEs and Grade 3-5 AEs was mainly due to IRRs, which occurred primarily during the first infusion of obinutuzumab. IRRs were experienced by 238/336 patients (70.8%) who received GClb and led to the treatment withdrawal of 27/336 patients (11.3%). To a lesser extent, differences between the treatment arms are also attributable to differences in the incidence of Grade 3-5 AEs within the body system “Blood and Lymphatic System”.

Study BO21004 includes two separate stages evaluating efficacy and the primary endpoint is progression-free survival (PFS). Stage 1 evaluated obinutuzumab + chlorambucil compared with chlorambucil alone.
In the Stage 1 analysis, median PFS of chlorambucil vs. obinutuzumab + chlorambucil was 11.2 vs. 27.2 months, respectively, (median observation time, 22.8 months; hazard ratio [HR], 0.19 [0.14–0.27]; $p < 0.0001$; stratified log-rank test) as assessed by independent review and is consistent with investigator-assessed PFS.

In the Stage 2 analysis of this study, the median PFS was 26.7 months vs. 14.9 months for obinutuzumab + chlorambucil vs. rituximab + chlorambucil, respectively with a median observation time of 18.7 months (HR: 0.42, 95% CI: 0.33-0.54, p-value < 0.0001). The ORR was 80% vs. 66%, and CR was 26% vs. 9%, respectively.

In the comparison of obinutuzumab + chlorambucil vs. chlorambuil alone, the most common AEs (all grades, Grades 3–4), respectively, were IRRs (69% vs. 0, 21% vs. 0), neutropenia (40% vs. 18%, 34% vs. 16%), thrombocytopenia (15% vs. 7%, 11% vs. 3%), anemia (12% vs. 10%, 4% vs. 5%), leukopenia (7% vs. 0, 5% vs. 0), pyrexia (10% vs. 7%, < 1% vs. 0), and cough (10% vs. 7%, 0 vs. < 1%). Hematologic laboratory abnormalities (all grades, Grades 3–4) with obinutuzumab + chlorambucil vs. chlorambucil alone, respectively, were neutropenia (77% vs. 53%, 46% vs. 27%), lymphopenia (80% vs. 9%, 40% vs. 2%), leukopenia (84% vs. 12%, 36% vs. < 1%), and thrombocytopenia (47% vs. 50%, 14% vs. 11%).

Non-hematologic laboratory abnormalities (all grades, Grades 3–4) with obinutuzumab + chlorambucil vs. chlorambucil alone, respectively, were hypocalcemia (32% vs. 29%, 3% vs. < 1%), hyperkalemia (31% vs. 17%, 5% vs. 2%), hyponatremia (29% vs. 11%, 8% vs. 22%), AST (SGOT increased; 28% vs. 12%, < 1% vs. 0), creatinine increased (28% vs. 18%, < 1% vs. < 1%), ALT (SGPT increased; 25% vs. 14%, < 1% vs. 0), hypoalbuminemia (22% vs. 14%, < 1% vs. < 1%), alkaline phosphatase increased (16% vs. 11%, 0 vs. 0), and hypokalemia (13% vs. 4%, 1% vs. < 1%) ([22]; Obinutuzumab USPI).

For more information related to safety and efficacy in the CLL indication, please refer to the Obinutuzumab Investigator's Brochure or the Obinutuzumab USPI.

2.3.2.4. Clinical Experience of Obinutuzumab in NHL

As of 2 July 2015, obinutuzumab has been administered to 2105 patients with NHL in 4 monotherapy studies and 6 combination therapy studies. The combination therapy studies include the following:

Study BO21000 (GAUDI): A Phase Ib, open-label study of obinutuzumab in combination with CHOP, fludarabine/cyclophosphamide (FC), or bendamustine in patients with CD20+ B-cell FL. A total of 137 patients were enrolled, including 56 with R/R disease (obinutuzumab + FC: n = 28; obinutuzumab + CHOP: n = 28) and 80 first-line patients (obinutuzumab + bendamustine: n = 41; obinutuzumab + CHOP: n = 40).

Study GAO4915g (GATHER): A Phase II, open-label study of obinutuzumab + CHOP in previously untreated advanced DLBCL. A total of 100 patients were enrolled.

Study GAO4753g (GADOLIN): A Phase III study of obinutuzumab + bendamustine (G-benda) vs. bendamustine alone in patients with rituximab-refractory CD20+ indolent NHL (iNHL). A total of 194 patients were randomized to the G-benda arm and 202 to bendamustine arm.

Study BO21223 (GALLIUM): A Phase III study of G-chemo vs. R-chemo in patients with advanced iNHL. Enrollment to the study has completed with 1401 enrolled patients; the study is ongoing.

Study BO21005 (GOYA): A Phase III study of G-CHOP vs. R-CHOP in patients with previously untreated CD20+ DLBCL. Enrollment to the study has completed with 1418 enrolled patients; the study is ongoing.

Study JO29737 (GATS): A Phase II, open-label study of obinutuzumab (shorter duration of infusion) in patients with CD20+ NHL. Enrollment is ongoing, with 14 patients enrolled (planned enrollment of 36).

In the monotherapy setting (studies BO20999, BO21003, YP25623, and JO21900), the proportion of patients who had a response (CR or PR) at the end of treatment ranged from 28% (11/40 patients) to 58% (7/12 patients). Although patients had treatment-refractory (including rituximab-refractory) or relapsed disease, some patients in studies BO20999, BO21003 (Phase II), and JO21900 achieved a CR by the end of treatment assessment.

In the chemotherapy combination studies BO21000 and GAO4915g, the proportion of patients achieving a response exceeded 90% among FL patients and was 82% among DLBCL patients. The CR rate was also higher (35%–50% of patients with FL and 55% of patients with DLBCL) than in the monotherapy studies. Data from the pivotal chemotherapy combination Phase III study (GAO4753g) in patients with FL showed that treatment with G-benda for 6 cycles (28 days per cycle) followed by 2-year monotherapy with obinutuzumab resulted in a clinically meaningful and statistically significant increase in PFS compared with bendamustine alone. The primary objective of the study was to evaluate PFS as determined by an Independent Review Committee (IRC). Median observation time was 21.1 months. The median IRC-assessed PFS in the bendamustine arm was 13.8 months. Median IRC-assessed PFS was not reached in the G-benda arm (PFS hazard ratio [HR] = 0.48, 95% CI: 0.34–0.68; stratified log-rank test p-value < 0.0001). The investigator-assessed PFS result was consistent with the IRC-assessed PFS. The median investigator-assessed PFS in the bendamustine arm was 13.7 months, and the median in the G-benda arm was 29.2 months (PFS HR = 0.48, 95% CI: 0.35–0.67; stratified log-rank test p-value < 0.0001). IRC-assessed best ORR within 12 months from the start of treatment was 78.7% in the G-benda arm (15.5% CR and 63.2% PR) and 74.7% (18.7% CR and 56.0% PR) in the bendamustine arm. An analysis conducted with 24.1 months of median observation time revealed that the median OS was not yet reached in either arm.

2.3.3. Overview of Safety of Obinutuzumab

As of 2 July 2015 (the safety data cutoff date for all studies except MO28543), obinutuzumab has been administered to a total of 3386 patients, including 1281 patients with CLL and 2105 patients with NHL, from doses of 50 mg to 2000 mg in monotherapy or in combination with CHOP, FC, bendamustine, or chlorambucil (Clb). Overall, the safety of monotherapy obinutuzumab, or obinutuzumab combination therapy with CHOP, FC, bendamustine, or Clb, was manageable.

The most frequent causes of death were disease progression and adverse events of infectious diseases. This is consistent with the study population and the disease being treated.

Of particular interest, IRRs were observed consistently in all obinutuzumab trials. In patients with CLL (study BO21004), the highest incidence of IRR was at the first infusion with the incidence decreasing rapidly with subsequent infusions. The incidence of IRR observed with combination therapy (FC, CHOP, or bendamustine) appears similar to that observed with monotherapy. Furthermore, the incidence of IRR appears to be higher with CLL compared with NHL, and higher in patients who received obinutuzumab compared with patients who received rituximab based on evidence from studies BO21003 and BO21999. There is no clear relationship between obinutuzumab dose and the incidence of IRR based on data from Study GAO4768g. In Stage 2 of the pivotal Phase III study, BO21004, investigating G-Clb vs. R-Clb in patients with CLL, the incidence of IRR, Grade 3–4 IRR, and IRR leading to discontinuation was higher in G-Clb arm compared with the R-Clb arm. This study implemented several measures to minimize the risk of IRRs, including: use of corticosteroids, withdrawal of antihypertensive treatments, slow infusion, and split dosing. The evidence suggests that these risk-minimization measures decreased the risk of IRRs (all grades); however, the impact on the incidence of Grade 3–4 events and treatment discontinuations due to IRRs was limited. In the pivotal study GAO4753g in patients with R/R iNHL, the majority of IRRs were Grade 1 or 2 and there were no fatal (Grade 5) IRRs. The overall incidence of IRRs was higher in the G-benda arm compared with the bendamustine arm (69% vs. 63%), as was the incidence of Grade 3–4 IRRs (11% vs. 6%), serious IRRs, IRRs leading to withdrawal from treatment, dose reductions, or dose interruptions.

In Study GAO4753g, the most common adverse reactions (incidence ≥ 10%) observed in patients with iNHL in the G-benda arm were IRRs, neutropenia, nausea, fatigue, cough, diarrhea, constipation, pyrexia, thrombocytopenia, vomiting, upper respiratory tract infection, decreased appetite, arthralgia, sinusitis,

anemia, asthenia, and urinary tract infection. The most common Grade 3–4 adverse reactions (incidence ≥ 10%) observed in patients with iNHL in the G-benda arm were neutropenia, thrombocytopenia, and IRRs. Due to the pharmacological class of obinutuzumab, as well as the evidence from monotherapy Phase I trials and chemotherapy combination trials GAO4779g (Phase I) and BO21004 (Phase III), the Sponsor considers acute thrombocytopenia and thrombocytopenia to be related to obinutuzumab. The main risk associated with thrombocytopenia is hemorrhage. In study BO21004, the overall incidence of hemorrhagic adverse events was comparable between the treatment arms (8.0% G-Clb; 7.2% R-Clb), with the majority of events being of Grade 1 or 2 severity. However, and importantly, all fatal hemorrhagic events in the G-Clb arm occurred in Cycle 1 in contrast to such events in the R-Clb arm, which occurred later (beyond 1 year after first administration of study drug). In the pivotal study GAO4753g in patients with R/R iNHL, the overall incidence of hemorrhagic events was 11% in the G-bendamustine arm and 10% in the bendamustine arm. No fatal hemorrhagic events occurred in the study. Grade 3–4 hemorrhagic events were similar in both treatment arms (5% in the G-bendamustine arm and 3% in the bendamustine arm).

adverse events of special interest include IRRs, TLS, thrombocytopenia (including acute thrombocytopenia), neutropenia (including late-onset and prolonged neutropenia), prolonged B-cell depletion, infections including progressive multifocal leukoencephalopathy (PML) and hepatitis B virus (HBV) reactivation, worsening of pre-existing cardiac conditions, gastrointestinal (GI) perforation, and second malignancies. Details on the safety concerns and mitigation plan for obinutuzumab are provided in Section 5.3.2.

2.3.4. Summary of Pharmacokinetic and Pharmacodynamic Data for Obinutuzumab

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

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

2.4 Study and Dose Rationale

Targeting kinases within the BCR signaling pathways in CLL and B-cell malignancies has become standard of care in the clinic. Ibrutinib and idelalisib, targeting BTK and PI3K, respectively, have received FDA approvals in CLL (both drugs), MCL, LPL (ibrutinib) and FL (idelalisib). However, kinase inhibitors rarely induce complete responses, and daily lifelong administration is required to maintain drug activity [9]. Reports of ibrutinib resistance due to mutations in the drug-binding cysteine in BTK have now emerged [10, 23]. Moreover, alternate mechanisms of resistance may account for reduced efficacy of the BCR-targeting agents. For example, *in vitro* data suggest that upregulation of the PI3Kα isoform might rescue

lymphoma cells from idelalisib, a PI3Kδ-specific inhibitor [24]. Entospletinib is a novel BCRi which targets Syk, a kinase located upstream of both BTK and PI3K in the BCR signaling cascade. Thus, entospletinib may not only serve a therapeutic alternative for patients with CLL and NHL, but also may be a potential therapy for patients who progress on currently available BCRi's.

Taking into account emerging resistance to BCRi, persistence of residual disease and ability of CLL cells to re-populate their niche, we recently proposed that targeting multiple compartments within the niche as well as targeting CLL cells outside of the lymph node through a rationally designed multidrug regimen may be the optimal approach required to achieve deep and long-lasting therapeutic effects in CLL [25]. This protocol addresses this need, combining a novel BCRi with a second-generation highly effective therapeutic antibody which targets CD20 (obinutuzumab).

2.4.1 Rationale for Syk inhibition in CLL

BCR is a transmembrane receptor complex which incorporates a surface immunoglobulin associated with a signal transduction moiety (CD79A/B). BCR signaling results in distinct outcomes in B-cell fate depending on its developmental stage. Signaling through BCR modulates clonal expansion in pre-B-cells, induces apoptosis of immature B-cells and, by contrast, growth and proliferation of mature B-cells. Other cell surface receptors (e.g., CD19, CD40) are able to modulate BCR signaling, providing both inhibitory and activating co-stimuli [26].

In a normal B-cell, BCR crosslinking mediates approximation of Src family protein kinases, i.e. Lyn, Fyn and Blk, to the intracellular tyrosine activation motifs (ITAMs) on CD79A/B, leading to recruitment and phosphorylation of SYK, a SH2-domain containing kinase. SYK phosphorylation is the key act in BCR signaling, without which further signal transmission cannot occur. SYK recruits a plasma membrane-associated signaling complex with involvement of several tyrosine kinases (including BTK) and adaptor molecules (such as Bcell linker protein [BLNK]). The complex signals to activate PLCγ and Ras. Ras binds to and activates Raf kinase which then propagates the signal down to extracellular regulated kinase (ERK). Meanwhile, PLCγ leads to activation of mitogen-activated protein kinase (MAPK) kinases (e.g., ERK, c-Jun NH_2-terminal kinase (JNK) and p38 MAPK) and transcription factors (e.g., Myc and NFκB). In parallel, association of CD19 with Lyn and PI-3K leads to activation of Akt.

Fostamatinib disodium (R788, Rigel Pharmaceuticals) is an ATP-competitive non-selective SYK inhibitor [16]. Fostamatinib has been investigated in a Phase I/II study in patients with relapsed NHL, leading to an ORR of 55% in CLL and 11% in MCL [27]. While the development of fostamatinib was halted, alternative SYK inhibitors demonstrate promising pre-clinical activity in CLL [28].

Entospletinib (GS-9973) is a novel selective SYK inhibitor (Gilead Sciences). Entospletinib inhibited phosphorylation of multiple kinases involved in B-cell activation and BCR signaling, from membrane proximal sites (pBLNK, pPLCγ2, pPYK2) to distal sites (pAKT, pMEK, pERK, pS6RP) with EC50s ≤ 200 nM, in multiple cell lines in vitro and inhibited chemokine release. Detailed description of pre-clinical studies may be found in Investigator's Brochure.

There is now a strong clinical rationale to pursue development of entospletinib in CLL. In a Phase II study of entospletinib in patients with relapsed/refractory CLL/SLL, responses were achieved in 61% of patients, with a progression-free survival (PFS) of 70% at 24 weeks [29]. Entospletinib is well tolerated and common grade ¾ laboratory abnormalities included neutropenia (14.5%) and reversible elevations of transaminases (13.4%), while colitis and pneumonitis have not been described. Importantly, entospletinib has shown activity in high risk CLL with responses observed independent of adverse prognostic features, including *IGHV* mutations and chromosomal abnormalities (del11q, del17p). Importantly, entospletinib has now

demonstrated efficacy in patients with CLL who received prior therapy with BCRi (Sharman JP et al., ASH 2015).

Finally, research performed in Dr. Danilov's laboratory demonstrates that SYK inhibition disrupts the cross-talk between the BCR and other pro-survival signals emanating from the tumor microenvironment. In our laboratory we mimicked the CLL lymph node niche by establishing a unique co-culture model of primary patient-derived CLL cells with BAFF ("B-cell activation factor")-expressing CHO cells. Soluble BAFF and APRIL ("a proliferation inducing ligand") are indispensable in survival of both normal and neoplastic B cells and BAFF receptor is highly expressed in CLL [30]. We found that when co-cultured with BAFF-expressing stromal cells, but not with control stroma, CLL cells were resistant to spontaneous apoptosis and chemotherapy (fludarabine, bendamustine). BAFF-stimulated CLL cells upregulated NFκB (Appendix F, Fig. 1) and the anti-apoptotic proteins Mcl-1 and Bcl-X. However, entospletinib induced apoptosis of BAFF-stimulated CLL cells in this model (Appendix F, Fig. 2). Importantly, entospletinib blocked BAFF signaling-induced activation of NFκB (Fig. 3) and abrogated BAFF-BCR crosstalk. Inhibition of SYK, but not BTK or PI-3K, downregulated the pro-survival Mcl-1 in BAFF-stimulated CLL cells (Appendix F, Fig. 4).

2.4.2 Rationale for dose selection (entospletinib)

The initial dose level tested is proposed to be 200 mg of entospletinib administered twice daily combined with the FDA-approved dosing of obinutuzumab.

Entospletinib has been well tolerated at doses of up to 800 mg twice daily in patients with CLL using first formulation (Mono-MSA ENTO) [29]. The dose and schedule used in the monotherapy setting resulted in consistent inhibition of a biomarker of SYK activity over the dosing interval. The dose of 400 mg twice daily using a second formulation (Bis-MSA SD ENTO) yields a PK distribution biologically equivalent to 800 mg twice daily the first entospletinib formulation (see Investigator's Brochure for details). A 200 mg once daily dose of entospletinib is expected to provide plasma concentrations above EC50 for approximately 12 hours a day and it is anticipated that target inhibition by entospletinib will be approximately 24% at trough drug levels. A starting dose of 200 mg of entospletinib twice daily is 1/4th of the total daily dose that has been shown to be well-tolerated in patients. If tolerated, the dose of entospletinib will subsequently be escalated to 400 mg twice daily.

2.5 Correlative studies background

2.5.1. Assessment of B-cell depletion

Entospletinib and obinutuzumab target B-cell survival via distinct mechanisms, as discussed above. Therefore, $CD19^+$ B-cell counts will be assessed over time in this study.

2.5.2. Pharmacodynamic endpoints

Lymph nodes and bone marrow are the sites of CLL cell proliferation, with expression of gene signatures indicating activation of the BCR and nuclear factor-κB (NFκB) pathways [32, 33]. Interactions between the malignant B cells and mesenchymal stromal cells, monocyte-derived nurse-like cells, and T cells in those niches enhance CLL cell survival and confer chemoresistance [34]. Such interactions occur through engagement of the BCR, chemokine receptors and tumor necrosis factor family member receptors (e.g., CD40, "B-cell activation factor receptor" BAFF-R among others). Both BCR and CD40 signaling upregulates activity of transcription factor NFκB and the anti-apoptotic proteins Bcl-2, Mcl-1, Bcl-X and others, thus perpetuating CLL cell survival [35, 36].

In our laboratory we have modeled the CLL lymph node niche by establishing a co-culture of primary patient-derived CLL cells with CD40L-expressing fibroblasts. Using this model, we demonstrated feasibility of pharmacologic targeting NFκB in CD40-activated CLL cells [37, 38]. Others have shown that treatment with ibrutinib abrogates BCR signaling-mediated NFκB pathway activation *in vitro* and *in vivo* [39].

Recognizing that BAFF/APRIL ("a proliferation inducing ligand") signaling is an important pro-survival mechanism in normal and neoplastic B cells and BAFF-R is highly expressed in CLL [30], we established a unique co-culture model with BAFF-expressing CHO cells. In this model CLL cells a) are resistant to spontaneous apoptosis and chemotherapy (fludarabine, bendamustine); b) upregulate NFκB (Appendix F, Fig. 1); and c) induce the anti-apoptotic proteins Mcl-1 and Bcl-X. Using this mew model, we have shown that entospletinib induces apoptosis of BAFF-stimulated CLL cells, more potently than ibrutinib (Appendix F, Fig. 2). Like ibrutinib, entospletinib abrogated canonical NFκB activation in BAFF-stimulated CLL cells (Appendix F, Fig. 3). Pharmacologic inhibition of Syk (R-406) also downregulated Mcl-1 in BAFF-stimulated cells (Appendix F, Fig. 4).

In this study, we will assess the effects of in vivo SYK inhibition on the activity of the canonical and non-canonical NFκB as well as expression of the pro-survival Bcl-2 family members.

3.0 STUDY POPULATION

3.1 Inclusion Criteria

3.1.1 Patients who are ≥ 18 years of age, who have the following diagnosis:

Phase I portion of the study:

- histologically or flow cytometry confirmed diagnosis of B-CLL/SLL according to NCI-WG 1996 guidelines [40].
- the following types of NHL as documented by medical records and with histology based on criteria established by the WHO:
  - -- Mantle cell lymphoma (MCL),
  - -- Follicular lymphoma (FL) - grades 1-3a,
  - -- Lymphoplasmacytic lymphoma (LPL),
  - -- Marginal zone lymphoma (MZL),
  - -- CLL in Richter's transformation,
  - -- B-cell prolymphocytic leukemia
- patients with histologically confirmed classical Hairy cell leukemia (HCL)

Phase II portion of the study

- histologically or flow cytometry confirmed diagnosis of B-CLL/SLL according to NCI-WG 1996 guidelines. Patients who lack CD23 expression on their leukemia cells should be examined for (and found NOT to have) either t(11;14) or cyclin D1 overexpression, to rule out mantle cell lymphoma.

3.1.2. Patients underwent ≥ 1 prior chemotherapy-based or immunotherapy-based regimen or targeted therapy (e.g., inhibitors of BTK, PI3K etc.) administered for ≥2 cycles, , and have had either documented disease progression or no response (stable disease) to the most recent treatment regimen.

Additional disease-specific criteria:

Patients with CLL/SLL must demonstrate active disease meeting at least 1 of the IWCLL 2008 criteria for requiring treatment [41]:

i) A minimum of any one of the following constitutional symptoms:

- Unintentional weight loss >10% within the previous 6 months prior to screening.
- Extreme fatigue (unable to work or perform usual activities).
- Fevers of greater than 100.5 F for ≥2 weeks without evidence of infection.
- Night sweats without evidence of infection.

ii) Evidence of progressive marrow failure as manifested by the development of, or worsening of anemia or thrombocytopenia.
iii) Massive (i.e., >6 cm below the left costal margin), progressive or symptomatic splenomegaly.
iv) Massive nodes or clusters (i.e., > 10 cm in longest diameter) or progressive lymphadenopathy.
v) Progressive lymphocytosis with an increase of >50% over a 2-month period, or an anticipated doubling time of less than 6 months.
vi) Autoimmune anemia or thrombocytopenia that is poorly responsive to corticosteroids.

Patients with HCL must be intolerant of or not candidates for purine analog-based therapy, or failed to achieve response (CR or PR) or relapsed within 2 years of such therapy, AND meet the standard treatment initiation criteria (ANC≤1000/µL, Hgb≤10 g/dL, platelet count≤100,000/µL).
Patients with indolent lymphoma (FL, LPL, MZL) and patients with B-cell prolymphocytic leukemia must have an indication for treatment in the opinion of the investigator.
Patients with MCL and patients with CLL in Richter's transformation should have previously received or not be candidates for high dose chemotherapy/autologous stem cell transplant.

3.1.4 For diseases other than CLL, LPL, and HCL, presence of radiographically measurable lymphadenopathy or extra-nodal lymphoid malignancy (defined as the presence of ≥1 lesion that measures ≥2.0 cm in the longest dimension [LD] and ≥1.0 cm in the longest perpendicular dimension [LPD] as assessed by CT or MRI). For LPL, measureable disease will be defined as serum monoclonal IgM > 0.5 g/dL or meeting at least 1 of the recommendations from the Second International Workshop on LPL for requiring treatment (Appendix E).

3.1.4 Patients must have ECOG performance status ≤2 (Refer to Appendix D).

3.1.5 Patients must have organ function as defined below:
i) direct bilirubin ≤2 X institutional ULN (unless due to known Gilbert's syndrome or compensated hemolysis directly attributable to CLL)
ii) AST or ALT less than 2.5 X institutional ULN
iii) estimated CrCL using the Cockroft-Gault equation ≥50 mL/min (see Appendix B).
iv) platelets ≥50,000/mm^3 independent of transfusion support, with no active bleeding, and absolute neutrophil count (ANC) ≥1000/mm^3, unless due to disease involvement in the bone marrow.

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

3.2. Exclusion criteria

3.2.1 Prior therapeutic intervention with any of the following:

- therapeutic anticancer antibodies within 4 weeks (rituximab), except within 6 months for obinutuzumab or a similar investigational type II monoclonal

antibody;

- radio- or toxin-immunoconjugates within 10 weeks;
- inhibitors of BTK (ibrutinib), PI-3K (idelalisib), BH3-mimetic venetoclax, lenalidomide and other "targeted" therapy (including but not limited to investigational BTK and PI-3K inhibitors, etc.) – within 6 half-lives (i.e., 36 hours for ibrutinib)
- all other chemotherapy, radiation therapy within 3 weeks prior to initiation of therapy.
- SYK inhibitors at any time

3.2.2 Inadequate recovery from adverse events related to prior therapy to grade ≤1 (excluding Grade 2 alopecia and neuropathy).

3.2.3 Chronic use of corticosteroids in excess of prednisone 30 mg/day or its equivalent.

3.2.4 Stem cell transplant recipients must have no evidence of and not receive treatment for graft-versus-host disease.

3.2.5 Concomitant use or use in the prior two weeks of moderate or strong CYP3A and CYP2C9 inducers or strong CYP2C9 inhibitors (Appendix C), including nutraceutical preparations, e.g., grapefruit juice and St John's Wort.

3.2.6 History prior malignancy except:

- malignancy treated with curative intent and no known active disease present for ≥ 2 years prior to initiation of therapy on current study;
- adequately treated non-melanoma skin cancer or lentigo maligna (melanoma in situ) without evidence of disease;
- adequately treated in situ carcinomas (e.g., cervical, esophageal, etc.) without evidence of disease;
- asymptomatic prostate cancer managed with "watch and wait" strategy;
- myelodysplastic syndrome which is clinically well controlled and no evidence of the cytogenetic abnormalities characteristic of myelodysplasia on the bone marrow at screening.

3.2.7 Uncontrolled immune hemolysis or thrombocytopenia (positive direct antiglobulin test in absence of hemolysis or history of immune-mediated cytopenias are not exclusions).

3.2.8 History of Human Immunodeficiency Virus (HIV) infection or active hepatitis B or C.

3.2.9 Major surgery (requiring general anesthesia) within 2 weeks prior to initiation of therapy.

3.2.10 Inability to swallow and retain an oral medication. Patients with clinically significant medical condition of malabsorption, inflammatory bowel disease, chronic conditions which manifest with diarrhea, refractory nausea, vomiting or any other condition that will interfere significantly with drug absorption are excluded. Patients must also have adequate venous access

3.2.11 Need for ongoing therapy with proton pump inhibitors. H2 antagonists are allowed.

3.2.12 Active uncontrolled infection

3.2.13 Women who are pregnant or lactating

3.2.14 Fertile men or women of childbearing potential unless 1) permanently sterile or 2) using a highly effective measure of contraception such as condoms in males and consistent and correct use of one of the following in females: intrauterine device, tubal sterilization, Essure micro-insert system, vasectomy in the male partner. Effective contraception is required for males during treatment with study drug and to continue for 3 months after the last dose of either entospletinib or obinutuzumab, whichever is later. For women, effective contraception is required to continue for 18 months after the last dose of obinutuzumab or for 30 days after the last dose of entospletinib, whichever is later.

Definition of childbearing potential: for this study, a female subject is considered of childbearing potential until becoming post-menopausal unless permanently sterile or with medically documented ovarian failure. Women are considered to be in a post-menopausal state when ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. Women of any age with amenorrhea of ≥ 12 months may also be considered post-menopausal if their follicle stimulating hormone (FSH) level is in the post-menopausal range and they are not using hormonal contraception or hormonal replacement therapy. Permanent sterilization in females includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age. Permanent sterilization in males include bilateral orchiectomy or medical documentation of alternative explanation.

3.2.15 Any condition for which participation in the study is judged by the Investigator to be detrimental to the patient with inter-current illness or psychiatric/social situations that would jeopardize compliance with study requirements.

4.0 REGISTRATION PROCEDURES

Accrual to this study will take place at the Knight Cancer Institute Center for Hematological Malignancies at Oregon Health and Science University (OHSU). Coordination of accrual for other participating sites will be centralized at OHSU.

4.1 Subject Registration

There is no randomization for treatment. This is a phase I/II dose escalation trial with an intention-to-treat all patients who are enrolled in this clinical trial. Potential subjects will be seen by investigators of this study as a new patient or consult visit or as a follow-up visit. Referral of potential subjects to co-investigators of this study is made as part of standard of care, with the referring physician seeking advice on the diagnosis, evaluation, and/or treatment of CLL and NHL.

4.1.1 Local registration.

Registration from all consented subjects must be entered into the electronic Clinical Research System (eCRIS). Registration of OHSU patients will include the minimum of the following:

- A completed Eligibility Checklist signed by the investigator
- Signed copies of the most recently IRB-approved, informed consent form and HIPAA authorization

5.0 TREATMENT PLAN

5.1 Administration of study agents.

This is an open-label, Phase I/II trial with a dose escalation phase. The primary objective of the dose escalation phase is to determine the recommended phase 2 dose (RP2D) of entospletinib in combination with obinutuzumab in patients with relapsed/refractory CLL and B-cell malignancies. The Phase II portion will further evaluate the efficacy and safety of this novel combination.

Treatment will be administered on an outpatient basis but will also be permitted inpatient.
Reported adverse events and potential risks associated with entospletinib and obinutuzumab are described in Section 7. Appropriate dose modifications for both drugs are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

The timing of study assessments and procedures is presented by study cycle and day and are abbreviated by the following references: Cycle (C) and Day (D) number, as in C1D1 (Cycle 1 Day 1). Cycles and days within each week are numbered sequentially thereafter.

Entospletinib will be administered as single agent for 7 days (during the run-in phase (days -7 to -1) for the purpose of correlative studies, followed by a combination with obinutuzumab (beginning with C1D1). C1D1 will occur immediately after Day -1 of the run-on phase (i.e., there is no "day 0").

Table 1. Treatment description

Agent	Pre-medications; Precautions	Dose	Route	Schedule	Cycle Length
Entospletinib*	None	According to dose level - see below	PO	BID or daily on Days -7 to -1 (run-in phase), and then beginning with C1D1	28 days (4 weeks)
Obinutuzumab	Benadryl Tylenol Dexamethasone	3000 mg split dosing in cycle 1, 1000 mg with each subsequent cycle	IV	C1D1 – 100 mg C1D2 – 900 mg C1D8 & 15 – 1000 mg Day 1 of cycles 2-6 – 1000 mg	
* The morning dose of entospletinib will be administered in the clinic on day -7 of the run-in phase, and subsequent doses will be self-administered					

5.1.1 Phase I (Dose Escalation)

Patients with CLL/SLL as well as all other histologic categories of NHL will be enrolled, as specified in the eligibility criteria.

Up to three dose levels will be evaluated in the Phase I portion of the study. The dose levels of entospletinib are 200 mg po twice daily (Dose Level 1), 400 mg po twice daily (Dose Level 2) and 200 mg po daily (Dose Level -1) beginning with day 1 of cycle 1 (Table 2). The starting dose of entospletinib will be 200 mg po bid on day -7 of the run-in phase, and the same dose will be administered on day 1 of cycle 1, which will occur immediately following day -1 of the run-on phase. The first dose of obinutuzumab will be administered IV on day 1. The dose of obinutuzumab will remain unchanged at each dose level, and the last dose will be administered with cycle 6. Each cycle will last for 28 days.

Each patient will be treated for at least 12 cycles, or until a qualifying event (Section 5.4 – Duration of therapy). Both drugs will be administered during cycles 1-6, and entospletinib alone will be administered during cycles 7-12.
The dose escalation phase will follow a standard 3+3 Phase I design. At a given dose level, 3 patients will be enrolled. If all 3 patients complete ***the run-in phase and the first cycle of therapy*** (28 days) without any dose-limiting toxicities (DLTs), the next cohort of 3 patients will be enrolled at Dose level 2. If 1/3 patients develops a DLT the cohort will be expanded to 6 patients. However, if either ≥ 2/3 or ≥ 2/6 patients in dose

level 2 have DLTs, Dose level 1 will be defined as the MTD of the combination. The MTD will be considered RP2D and enrollment onto the Phase II part of the study will begin.

Table 2. Dose levels planned for dose escalation phase of the study

Dose Level	**Entospletinib (Cycles 1-12 and thereafter)** PO starting on Day -7 of the run-in phase	**Obinutuzumab (Cycles 1-6)** IV
-1*	200 mg daily	C1D1 – 100 mg; C1D2 – 900 mg C1D18 & 15 – 1000 mg C2-6 – 1000 mg on day 1
1	200 mg BID	
2	400 mg BID	

*Dose Level -1 will be studied only if more than one patient develops a DLT in Dose Level 1

For all the Dose Levels, should more than one patient develop a DLT in the respective Dose Level; the dose of entospletinib will be reduced according to the plan shown in Table 3. Should more than one patient develop a DLT in the Dose Level "-1", the study will be stopped.

The decisions to escalate of de-escalate the dose of entospletinib will follow the schema in Table 3.

Table 3. Decision rules regarding dose modification for Entospletinib

Dose level (entospletinib)	**Number of Participants with DLT at a Given Dose Level with C1**	**Decision Rule**
200 mg po daily (dose level -1)	0/3	Enroll Phase II part at this dose
	1/3	Enroll 3 additional subjects
	1/6	Enroll Phase II part at this dose
	≥ 2/6	STOP the study
200 mg po BID (**START** dose level 1)	0/3	Escalate dose to 400 mg BID
	1/3	Enroll 3 additional subjects
	1/6	Escalate dose to 400 mg BID
	≥ 2/6	De-escalate dose to 200 mg daily
400 mg po BID (dose level 2)	0/3	Enroll Phase II part at this dose
	1/3	Enroll 3 additional subjects
	1/6	Enroll Phase II part at this dose
	> 2/6	Enroll Phase II at Dose level 1.

If no significant toxicities are observed, the dose escalation part of the study is anticipated to enroll between 6 and 12 patients. Any patient discontinuing study treatment prior to completion of the first cycle for reasons other than AEs related to the study drugs will be replaced.

5.1.2 Phase II

In the Phase II, patients will be treated at the MTD of entospletinib in combination with obinutuzumab, determined in the dose escalation part of the study. Patients will be assessed for efficacy and safety (CTCAE v.4.03) parameters. **Only patients with CLL/SLL will be enrolled on Phase II part of the study**.

Each patient will be treated for at least 12 cycles, or until a qualifying event (Section 5.4 – Duration of therapy). Both drugs will be administered during cycles 1-6 (starting with the run-in phase), and entospletinib alone will be administered during cycles 7-12. Any patient discontinuing study treatment prior to completion of the first cycle for reasons other than AEs related to the study drugs will be replaced.

5.2 Definition of Dose-Limiting Toxicities (DLT)

Dose escalation will stop for DLT defined as any of the following occurring with cycle 1 (including run-in) in the dose escalation phase, deemed related (possibly, probably or definitely) to the study drug:

1. Non-hematologic toxicity: all ≥Grade 3 toxicities *except*
    a. Grade 3 nausea, vomiting or diarrhea reversible within 72 h with supportive care
    b. Grade 3 infusion-related toxicity
    c. Asymptomatic Grade 3-4 laboratory abnormalities that are reversible to ≤ Grade 2 within 72 hours (for example, Grade 3-4 elevation of uric acid, AST, ALT, changes in phosphorus and magnesium levels, changes in glucose levels)
    d. Grade 3 only: tumor lysis syndrome (TLS) or hyponatremia (equals Na 120-130 mEq/L)

2. Hematologic toxicity:
    a. Grade 4 neutropenia lasting more than 7 days in a subject with ANC>1500 µL before beginning therapy
    b. Febrile neutropenia of any duration (ANC < 500/µL, fever > 38.5 C)
    c. Grade 4 thrombocytopenia/anemia or grade 3 thrombocytopenia with bleeding or any requirement for platelet transfusion, unexplained by underlying disease

Grading of toxicities will be according to NCI CTCAE v.4.03. Grading of hematologic toxicity in patients with CLL/SLL will be conducted according to the 1996 modified NCI-WG criteria for CLL/small lymphocytic lymphoma (SLL), updated in 2008 [41]. A toxicity deemed to be unrelated to therapy (such as hip fracture due to a traumatic fall), will NOT be considered as a DLT.

Patients who completed 1 cycle of study treatment will be evaluable for dose escalation decision purpose. Patients who receive < 50% of doses of entospletinib or < 2 doses of obinutuzumab during cycle 1 and who do not experience DLT, will NOT be evaluable for dose escalation decision purpose and will be replaced. Intra-patient dose escalation will be allowed to the level of MTD, once MTD has been determined.

Management and dose modifications associated with the above adverse events are outlined in Section 6.

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 Prophylaxis of Tumor Lysis Syndrome (TLS)

Patients who receive therapy for NHL and CLL are at risk for tumor lysis syndrome (TLS). TLS is an oncologic emergency that can occur spontaneously and/or after treatment in malignant conditions, particularly lymphomas and leukemias. These complications are caused by the breakdown products of dying malignant cells and include hyperkalemia, hyperphosphatemia, hyperuricemia and hypocalcemia, and, if left untreated, acute renal failure.

TLS definitions [42]

Grade 3 (present but not life-threatening): Occurrence of two or more of the following serum values after anticancer treatment:

i. Uric acid: increase by more than 25% from baseline, or values ≥8 mg/dL;
ii. Potassium: increase by more than 25% from baseline, or values ≥6.0 mmol/L;
iii. Phosphorus: increase by more than 25% from baseline, or values ≥4.5 mg/dL;
iv. Calcium: decrease by more than 25% from baseline, or values ≤7 mg/dL.

Grade 4: a life-threatening and/or requiring immediate intervention such as but not limited to new renal failure requiring hemodialysis, or decrease in estimated creatinine clearance (eCrCL) of >50%; symptomatic cardiac arrhythmias incompletely controlled or controlled using a device (defibrillator); any seizure.

Certain patients (for example, those with WBC>50,000 and/or hepatosplenomegaly and/or renal dysfunction [CrCL<70 mL/min] and/or pretreatment hyperuricemia) are at an increased risk of developing TLS.

All patients enrolled on this study will receive the following supportive care:

IV hydration on C1D1 (prior to administration of obinutuzumab). Patients will be encouraged to hydrate orally prior to C1D1 of therapy, aiming to consume >2 L of liquids per day. On day 1 of treatment, patients will receive IV hydration with 0.9% sodium chloride OR D5W with 100 mEq of sodium bicarbonate per 1 Liter at 250 mL/hour beginning at least 1 hour prior to the first dose of obinutuzumab. Hydration will continue for at least 2 hours. The rate of hydration may be adjusted by the Investigator depending on the clinical situation. Diuretics (such as furosemide IV or PO) may be given if deemed necessary.

Allopurinol 300 mg PO daily (or renally adjusted dose, per treating physician). Patients will start taking allopurinol at least 3 days prior to the first dose of entospletinib (day -7) and continue for at least 14 days.

CBC and serum biochemistry/metabolic panel will be measured on C1D1, C1D2, C1D8 and C1D15. Optional serum biochemistry/metabolic panel measurements may be considered by the investigator at the end of C1D1 and C1D2.

Patients whose blood uric acid level exceeds 8.0 mg/dL on C1D1 or C1D2, and who are high risk in the investigator's clinical judgement (i.e., have high tumor burden, high circulating lymphocyte count [$> 25 \times 10^9$/L] or renal impairment), should be given IV rasburicase (3 mg for patients who weigh <100 kg; 6 mg for patients who weight >100 kg). Uric acid levels will be measured 2 hours after rasburicase is given and every 2 hours thereafter until level is lowered to ≤8.0 mg/dL and drug treatments will be delayed. Those measurements should occur in a chilled heparinized tube, delivered to the laboratory and analyzed STAT. Rasburicase treatment should be repeated if uric acid levels do not decrease by at least 50% within 6 hours and may be repeated at the discretion of the Investigator thereafter.

Patients whose serum potassium exceeds 5 mmol/L will receive 30 g of Kayexalate, additional 1 liter fluid bolus and 20-40 mg of IV furosemide (at the discretion of the Investigator). Potassium levels will be rechecked STAT 1 hour later and every 2 hours thereafter until serum levels are ≤5 mmol/L.

5.3.2. Risks Associated with obinutuzumab therapy

Important risks identified in clinical investigations with obinutuzumab were: IRRs, TLS, thrombocytopenia (including acute thrombocytopenia), neutropenia (including prolonged and late onset neutropenia),

prolonged B-cell depletion, infections (including hepatitis B reactivation and PML), worsening of pre-existing cardiac conditions and GI perforation. See the Obinutuzumab IB for additional details.

5.3.2.1. Hepatitis B Reactivation

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

Positive serology for Hepatitis B is defined as positivity for Hepatitis B surface antigen (HBsAg) or Hepatitis B core antibody (anti-HBc). Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with obinutuzumab. For patients who show evidence of hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult physicians with expertise in managing hepatitis B regarding monitoring, and consideration for HBV antiviral therapy.

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

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

For the subset of patients who are Hepatitis B viral DNA-negative and anti-HBc positive and have undetectable Hepatitis B viral DNA levels at screening, Hepatitis B viral DNA levels must be followed approximately every 4 weeks. Guidelines for the management of hepatitis B reactivation are outlined in Table 1.

Table 4. Management of Hepatitis B Reactivation

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

5.3.2.2. Progressive Multifocal Leukoencephalopathy

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

5.3.2.3. Infusion-Related Reactions

Obinutuzumab can cause severe and life-threatening IRRs; 65% of patients with CLL experienced a reaction to the first 1000 mg infusion of obinutuzumab, and 38% of iNHL patients experienced a reaction on Day 1 of obinutuzumab infusion. IRRs within 24 hours of receiving obinutuzumab have occurred. IRRs can also occur with subsequent infusions. Symptoms may include hypotension, tachycardia, dyspnea, and respiratory symptoms (e.g., bronchospasm, larynx and throat irritation, wheezing, and laryngeal edema). Most frequently reported symptoms include nausea, fatigue, dizziness, vomiting, diarrhea, hypertension, flushing, headache, pyrexia, and chills.

Medications (including subcutaneous epinephrine, corticosteroids, and intravenous diphenhydramine) and resuscitation equipment should be available for immediate use.

For patients with preexisting cardiac or pulmonary conditions, monitor more frequently throughout the infusion and the post-infusion period because patients may be at greater risk of experiencing more severe reactions. Hypotension may occur as part of the obinutuzumab IRR. Consider withholding antihypertensive treatments for 12 hours prior to administration, during each obinutuzumab infusion, and for the first hour

after administration until blood pressure is stable. For patients at increased risk of hypertensive crisis, consider the benefits versus the risks of withholding antihypertensive medication as suggested above.

Certain patients are at risk and need to be closely monitored: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells (>25,000/mm^3). This protocol prescribes a divided dose of obinutuzumab in all patients (100 mg on day 1 and 900 mg on day 2).

Institutional guidelines may be used for obinutuzumab administration. We suggest this general approach: vital signs should be taken every 15 minutes for the first hour of infusion until stable, then every 30 minutes until the completion of infusion. Pulse oximetry on room air should be performed at baseline and as needed if dyspnea occurs. Epinephrine 1 mg/ml, dyphenhydramine 50 mg IV and hydrocortisone 100 mg IV should be readily available during obinutuzumab infusion. For first infusion (C1D1), obinutuzumab is administered at a rate of 25 mg/hour for four hours. On C1D2 obinutuzumab is started at 25 mg/hr (50 mg/hr if no IRR occurred on C1D1) and rate escalated by 50 mg/hour every 30 minutes until a maximum rate of 400 mg/hour provided no infusion reaction occurs. For subsequent infusions, infusion may be started at 50 mg/hour (100 mg/hour if no reactions with previous infusion) and increased by 100 mg/hour increments every 30 minutes until a maximum rate of 400 mg/hour.

If a patient experiences an infusion reaction of any grade during infusion, adjust the infusion as follows:
Grade 4 (life threatening): Stop infusion immediately and permanently discontinue obinutuzumab therapy.
Grade 3 (severe): Interrupt infusion and manage symptoms. Upon resolution of symptoms, consider restarting obinutuzumab infusion at no more than half the previous rate (the rate being used at the time that the infusion reaction occurred) and, if patient does not experience any further infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose. Permanently discontinue obinutuzumab treatment if patients experience a Grade 3 infusion-related symptom at re-challenge.
For CLL patients only, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour but not increased further.
Grade 1 – 2 (mild to moderate): Reduce infusion rate or interrupt infusion and treat symptoms. Upon resolution of symptoms, continue or resume infusion and, if patient does not experience any further infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose.
For CLL patients only, the Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour but not increased further.
Any overdose or incorrect administration of study drug should be noted in the medical chart. Adverse events associated with an overdose or incorrect administration of study drug should be reported.

For fevers, chills and rigors demerol 12.5 mg IV may be administered and repeated every 15 minutes up to a maximum dose of 50 mg. For severe dyspnea and bronchospasm, administer 100 mg hydrocortisone IV and/or 50 mg benadryl IV. In an emergent situation give epinephrine 0.3 mg/0.3 ml IM. For systolic blood pressure ≤80 mm Hg infuse 0.9% sodium chloride at 250 ml/hr, check blood pressure at least every 10 minutes until it reaches baseline±10%. After symptoms have resolved resume the infusion at 50% the previous rate and increase as above, or at 10 mg/hr every 15 minutes (if severe reaction observed).
Premedication to reduce the risk of infusion reactions is outlined in Table 5.

Table 5. Obinutuzumab Dosing Schedule for Six 28-Day Treatment Cycles for Patients with CLL and NHL

Day of Treatment Cycle	Patients Requiring Premedication	Premedication	Administration
Cycle 1 Days 1 and 2	All patients	Intravenous glucocorticoid: 20 mg dexamethasone or 80 mg methylprednisolone	Completed at least 1 hour prior to obinutuzumab infusion.
		650–1000 mg PO acetaminophen	At least 30 minutes before obinutuzumab infusion.
		anti-histamine (e.g., 50 mg diphenhydramine IV/ PO)	
All subsequent cycles	All patients	650–1000 mg PO acetaminophen	At least 30 minutes before obinutuzumab infusion.
	Patients with an IRR (Grade 1-2) with the previous infusion	650–1000 mg PO acetaminophen	At least 30 minutes before obinutuzumab infusion.
		anti-histamine (e.g., 50 mg diphenhydramine IV/PO)	
	Patients with a Grade 3 IRR with the previous infusion OR with a lymphocyte count > 25×10^9/L prior to next treatment	Intravenous glucocorticoid: 20 mg dexamethasone or 80 mg methylprednisolone	Completed at least 1 hour prior to obinutuzumab infusion.

5.3.2.4. Infections

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

5.3.2.5. TLS with obinutuzumab

TLS, including fatal cases, has been reported in patients receiving obinutuzumab. Patients with high tumor burden, high circulating lymphocyte count (> 25×10^9/L) or renal impairment are at greater risk for TLS and should receive appropriate tumor lysis prophylaxis with anti-hyperuricemics (e.g., allopurinol or rasburicase) and hydration prior to the infusion of obinutuzumab. Continue prophylaxis prior to each subsequent obinutuzumab infusion, as needed. See section 5.3.1 for detailed recommendations on management of TLS.

During the initial days of obinutuzumab treatment, monitor the laboratory parameters of patients considered at risk for TLS. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

For patients with evidence of TLS, obinutuzumab should be discontinued and the patient treated as clinically indicated. Following the complete resolution of TLS complications, obinutuzumab may be re administered at the full dose during the next infusion in conjunction with prophylactic therapy.

5.3.2.6. Hematologic Toxicities

Neutropenia

Severe and life threatening neutropenia, including febrile neutropenia, has been reported during treatment with obinutuzumab. Patients with Grade 3–4 neutropenia should be monitored frequently with regular laboratory tests until resolution. Anticipate, evaluate, and treat any symptoms or signs of developing infection (see Section 6.1 for management of neutropenia). Consider administration of granulocyte colony-stimulating factors (G-CSF) in patients with Grade 3 or 4 neutropenia (outside of the DLT window).
Neutropenia can also be of late onset (occurring more than 28 days after completion of treatment) and/or prolonged (lasting longer than 28 days).
Dose delays may be considered in the case of Grade 3 or 4 neutropenia. Patients with severe and long lasting (> 1 week) neutropenia are strongly recommended to receive antimicrobial prophylaxis until resolution of neutropenia to Grade 1 or 2. Antiviral and antifungal prophylaxis should be considered.

Thrombocytopenia
Severe and life threatening thrombocytopenia has been reported during treatment with obinutuzumab in combination with chlorambucil or bendamustine. Fatal hemorrhagic events during Cycle 1 have also been reported in patients with CLL treated with obinutuzumab.
Monitor all patients frequently for thrombocytopenia and hemorrhagic events, especially during the first cycle. In patients with Grade 3 or 4 thrombocytopenia, monitor platelet counts more frequently until resolution (see Section 6.1 for management of thrombocytopenia). Transfusion of blood products (i.e., platelet transfusion) may be necessary. Consider withholding concomitant medications which may increase bleeding risk (platelet inhibitors, anticoagulants), especially during the first cycle.

Hematological Toxicities in Patients with CLL
The evaluation of potential treatment-induced toxicity in patients with advanced CLL may be quite difficult and requires careful consideration of both the manifestations of the underlying disease, as well as adverse reactions to the therapy under study. Some of the conventional criteria for toxicity are not applicable, especially under circumstances of progressive bone marrow failure from the CLL itself.
Dose modifications for hematologic toxicity in patients with CLL must be made with consideration of the increased frequency of hematologic compromise at the initiation of therapy. Therefore, the standard criteria used for solid tumors are difficult to be applied directly; many patients would be considered to have Grade 2 – 4 hematologic toxicity at presentation.
As a consequence, dose modification decisions for patients with cytopenia (below the lower limit of the normal range) at baseline will be based on the NCI sponsored Working Group (NCI-WG) grading scale for hematologic toxicity in CLL studies.

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

5.3.3. CYP Inhibitors and Inducers

In vitro data indicates that entospletinib is a substrate of CYP2C9 and to a lesser extent CYP3A. Co-administration of CYP2C9 inhibitors or CYP2C9 or CYP3A inducers may increase or decrease entospletinib exposure, respectively. As such, coadministration of moderate and strong CYP3A and CYP2C9 inducers, and strong CYP2C9 inhibitors is prohibited in this study.

Caution should be exercised when coadministering drugs that are moderate inhibitors of CYP2C9 (e.g., fluconazole, voriconazole, and amiodarone). Administration of strong and moderate CYP3A and CYP2C9 inducers and strong CYP2C9 inhibitors is also prohibited for 2 weeks prior to study drug

administration. Examples of strong CYP2C9 inhibitors and strong/moderate inducers are provided in Appendix 3.

In vitro data indicates that entospletinib has the potential to inhibit several transporters and the metabolizing enzyme UGT1A1, which may affect the plasma concentrations of substrates of these transporters and/or enzyme. Caution should be exercised when coadministering medications that are metabolized or transported by UGT1A1, OATP1B1, OATP1B3, MATE1, P-gp, and BCRP, such as rosuvastatin and atorvastatin. The investigator should review the prescribing information of the concomitant medication for guidance on co-administration with an inhibitor of these transporters, such as additional monitoring, dose modifications or avoiding co-administration. In a study in healthy volunteers, entospletinib 400 mg twice daily increased rosuvastatin exposure by approximately 3.3-fold; as such the following restrictions apply for subjects receiving entospletinib in this study: atorvastatin, pravastatin, simvastatin, lovastatin and fluvastatin dose needs to be limited to 20 mg daily; rosuvastatin – to 10 mg daily.

5.3.4. Proton Pump Inhibitors

Studies in healthy volunteers have demonstrated a significant reduction in entospletinib exposure when proton pump inhibitors are co-administered. Therefore, proton pump inhibitors (e.g., omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole) are prohibited in combination with entospletinib. H2 antagonists are allowed.

5.3.5. QT Prolonging Agents

Neither entospletinib nor obinutuzumab have been shown to prolong QT interval. However, any medications known to cause QT prolongation should be used with caution; periodic monitoring with ECGs and electrolytes should be considered.

5.3.6. Growth Factors

Patients may receive filgrastim, peg-filgrastim, erythropoietin or related growth factors at the discretion of the treating physician. Growth factors cannot be administered within the DLT window.

5.3.7. Anti-Emetic Therapy

Nausea is not common with either entospletinib or obinutuzumab. Grade 3 nausea occurred in <4% of patients who received entospletinib on a recent Phase II study [29], thus considered low risk for emetogenesis.

Anti-emetic therapy may be instituted for any patient. Premedication with a single dose of Compazine 10 mg is preferred, and pre-medication with 5-HT3 antagonists (e.g., ondansetron 4-8 mg po) is allowed. Rescue therapy with 5-HT3 antagonists (ondansetron) is allowed according to standard dosing guidelines, not to exceed the maximum daily dose. Other antiemetics (aprepitant, benzodiazepines etc.) may be used as indicated.

5.4 Duration of Treatment

In the absence of treatment delays due to adverse events, treatment will continue for at least 12 cycles (treatment with entospletinib may continue beyond 12 cycles, as noted elsewhere; obinutuzumab will be administered for 6 cycles) or until one of the criteria below applies.

- Disease progression
- Unacceptable adverse event(s),
- Intercurrent illness that prevents further administration of treatment,
- Participant decides to withdraw from the study, or
- Pregnancy, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating physician.
- Closure of study by sponsor investigator or discontinuation of drug availability.

5.5 Duration of Follow-up

Study participants will remain on study until disease progression, until study drug-related toxicities have resolved or are deemed irreversible by the sponsor-investigator (in discussion with a treating physician), whichever is later, or until the study is closed. If a study participant discontinues study treatment due to reasons other than progressive disease they will continue to be followed for disease assessments for 12 months after the End of Treatment visit, and for EFS until the end of study or study closure.

The expected duration of study will be 5 years, including enrollment (2 years), treatment (at least 1 year) and follow-up and EFS (2 years).

In the event of a study closure, participants currently receiving study drug will stop taking study drug and complete an abbreviated End of Treatment visit. Follow up and EFS will not continue after the End of Treatment visit.

5.6 Criteria for Removal from Study

Participants will be removed from study under the following circumstances:

Disease progression or start of new therapy of CLL/NHL
Participant decides to withdraw from the study
Pregnancy
Patient is off treatment and has been on study for at least 4 years since the date of consent
Study closure

The reason for study removal and the date the participant was removed must be documented in the study-specific case report form. Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, a lead PI (Alexey Danilov, M.D.) needs to be immediately notified at danilov@ohsu.edu.

5.7 Trial Discontinuation

The trial will cease when participants

- have started a subsequent treatment for CLL, *or*

- have been followed for 3 years since beginning of therapy, and are no longer receiving therapy, *or*

- have died of any cause
-come off study due to study closure

The last scheduled follow-up will occur on a post-treatment visit as defined in study procedures.

6.0 DOSING DELAYS/DOSE MODIFICATIONS

6.1 Dose Modifications/Delays for Toxicities Encountered During Therapy.

Table 6. Dose Modifications and Delays for Entospletinib and Obinutuzumab

Description		**Grade**	**Dose modification**
Non-hematologic	Initial or first recurrence	3-4 and clinically significant*	Hold treatment with ***both*** drugs and evaluate at least weekly as clinically indicated. Delay dose until toxicity resolves to Grade ≤2, then complete current cycle or start next cycle with reduction in ***entospletinib*** by one dose level (Table 5)
	Second recurrence		Discontinue
Description		**Grade**	**Dose modification**
Hematologic	Initial or first recurrence	As defined in DLTs: Grade 4 neutropenia lasting > 7 days. Grade 4 thrombocytopenia/ anemia or grade 3 thrombocytopenia with bleeding or any requirement for platelet transfusion, unexplained by underlying disease Febrile neutropenia	Hold treatment with both drugs. Initiate at least weekly CBC checks, growth factor (G-CSF allowed at Investigator's discretion) and transfusion support as clinically indicated until resolved to Grade 1 or >75% baseline. May continue this cycle or start next cycle with reduction in entospletinib by one dose level (Table 5).
	Second recurrence		Discontinue

*Not clinically significant includes: Grade 3 nausea or vomiting occurring without optimal treatment; asymptomatic Grade 3 laboratory abnormalities that are not life-threatening and respond to treatment; grade 3 obinutuzumab infusion reactions; grade 4 infusion reaction, which will be an investigator dependent decision

Note: Grading of non-hematologic toxicities will be according to NCI CTCAE v.4.03. Grading of hematologic toxicity will be according to the 1996 modified NCI-WG criteria for CLL/SLL, updated in 2008.

Table 7. Restarting Doses of Entospletinib after Treatment Interruption for Drug-Related Toxicity

Entospletinib dose at the time of first toxicity	1st reduction	2nd reduction
200 mg daily	Discontinue	-
200 mg BID	200 mg daily	Discontinue
400 mg BID	200 mg BID	200 mg daily

There are NO dose reductions for obinutuzumab.

In cases where toxicities led to dose reduction, dose re-escalation of entospletinib may be considered in subsequent cycles at the discretion of the treating physician after at least two cycles of study therapy are well tolerated without any recurrent toxicities at the reduced dose.

Treatment delays due to hematologic, non-hematologic and renal toxicities are permitted for up to 28 days from the end of a previous 28-day cycle. For longer delays, the study treatment will end (Section 5.5). In case of a treatment delay subsequent study assessment days will be adjusted accordingly. If a treatment delay occurs, both drugs (entospletinib and obinutuzumab) will be delayed.

For less severe toxicities not described above, holding one or both drugs and dose reductions are discouraged, but remain at the discretion of the treating physician.

Treatment with entospletinib and obinutuzumab will be discontinued if one of the following occurs despite dose modifications:

1. Second recurrence of grade 3-4 non-hematologic toxicities.
2. Second recurrence of grade 3-4 hematologic toxicities.
3. Treatment delay of >28 days from the end of a previous 28-day cycle.

6.3 Special Considerations

Surgery

The following guidance should be applied during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving entospletinib:

- For any surgery or invasive procedure requiring sutures or staples for closure, entospletinib should be held 48 hours prior to the intervention and at least 48 hours after the procedure, and restarted at the discretion of the investigator when the surgical site is reasonably healed without the need for drainage tubes.
- For emergency procedures, entospletinib should be held after the procedure until the surgical site is reasonably healed, for at least 48 hours after the urgent surgical procedure.

7.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting.

7.1 Adverse Events and Potential Risks Lists

7.1.1 Entospletinib

Based on the data available, the following is a list of effects that could be encountered in patients administered entospletinib PO.

- Rash
- Transaminases Increased
- Bilirubin, indirect, transient elevation

7.1.2 Obinutuzumab

Please refer to the prescribing information (Appendix A) for complete lists of anticipated toxicities associated with obinutuzumab.

7.2 Adverse Event Characteristics

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product or other protocol-imposed intervention, regardless of attribution. An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline

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 NHL/CLL that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Adverse events will be graded according to the NCI Common Toxicity Criteria Version 4.03. A copy of the CTC version 4.0 can be downloaded from http://ctep.info.nih.gov. Reporting of AEs will begin following the first dose of entospletinib and continue until End of Treatment visit. AEs after the End of Treatment visit should also be reported if considered related to study drug.

Safety is the primary study endpoint and will be assessed continuously. The safety profile will be assessed from the findings of physical examination, laboratory data, electrocardiograms (ECG), concomitant medications and treatments, and date of treatment withdrawal and cause. The safety profile will be based on incidence, severity, and cumulative nature of AEs. Adverse event seriousness, severity grade, and relationship to study medications will be assessed by the lead PI.

All subjects who completed 1 cycle of therapy or who did not complete 1 cycle of therapy (or the run-in phase) because of a DLT will be considered evaluable for toxicity. All AEs, with the exception of progressive disease, will be reported from the start of therapy until the End of Treatment visit or until the start of an alternative systemic anti-leukemic therapy, if it occurs earlier.

All grade 3 or Grade 4 AEs considered related to study regimen must be followed until recovery to Grade ≤1 or baseline. The unresolved aforementioned events will be followed until, in the opinion of a lead PI (in discussion with a treating physician), resolution can no longer be expected.

All grade 3 and 4 hematological and non-hematological adverse events will be recorded on the case report forms.

7.2.1 Serious adverse event (SAE)

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).

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

7.2.2. Obinutuzumab adverse events of special interest

Obinutuzumab events of special interest are:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law.
- Suspected transmission of an infectious agent by the study drug, as defined below

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

-The following events, if considered serious by the investigator:

- Serious neutropenia
- Serious infection
- Serious IRR
- Serious TLS

7.2.3. Selected Adverse Events

Selected events (in clinical trials, these are events for which additional data collection or analyses will be performed; no special case handling or follow-up is required) include the following:

- IRRs
- Infections (including PML)
- Neutropenia (including late-onset neutropenia, defined as neutrophil count < 1000 cells/mm^3, occurring 28 days or more after obinutuzumab treatment has been completed or stopped; prolonged neutropenia, defined as neutrophil count < 1000 cells/mm^3, that does not resolve after 28 days (without obinutuzumab treatment)
- Thrombocytopenia (including acute thrombocytopenia occurring during and within 24 hours post

obinutuzumab infusion)

- Hepatitis B reactivation
- Cardiac events
- Second malignancies
- GI perforation

7.2.4. 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), Gilead Sciences, and Genentech in accordance with instructions provided in this section, as well as in accordance with CFR 312.32 (IND Safety Reports).

7.2.4.1. 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. From the time of consent to the initiation of treatment, any AEs and SAEs related to study procedures should be reported.

7.2.4.2. 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 entospletinib or obinutuzumab, 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 entospletinib or obinutuzumab, 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 entospletinib or obinutuzumab; 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 USPI or current Investigator's Brochure. Unexpected AEs are those not listed in the USPI 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 USPI or Investigator's Brochure. For example, under this definition, hepatic necrosis would be unexpected if the USPI or Investigator's Brochure only referred to elevated hepatic enzymes or hepatitis.

7.2.5. Procedures for Eliciting, Recording, and Reporting Adverse Events

7.2.5.1. 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?"

7.2.5.2. Specific Instructions for Recording Adverse Events

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

Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction" or "anaphylactic reaction." If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately, with signs and symptoms also recorded separately.

Diagnosis versus Signs and Symptoms

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

Deaths

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

Preexisting Medical Conditions

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

Hospitalizations for Medical or Surgical Procedures

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

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or

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

Pregnancies

- Pregnancies in Female Patients

If a female patient becomes pregnant while receiving study drug or within 18 months after the last dose of entospletinib or obinutuzumab, a report should be completed and expeditiously submitted to Gilead Sciences and Genentech. Follow-up to obtain the outcome of the pregnancy should also occur.

- Pregnancies in Female Partners of Male Patients

If the female partner of male patients become pregnant while receiving the study drug or within 6 months after the last dose of entospletinib or obinutuzumab, a report should be completed and expeditiously submitted to Gilead Sciences and Genentech. The pregnant partner will need to sign an IRB approved Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow up on her pregnancy. After the authorization has been signed, the investigator will submit a Pregnancy Report when updated information on the course and outcome of the pregnancy becomes available.

Congenital Anomalies/Birth Defects and Abortions

Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female patient exposed to obinutuzumab or the female partner of a male patient exposed to obinutuzumab or entospletinib should be classified as an SAE.

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 entospletinib or obinutuzumab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female patient who participated in the study, this should be reported as an SAE.

7.2.5.3. Reconciliation (Genentech)

The Sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange 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. The Sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

7.2.6 Definitions of Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

7.2.6.1. Expected Adverse Event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the package insert or is included in the informed consent document as a potential risk. Refer to the prescribing information for a listing of expected adverse events associated with the study agents.

7.2.6.2. Unexpected Adverse Event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the package insert or when it is not included in the informed consent document as a potential risk.

7.2.7 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely – The AE is doubtfully related to the study treatment.
- Unrelated –The AE is clearly NOT related to the study treatment.

7.3 OHSU IRB Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems and Adverse Events (AE) will be reported to OHSU IRB according to the policies, procedures and guidelines posted on the OHSU IRB web site http://www.ohsu.edu/xd/about/services/integrity/policies/all-irb-documents.cfm.Reportable New Information (RNI) will be reported to the OHSU as defined in the OHSU Investigator Guidance document titled Prompt Reporting Requirements (HRP-801). Fatal and life-threatening events must be reported to OHSU IRB within 5 business days after the PI learns of the event. If any of these require a change (as determined by the PI or the IRB) to the protocol or consent form, the PI will make those changes promptly and submit the revised documents to the OHSU IRB.

All other UP reports will be submitted to OHSU IRB no later than 15 calendar days of notification of the event. If the event requires changes as determined by the PI or the IRB to the protocol or consent form, the PI will make the changes promptly and submit the revised documents to the IRB. Unanticipated Problems and AE reports are submitted through OHSU e-IRB and will be reviewed by OHSU IRB.

7.5 MedWatch Reporting

For this investigator-initiated study, the investigator is the study sponsor. The investigator / sponsor is required to report adverse experiences to the FDA through the MedWatch reporting program, even if the trial involves a commercially available agent. Adverse experiences to be reported include any unexpected (not listed in the package label), serious adverse experiences with a suspected association to the study drug.

Adverse events that occur during clinical studies are to be reported to FDA as specified in the investigational new drug/biologic regulations using Form FDA 3500, the MedWatch Voluntary Reporting form, which is available online at:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf.

Investigators may also complete Form FDA 3500 online at:
https://www.accessdata.fda.gov/scripts/medwatch/.

Serious adverse events experienced by subjects at the participating sites require completion and submission of the OHSU Safety Reporting Form along with supporting materials to OHSU within 24 hours of participating investigator's knowledge of the event. The OHSU Safety Reporting Form can be found in the study operations manual. OHSU will report the event to the FDA via Voluntary Form 3500.

A copy of Form FDA 3500 and supporting materials will be kept on file in the study regulatory binder. All SAEs occurring on study will be disseminated to the coordinating center by OHSU.

For sponsor-investigators who hold an IND, Form FDA 3500 will be submitted to the IND/IDE associate who will assist the study team in a formal safety report to the FDA.

7.6 Sponsor or additional reporting requirements.

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 7 calendar days after initial receipt of the information.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

Events will be reported to the FDA using Form FDA 3500, the MedWatch Voluntary Form. Forms are available at http://www.fda.gov/medwatch/getforms.htm.

7.6.1. Reporting to Gilead Sciences

SAE reporting
Investigators are not obligated to actively seek SAEs after the protocol defined follow up period. However, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event to Gilead Drug Safety and Public Health within 24 hours. All deaths which occur during study follow-up will be reported to Gilead Drug Safety and Public Health within 24 hours.

Pregnancy reports
The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period to Gilead Drug Safety and Public Health within 24 hours of becoming aware of the pregnancy.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons. Any premature termination of pregnancy (e.g., a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term. A spontaneous abortion is always considered to be an SAE. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead Drug Safety and Public Health. The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead Drug Safety and Public Health. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead Drug Safety and Public Health.

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead Drug Safety and Public Health within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead Drug Safety and Public Health.

Gilead Drug Safety and Public Health contact information is as follows:
Fax: 1-650-522-5477

Email: Safety_FC@Gilead.com

7.6.2. Reporting to Genentech

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 Drug Safety at:

(650) 225 4682
OR
(650) 225 4630

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

Please see Appendix H.

SAEs, pregnancy reports, and AESIs, where the patient has been exposed to the study drug (Product), will be sent on a MedWatch or CIOMS I form to the Genentech contact specified in Addendum 2 of this SDEA. Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below.

Serious Adverse Drug Reactions
Serious adverse event reports that are related to the Product shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.

Other Serious Adverse Events
Serious adverse event reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

Pregnancy Reports
While such reports are not serious adverse events or ADRs per se, as defined herein, any reports of pregnancy, where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

Adverse Events of Special Interest
AESIs requiring expedited reporting shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date. Others shall be sent within thirty (30) calendar days.

Special Situation Reports
In addition to all adverse events, pregnancy reports and AESIs, the following Special Situations Reports should be collected and transmitted to Genentech even in the absence of an AE within thirty (30) calendar days:
- Data related to the Product usage during pregnancy or breastfeeding
- Data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol
- Data related to a suspected transmission of an infectious agent via a medicinal product (STIAMP)

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

Aggregate Reports
OHSU will forward a copy of the Publication to Gilead Sciences and Genentech upon completion of the Study.

Reporting to Gilead Sciences and Genentech at Study Close Out
Any study report submitted to the FDA by the Sponsor-investigator should be copied to Gilead Sciences and Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Gilead Sciences and Genentech. Copies of such reports should be mailed to the assigned Genentech Clinical Operations contact for the study (e-mail: ga101-gsur@gene.com; fax: 866-706-3927) and Gilead Sciences Clinical Operations contact personnel.

IND Annual Reports
Copies to Gilead Sciences and Genentech:
All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Gilead Sciences and Genentech. Copies of such reports should be faxed to Genentech Drug Safety [fax (650) 225-4682 or (650) 225-4630] and Gilead Sciences Clinical operations contact personnel.

Product Complaints

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

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

8.0 PHARMACEUTICAL AGENT 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 Agent Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of the study agent. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage).
http://ctep.cancer.gov/investigatorResources/investigators_handbook.htm

Responsibility for drug accountability at the study site rests with the Investigator; however, the Investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities.

The Investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study medication until the end of the study. The Investigator or designee must maintain

records that document:

- investigational product delivery to the study site
- the inventory at the site
- use by each subject including pill/unit counts from each supply dispensed
- return to the Investigator or designee

These records should include dates, quantities, batch/serial numbers (if available), and the unique code numbers (if available) assigned to the investigational product and study subjects.

The investigational product must be used only in accordance with the protocol. The Investigator will also maintain records adequately documenting that the subjects were provided the correct study medication specified.

Completed accountability records will be archived by the site. At the completion of the study, the Investigator or designee will oversee destruction of any remaining study drug according to institutional standard operating procedures.

Please refer to the Pharmacy Manual located in the separate Study Operations Manual for details on drug supply, ordering and shipment process.

8.2 Entospletinib.

Entospletinib will be obtained from Gilead Sciences, Inc. Up to 4,600 tablets (200 mg dose) and up to 26,000 tablets (200 mg dose) will be provided for the first year of entospletinib therapy. Additionally, it is estimated that up to 32,000 200 mg dose tablets may be provided for patients who desire to continue therapy with entospletinib single agent beyond 1 year.

8.2.1. Formulation

Entospletinib may be supplied as either Clinical Trade Dress or Commercial Trade Dress.

Clinical Trade Dress

Entospletinib is available as 200 mg strength capsule-shaped, plain-faced, film-coated blue tablets. Each tablet contains the equivalent of 200 mg entospletinib free base in the form of an entospletinib spray-dried dispersion prepared using the entospletinib bismesylate monohydrate. In addition to the active ingredient, entospletinib tablets contain the following inactive ingredients: Methanesulfonic acid, hydroxypropyl methylcellulose (hypromellose), mannitol, microcrystalline cellulose, crospovidone, poloxamer 188, silicon dioxide, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and FD&C blue #2 aluminum lake.

Commercial Trade Dress

Entospletinib is also available as 200 mg strength capsule-shaped, debossed, film-coated beige tablets. The tablet is debossed with "GSI" on one side and "9973" on the other side. Each tablet contains the equivalent of 200 mg entospletinib free base in the form of an entospletinib spray-dried dispersion prepared using the entospletinib bismesylate monohydrate. In addition to the active ingredient, entospletinib tablets contain the following inactive ingredients: Methanesulfonic acid, hydroxypropyl methylcellulose (hypromellose), mannitol, microcrystalline cellulose, crospovidone, poloxamer 188, silicon dioxide, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, ferrosoferric oxide/black iron oxide, iron oxide red, and iron oxide yellow.

8.2.2. Packaging and Labeling

Entospletinib tablets are packaged in white, high-density polyethylene bottles with silica gel desiccant, and polyester packing material in each bottle. Each bottle contains 60 tablets and is capped with a child-resistant polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

Study drug(s) will be distributed to centers in the US and will be labeled by at the corresponding pharmacies to meet applicable requirements of the United States Food and Drug Administration (FDA).

8.2.3. Storage and Handling

Entospletinib tablets should be stored at a controlled room temperature of 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F and 86 °F). To ensure stability of the tablets and proper product identification, the drug should not be stored in a container other than the container in which it is supplied. Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures.

8.3 Obinutuzumab.

Obinutuzumab will be provided by Genentech Inc. 8000 mg of obinutuzumab will be provided per patient, up to 240,000 mg total drug for this study.

8.3.1. Obinutuzumab Formulation

Obinutuzumab is provided as a single-use vial. Each vial contains 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).

8.3.2. Obinutuzumab Storage

The recommended storage conditions for the obinutuzumab drug product are between 2°C and 8°C, protected from light. Chemical and physical in-use stability for obinutuzumab dilutions in 0.9% sodium chloride (NaCl) at concentrations of 0.2 to 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 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.

8.3.3. Obinutuzumab Dosage

Obinutuzumab is administered in six treatment cycles. The first 1000 mg is administered over the first 2 days of the first cycle of treatment. On Day 1, Cycle 1, 100 mg is administered. On the following day (Day 2), 900 mg is administered. On Days 8 and 15 of Cycle 1, 1000 mg is administered on each day for a total of 3000 mg in the first cycle. For Cycles 2 − 6, 1000 mg of obinutuzumab is administered on Day 1 of each 28-day cycle.

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

Obinutuzumab must be administered in a clinical setting (inpatient or outpatient). Full emergency resuscitation facilities should be immediately available, and patients should be under close supervision by the investigator 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 AEs occur after 2 hours, the IV line may be removed. For subsequent infusions, the IV line should remain in place for at least 1 hour from the end of infusion; if no AEs occur after 1 hour, the IV line may be removed. Obinutuzumab will be provided by the Sponsor to investigational centers.

8.3.4 Obinutuzumab Preparation

Prepare the solution for infusion, using aseptic technique, as follows:
• Inspect visually for any particulate matter and discoloration prior to administration. Dilute into a 0.9% sodium chloride PVC or non-PVC polyolefin infusion bag.
• Do not use other diluents such as dextrose (5%).
• Do not use obinutuzumab beyond the expiration date stamped on the carton.

Preparing the First 1000 mg for Administration over Days 1 and 2 of Cycle 1:
The administration of the first 1000 mg of obinutuzumab must occur over 2 days. On day 1 of the first treatment cycle, 100 mg should be administered. On the following day (Day 2), 900 mg should be administered.

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 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 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.

- Withdraw 40 mL of obinutuzumab solution from the vial.
- Dilute 4 mL (100 mg) of obinutuzumab into a 100 mL 0.9% sodium chloride infusion bag for immediate administration.
- Dilute the remaining 36 mL (900 mg) into a 250-mL 0.9% sodium chloride infusion bag at the same time for use on Day 2 and store at 2°C to 8°C (36°F− 46°F) for up to 24 hours. After allowing the diluted bag to come to room temperature, use immediately.
- Clearly label each infusion bag.

Preparation of 1000 mg Solution for Infusion on Days 8 and 15 of Cycle 1 and Day 1 of Cycles 2 − 6:

- Withdraw 40 mL of obinutuzumab solution from the vial.
- Dilute 40 mL (1000 mg) into a 250-mL 0.9% sodium chloride infusion bag.
- Mix diluted solution by gentle inversion. Do not shake or freeze.

8.3.5. Obinutuzumab distribution

Study drug(s) to be distributed to centers in the US shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA).

Please refer to the package insert for further information regarding the storage, handling and administration of obinutuzumab (Appendix A).

8.4. Dosage and Administration of Study Drugs

Entospletinib tablets will be provided by Gilead Sciences, Inc. and will be taken orally. Initiation of treatment with the study drug will take place after enrollment and cohort assignment. Subjects will take entospletinib on Day -7 of the run-in phase. Starting on Day -6, subjects will continue to take entospletinib at approximately the same time each day. To reduce variability, subjects will be instructed to take entospletinib approximately 1 hour before or 2 hours after a meal.

Obinutuzumab will be obtained from Genentech. Obinutuzumab is administered as an infusion and requires pre-medications due to the risk of infusion reactions. See section 5.3.2 and the package insert for details. On days when obinutuzumab is administered with entospletinib, obinutuzumab will be given after entospletinib.

If the subject misses a dose of entospletinib, he/she should be instructed to take the study drug as soon as he/she remembers, unless more than 12 hours has elapsed since the scheduled time of the missed dose of entospletinib if administered once daily or 6 hours has elapsed if administered twice daily. In this case, the subject should be instructed to wait and take the next dose at the regularly scheduled time.

9.0 BIOMARKER, CORRELATIVE AND SPECIAL STUDIES

9.1. Biomarker/lab correlative studies

9.1.1. Rationale and Hypothesis

SYK is a key kinase which ensures activation of the B-cell receptor signaling cascade. BAFF receptor co-opts BCR signaling in CLL via a poorly described mechanism, which involves functional SYK. Thus, downstream events of BCR activation, either via antigen engagement or soluble BAFF receptor ligands, cannot occur if SYK kinase is rendered inactive. BCR is involved in activation of NFκB and thereby upregulation of anti-apoptotic Bcl-2 family members Bcl-2, Bcl-X and Bfl-1, and repression of pro-apoptotic BH3-only protein Bim. SYK is also directly involved in stabilization of the pro-survival protein Mcl-1. Thus, we hypothesize that SYK inhibition in CLL (lymphoma) cells in vivo will abrogate NFκB activity and modulate the balance between pro- and anti-apoptotic Bcl-2 family members in favor of cell death.

9.1.2. Intended Use of Data

The biomarker studies from treated subjects will provide evidence of the drug mechanism, and findings will be correlated with disease response.

9.1.3. Preclinical Data and Sample Data Supporting the Biomarker Analysis

Supporting data is discussed in Section 2.5.3 and Appendix F, Figures 1-4.

9.1.4. Assay Method and Validity

Peripheral blood mononuclear cells will be isolated from each subject using standard Ficoll techniques. Samples will be analyzed by western blotting, NF-κB Transcription Factor Assay and RT-PCR.

9.1.5. Investigator Experience

The Sponsor Investigator has used these assays to measure these biomarkers in more than 50 CLL patient samples ex vivo. All of the above methods have been previously published by us [37, 38, 43].

9.1.6 Number of Subjects

The number of subjects to be accrued is driven by the study primary objectives. The biomarker analysis will be performed on all subjects. In patients who do not have circulating tumor cells, peripheral blood mononuclear cells will be collected and studied based on the availability of biologic material.

9.1.7 Risk to the Subject

The risk to the subject based on the biomarker studies is only the collection of blood at two time points in cycle 1. The benefit to the study will be to facilitate further development of this therapeutic rationale.

9.1.8. Collection of Specimen(s)

Blood (20 ml with each collection) will be obtained on Day -7 of the run-in phase (prior to entospletinib dosing) and on C1D1 (prior to administration of obinutuzumab or any pre-medications; patient may have taken entospletinib); on C7D1, at the end of study treatment and at relapse.
Bone marrow aspirate (10 mL in a heparinized syringe) will be obtained with each bone marrow biopsy performed on study, including at screening (if performed) and at the time of CR confirmation biopsy (if performed) or End-of-Treatment biopsy.

In the event of study closure, specimens mentioned above will not be collected at the end of treatment visit.

9.1.9. Handling of Specimens(s)

Venous blood samples and bone marrow aspirates collect at OHSU will be transported to Dr. Danilov's laboratory within 2 hours after collection. Samples will be transported at room temperature. Blood samples collected at participating sites will be shipped ambient to Dr. Danilov's laboratory the day of collection. Sample shipments from participating sites can only be accepted at Dr. Danilov's Monday-Friday. Please see the Study Operation Manual for the shipping address.
Peripheral blood mononuclear cells (including CLL B-cells, or lymphoma B-cells where present in the blood) will be isolated using Ficoll-Hypaque gradient and used for preparation of protein, RNA and DNA at Dr. Danilov laboratory or laboratories identified at participating sites. Protein and RNA will then be stored at -80C, and DNA will be stored at -20C.

The following analysis will be conducted:

- *IGHV* mutational status (if not available after routine testing) will be assessed employing IgH Somatic Hypermutation Assay v.2.0 (InVivoScribe Technologies). This testing will be performed at Dr. Danilov's laboratory [44], unless otherwise available;
- Expression of BCR activation markers (immunoblotting:, pSyk, pBTK, pErk, pAkt)
- Expression of Bcl-2 family proteins (immunoblotting: Bcl-2, Mcl-1, Bim, Bcl-X)
- Markers of apoptosis (immunoblotting: PARP)

- NF-κB transcription targets (RT-PCR: cFLIP, CCND1)
- NF-κB activity – NF-κB Transcription Factor assay [37];

Comparison of the above biomarkers will be conducted: before/after in vivo exposure to entospletinib. Exploratory analysis will be performed using paired t-test statistics.

Remaining cells will be viably frozen (10% DMSO/FBS), and stored in liquid nitrogen, until further processing. Remaining cell lysates will also be stored and may be used to assess additional biomarkers that may be correlated with response to entospletinib.

10.0 STUDY PROCEDURES AND SCHEDULE OF EVENTS

Patients will be considered on study upon signing the informed consent. Toxicities which occur prior to administration of the first dose of entospletinib will *not* be subject to analysis. The study consists of a Screening Period with baseline tumor assessment before entospletinib administration and Treatment Period of at least ***twelve*** cycles (28 days per cycle), and a Follow-up and EFS Period, unless participants come off study in the event of study closure. Subjects will receive a total of ***six*** cycles of combination therapy (entospletinib and obinutuzumab) and an additional six cycles or more of entospletinib single agent therapy, unless treatment is discontinued for one of the pre-specified reasons (Section 5.4).

10.1 Screening/Baseline Visit

During the Pretreatment Period, subjects are screened and consented for the study. Informed consent must be obtained before initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for this research study. Evaluations performed as part of routine care before informed consent can be utilized as screening evaluations if done within the defined time period. Informed consent should be obtained within 30 days before the first dose of study treatment.

Subjects will undergo screening evaluations to determine study eligibility. All qualifying screening and eligibility assessments must be performed within 30 days before the first dose of study treatment. Tests used for baseline disease assessments must be performed within specified time frame of the initial dose of study treatment. Refer to section 10.4 and 10.5. Those assessments will be performed at OHSU or the participating sites. However, results provided by other institutions are acceptable as long as they satisfy the timing criteria.

10.2 Treatment Period

Clinic visits will be performed every cycle on Day 1. Under certain circumstances (e.g., clinic holiday, inclement weather) Day 1 may be delayed by not more than 3 days or occur earlier than scheduled by not more than 3 days during cycles 2-12; Days 8 and 15 of Cycle 1 may be delayed by 1 day or occur 1 day early.

Clinical laboratory assessments are to be collected on D1 of each cycle visit, or ≤ 48 hours before those visits, and the test results must be available and reviewed before obinutuzumab is given (C1-6). Screening assessment tests can be considered as Day -7 tests (start of treatment) if performed ≤72 hours before the first dose of study treatment; otherwise, the required evaluations must be repeated within this timeframe.

On Day -7 and C1D1 all patients with CLL/SLL will provide samples for biomarker analysis.

After the initial 12 treatment cycles subjects in whom it is clinically safe to do so, are benefitting from entospletinib, and who desire to continue entospletinib monotherapy may continue entospletinib therapy beyond the initial twelve cycles, with approval from the treating physician and sponsor-investigator, until disease progression or removal from treatment (see Section 5.4).

10.2.1 Pre-Treatment Criteria - Day -7

Hematologic parameters: platelets must be ≥50,000/mm^3 (in absence of transfusion support), ANC ≥ 1000/mm^3 unless due to disease involvement in the bone marrow; hemoglobin > 8 g/dL (transfusion support permissible);

Non-hematologic parameters: bilirubin (total, and if elevated – direct) ≤ 2 X institutional ULN (unless due to known Gilbert's syndrome or hemolysis directly attributable to CLL/SLL); AST or ALT < 2.5 X institutional ULN.

Vital signs, all laboratory data (including pregnancy testing) must be reviewed by the treating physician prior to administering the first dose of a study agent.

The study treatment period ends on day 28 of the last cycle of study treatment. Subjects will return to the study site 2 months (±7 days) after the last 28-day cycle of study treatment for an End of Treatment visit unless early study closure procedures are in affect (see section 5.4). A bone marrow biopsy will be performed no later than 3 months after the End of Treatment visit unless early study closure procedures are in affect (See section 5.4). Adverse events that are related to study treatment and are ongoing at the time of this visit will be followed until resolution or until considered irreversible by the sponsor-investigator unless early study closure procedures are in affect.

10.2.2 Pre-Treatment Criteria – from C2 until end of treatment

Hematologic parameters: platelets must be ≥50,000/mm^3 or >75% of baseline, whichever is lower (without transfusion support); hemoglobin > 8 g/dL (transfusion support permissible); ANC≥1000/mm^3 or >75% of baseline, whichever is lower (G-CSF support permissible at the discretion of the investigator in case of ANC<1000).

Non-hematologic parameters: bilirubin (total, and if elevated – direct) ≤2 X institutional ULN (unless due to known Gilbert's syndrome or hemolysis directly attributable to CLL); AST or ALT < 2.5 X institutional ULN.

10.3 Follow-up

Follow-up visits will occur every 3 months for the first 12 months following the End of Treatment visit. Disease assessments will be obtained every 3 months or earlier, if clinically indicated. Laboratory assessments and physical examinations will be completed at every visit. CT scans will be obtained at 6 and 12 months after the end-of-treatment visit (±7 days) and as clinically indicated thereafter. All subjects will participate in EFS analysis upon completion of the Follow-up period.
In the event of Study Closure, patients who are receiving study drug at the time of closure will complete an abbreviated End of Treatment visit. No additional follow up will occur.

10.4 Study Assessments and Procedures

- **Demographics and Medical History**: Demographic data will be collected at screening and a complete medical history will be collected at visits prior to starting study treatment. Medical history in between visits should be documented at each study visit once study treatment has started. All transfusions including date, product transfused, number of units, and reason for transfusion should also be collected as part of the interval medical history.

- **Concomitant Medications**: All concomitant medications and treatments must be recorded in the case report form (CRF). Any prior medication received up to 30 days prior to the screening visit will be recorded in the CRF. Concomitant treatments that are required to manage a subject's medical condition during the study will also be recorded in the CRF. Prior and/ or ongoing medications will be reviewed during screening to determine subject eligibility. The medication record will be maintained following enrolment including any changes to the dose or regimen. Prior and concomitant medication including any prescription, over the counter or natural/herbal/multivitamin preparations taken will be recorded.

- **Physical Exam**: Physical examination consists of a review of all major body systems at screening and on day 1 visits of each cycle only (Day -7 during the run-in phase in lieu of C1D1). Symptom-directed physical examination relevant to the subject's symptoms is performed during the treatment period and at the post-treatment periods. Symptom-directed physical examinations must at a minimum document changes in lymphadenopathy, hepatomegaly, and splenomegaly.

  If abnormal findings emerge or worsen from baseline assessment, then the AE page of the CRF should be completed for these findings. If a finding meets the criteria for an SAE, then the appropriate procedures for reporting such events will be followed as described in Section 7.

- **Performance Status**: ECOG will be determined and performed at the visits indicated in the schedule of events in section 10.5. Refer to Appendix D for ECOG scale.

- **Pregnancy Test**: A serum or urine pregnancy test is required for all female subjects during screening for women of childbearing potential. If the urine pregnancy test is positive, serum pregnancy tests must be performed per institutional standards.

- **Vital Signs**: Vital sign measurements should include: blood pressure, heart rate, temperature, respiration rate, and oxygen saturation.

- **Complete Blood Count**: 5-part differential, hemoglobin, white blood cell count (WBC), platelet count, absolute neutrophil count (ANC), and absolute lymphocyte count (ALC) are required at each time point as described in the schedule of events. Direct antiglobulin test and % reticulocyte count are required at screening only.

  CBC performed $\leq$ 72 hours prior to D1 of each cycle can be used in lieu of repeating on D1.

- **Coagulation Panel**: activated partial thromboplastin time (aPTT) and prothrombin time or INR (PT/INR).

- **Chemistry**: LDH, creatinine, urea (BUN), potassium, sodium, chloride, bicarbonate, glucose,

alkaline phosphatase, AST, ALT, phosphorus, total bilirubin, direct bilirubin (if total bilirubin is elevated only), albumin, uric acid are required.

Chemistry performed ≤ 72 hours prior to D1 of each cycle can be used in lieu of repeating on D1.

- **Urinalysis**: performed per institutional standards.

- **β2-microglobulin:** performed per institutional standards

- **Hepatitis Screening**: hepatitis B surface antigen and hepatitis C antibody are required. Results from within 12 months prior to the first dose of study treatment are acceptable.

- **Serum Immunoglobulins**: IgG, IgM and IgA are required.

- **Genetic and Molecular Prognostic Markers**: Testing results are NOT required to proceed with study enrollment. Testing for *IGHV* mutational status (if not previously available) and GeneTrails analysis will be performed on a blood sample obtained on day 1 of the study (see Section 9 of the protocol).
    - CLL FISH panel (trisomy 12, deletion 11q, deletion 17p, deletion 13q), results acceptable if performed within 6 months prior to the first dose of study treatment, and if no intervening treatment occurred
    - ZAP-70 expression - results acceptable if performed at any time since diagnosis and will be documented where available, but not required
    - *IGHV* mutational status, if available - results acceptable if performed at any time since diagnosis. If this result is not available, testing for *IGHV* mutational status will be performed in Dr. Danilov's laboratory (see Section 9: Correlative studies).

- **Electrocardiogram (ECG):** 12-lead ECG must be performed at screening. QTc interval should be measured per institutional standard. ECGs will be repeated as clinically indicated.

- **Echocardiogram (ECHO):** will be performed at screening if clinically indicated. LVEF will be measured per institutional standard. Echocardiograms will be repeated as clinically indicated.

- **Computerized Tomography Scan (CT):** neck, chest, abdomen and pelvis are required with contrast. If contrast cannot be used for clinical reasons, a CT without contrast will be acceptable. Cheson criteria should be used to read each scan.

  CT scans performed within 30 days of the first study treatment are acceptable for baseline assessment. Additional CT scans will be obtained at C4D1, C7D1, C10D1 (or ≤72 h prior), C18D1 and C24D1, if appropriate, at the end of treatment visit, at 6 and 12 months after the end of treatment visit (±7 days) and as clinically indicated thereafter. CT scanning may be performed at any point where it is suspected that disease progression has occurred between scheduled assessments.

  NOTE: In subjects with NHL (FL, MZL, MZL) – PET-CT scans *may* be performed in place of CT scans at screening, during the study and at follow-up. However, the same modality should be used for each individual patient during the study.

NOTE: In subjects with LPL, CT scans on C4D1, C10D1 and during follow-up will be performed only if lymphadenopathy is present at screening, or if new lymphadenopathy develops during scheduled CT scans on C7D1 or the EOT visit.

- **Adverse Event Assessments:** Toxicities and adverse experiences will be assessed at each visit using the NCI Common Toxicity Criteria for Adverse Events 4.0. Adverse events will be reported and recorded as indicated in section 7 of this protocol. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

- **Bone Marrow Aspirate and Biopsy** (optional at screening unless ANC<1,000/mm^3 or platelets<50,000/mm^3; optional at the end of treatment)**:** will include cytogenetics and FISH, per institutional standards. Bone marrow biopsy performed within 6 months prior to the first dose of study treatment is acceptable.

  Bone marrow biopsy should also be performed between 1 and 3 months at any time CR is suspected (e.g., C7D1, C10D1, C18D1, C24D1). An End-of-Treatment visit bone marrow biopsy will be performed between 1 and 3 months after the End of Treatment visit, unless study closure occurs. However, if CR is confirmed by bone marrow biopsy after C7D1, an EOT biopsy will not be performed.

- **Biomarker Blood Samples:** see protocol section 9 – Correlative studies for detailed description of collection

- **Overall Response Assessment:** performed at C7D1, EOT and during the first year following EOT to coincide with CT scans at 6 and 12 months post EOT.

-

- **Event-Free Survival (EFS) Assessment**: performed every 3 months during the Follow-up period, and every 6 months after the Follow-up period unless study closure is in effect. EFS is defined as the date of objective signs of disease recurrence, subsequent anti-leukemic therapy, or death, whichever is first reported.

10.5 Schedule of Events

Table 8. SCREENING AND CYCLE 1

Visit/Cycle	Screening	Day -7 (Run-in Phase)	Cycle 1			
Cycle Day			1	2	8	15
Study Windows	-30 days	-3 days for screening tests to count for Day -7			±1 day	±1 day
Entospletinib		Days -7 to -1	Days 1-28			
Obinutuzumab			X	X	X	X
Informed consent	X					

Medical history	X	X	X	X	X	X
Concomitant medication (s)	X	X	X	X	X	X
Adverse events assessment		X	X	X	X	X
Height, weight	X	X				
Vital signs	X	X	X	X	X	X
ECOG performance status	X	X				
Physical examination	X	X				
12-lead ECG	X					
ECHO	X[A]					
Bone marrow aspirate and biopsy (includes biomarker aspirate)	X[B]					
Hematology	X	X	X	X	X	X
Chemistry	X	X	X[C]	X[C]	X	X
Hepatitis serologies	X					
aPTT, INR	X					
Serum immunoglobulins	X					
Reticulocyte count	X					
Direct antiglobulin test	X					
β2-microglobulin	X					
Genetic and molecular prognostic markers	X[D]	X[D]				
Biomarker blood samples		X	X			
Serum/Urine pregnancy test	X					
Urinalysis	X					
CT neck, chest, abdomen and pelvis (with contrast when clinically acceptable)[E]	X					

KEY

[A]ECHO will be performed only if clinically indicated

[B]Bone marrow aspirate and biopsy is optional unless ANC<1,000/mm^3 or platelets<50,000/mm^3. Results acceptable if performed within 6 months prior to screening visit. Biomarker sample (10 mL aspirate) should be obtained (see 9.0 Correlative studies).

[C]Optional serum biochemistry/metabolic panel measurements may be considered by the investigator at the end of C1D1 and C1D2.

[D]CLL FISH panel results acceptable if performed within 6 months prior to the first dose of study treatment, and if no intervening treatment occurred; ZAP-70 expression results acceptable if performed at any time since diagnosis and will be documented, but not required; IGHV mutational status - results acceptable if performed at any time since diagnosis. If this result is not available, testing for IGHV mutational status will be performed in Dr. Danilov's laboratory.

[E]In subjects with NHL (FL, MZL, MCL) – PET-CT scans *may* be performed in place of CT scans at screening, during the study and at follow-up. However, the same modality should be used for each individual patient during the study.

Table 9. CYCLE 2-

Visit/Cycle	Cycle 2-6	Cycles 7-12	Cycles 13, 14, 16, 18, 20 and then every two cycles until end of therapy
Cycle Day	**1**	**1**	**1**
Study Windows	**+/- 3 days**	**+/- 3 days**	**+/- 7 days**
Entospletinib[E]	**Days 1-28**	**Days 1-28**	**Days 1-28**
Obinutuzumab	**X**		
Medical history	**X**	**X**	**X**
Concomitant medication (s)	**X**	**X**	**X**
Adverse events assessment	**X**	**X**	**X**
, Weight	**X**	**X**	**X**
Vital signs	**X**	**X**	**X**
ECOG performance status	**X**	**X**	**X**
Physical examination	**X**	**X**	**X**
Hematology	**X**	**X**	**X**
Chemistry	**X**	**X**	
CT neck, chest, abdomen and pelvis (with contrast when clinically acceptable)[A]	**X**[B] **(C4D1 or ≤72 h prior)**	**X**[B] **(C7D1 and C10D1 or ≤72 h prior)**	**C18D1 and C24D1**
Assessment of B-cell depletion		**X (C7D1)**	
Biomarker blood sample		**X (C7D1)**	
Bone marrow aspirate and biopsy (includes biomarker aspirate)[C]		**X**	**X**
Overall response assessment[D]	**X**	**X**	**X**[B]

KEY:
[A]In subjects with NHL (FL, MZL, MCL) – PET-CT scans *may* be performed in place of CT scans at screening, during the study and at follow-up. However, the same modality should be used for each individual patient during the study.
[B]In subjects with LPL, CT scans on C4D1, C10D1 and during follow-up will be performed only if lymphadenopathy is present at screening, or if new lymphadenopathy develops during scheduled CT scans on C7D1 or the EOT visit.
[C]If radiographic and laboratory findings suggest that CR has been obtained, a bone marrow aspirate/biopsy should be obtained to confirm CR between 1 and 3 months after the corresponding CT, accompanied by a biomarker sample (10 mL aspirate) – see 9.0, Correlative studies
[D]Overall response assessment should be performed when CTs or PET-CTs are performed
[E]Subjects may continue entosplentinib monotherapy beyond C12.

Table 10. End of Treatment and Follow-up prior to study closure

Visit/Cycle	EOT[F]	Follow up[F]	
Cycle Day	8 weeks after last dose of study drug	Every 3 months for the first year following EOT	Every 6 months for EFS thereafter
Study Windows	+/- 7 days	+/- 7 days	+/-2 months
Medical history	X		
Concomitant medication (s)	X		
Adverse events assessment	X		
Height, weight	X		
Vital signs	X	X	
ECOG performance status	X	X	
Physical examination	X	X	X
MRD assessment, peripheral blood	X		
Bone marrow aspirate and biopsy; includes biomarker aspirate (all patients)	X[A]		
Hematology	X	X	X
Chemistry	X	X	
Serum immunoglobulins	X		
CT neck, chest, abdomen and pelvis (with contrast when clinically acceptable)[B]	X	X[C, D]	
Overall response assessment[E]	X	X	
Event-free survival assessment		X	X

KEY:

[A]An optional bone marrow aspirate/biopsy should be obtained between 1 and 3 months after End of Treatment visit, accompanied by MRD assessment and a biomarker aspirate. Exception: patients who underwent a bone marrow biopsy to obtain CR confirmation after 6 cycles of therapy will not undergo EOT bone marrow biopsy

[B]In subjects with NHL (FL, MZL, MCL) – PET-CT scans *may* be performed in place of CT scans at screening, during the study and at follow-up. However, the same modality should be used for each individual patient during the study.

[C]CT scans will be obtained at 6 and 12 months after the end of treatment visit (±7 days), and as clinically indicated thereafter.

[D]In subjects with LPL, CT scans on C4D1, C10D1 and during follow-up will be performed only if lymphadenopathy is present at screening, or if new lymphadenopathy develops during scheduled CT scans on C7D1 or the EOT visit.

[E]Overall response assessment should be performed when CTs or PET-CTs are performed.

[F] Participants still participating at study closure will complete an abbreviated EOT visit and no additional follow up will occur.

Table 11. Modified End of Treatment SoE: participants on study at time of study closure

Visit	**EOT**
Timing	At the time of study drug discontinuation
Window	+30 days
Medical History	X
Concomitant medications	X
Adverse Events Assessment	X
Height, weight	X
Vital signs	X
ECOG performance status	X
Physical examination	X
Hematology	X
Chemistry	X

11.0 MEASUREMENT OF EFFECT

All subjects who received at least one dose of study drug (ITT, section 13.3) will be evaluable for efficacy.

11.1 Disease Evaluations

Physical examination, which will focus on documenting a change in the number of sites and size of lymphadenopathy, hepatomegaly and splenomegaly, will be done as part of the full disease evaluation during treatmenth. More extensive physical exams will be performed if guided by the development of new symptoms.

Complete blood count (CBC) with measurement of parameters including ALC will be obtained before start of treatment (Day -7), Days 1, 2, 8 and 15 of C1; on day 1 for the remaining twelve cycles, every 3 months for the first 12 months, and every 4-6 months thereafter until disease progression or death.

Serum biochemistry/metabolic panel will be obtained on will be obtained on Days -7, 1, 2, 8 and 15 of C1; on day 1 for the remaining twelve cycles, every 3 months for the first 12 months, and every 4-6 months thereafter until disease progression or death.

Computed tomography (CT) scan of neck, chest, abdomen and pelvis with intravenous contrast where possible will be performed at screening, on C4D1, C7D1, C10D1 (or ≤72 hours prior), at C18D1 and C24D1 should patients opt to continue Entospletinib monotherapy
A unilateral bone marrow aspirate and biopsy must be obtained during screening or up to 6 months before the first dose of study drug. Subjects who have bone marrow aspirate and biopsy results since completion of their last therapy for CLL may use those results if they were obtained within 6 months prior to the first dose of study drug. If the subject's physical examination findings, laboratory and radiographic evaluations suggest that CR has been obtained during C7D1,a bone marrow aspirate/biopsy should be obtained to confirm the CR within the timeframe specified above.

11.2 Criteria for Response

11.2.1. Subjects with CLL/SLL

Modified IWCLL guidelines [41] will be used to measure response in CLL/SLL subjects.

ORR for CLL/SLL subjects is defined as CR, CRi, nPR and PR, PD and SD. Subjects will be assessed for response at the end of treatment. If there is a clinical suspicion for progression, disease assessment may be performed at any time.

Complete Remission (CR)

Requires all of the following:

- Peripheral blood lymphocytes (evaluated by blood and differential count) below 4×10^9/L
- Absence of significant lymphadenopathy (eg,lymph nodes >1.5 cm in diameter) by physical examination and imaging, if baseline scans were abnormal
- No hepatomegaly or splenomegaly by physical examination and imaging, if baseline scans were normal
- Absence of constitutional symptoms (B symptoms)
- Blood counts must have the following findings:
  a) Neutrophils > 1.5×10^9/L without need for exogenous growth factors
  b) Platelets > 100×10^9/L without need for exogenous growth factors
  c) Hemoglobin > 11.0 g/dL without red blood cell transfusion or need for exogenous erythropoietin
- Bone marrow aspirate and biopsy must have the following findings:
  a) Normocellular for age
  b) Less than 30% of nucleated cells being lymphocytes
  c) No B-lymphoid nodules (confirmed by IHC)

Complete Response with Incomplete Marrow Recovery (CRi)

Subjects who fulfill all the criteria for a CR but who have a hypocellular marrow and persistent anemia or thrombocytopenia or neutropenia unrelated to CLL but secondary to drug toxicity. If the marrow is hypocellular, a repeat determination should be performed after 4 weeks, or when peripheral blood counts have recovered.

Nodular Partial Response (nPR)

Subjects who fulfill all the criteria for CR but who have bone marrow evidence of B-lymphoid nodules by IHC.

Partial Remission (PR)

Blood count should show at least one of the following results:

- Neutrophils more than 1.5×10^9/L without need for exogenous growth factors
- Platelet counts > 100×10^9/L or 50% improvement over baseline without need for exogenous growth factors
- Hemoglobin > 11.0 g/dL or 50% improvement over baseline without requiring red blood cell transfusions or exogenous erythropoietin

AND two of the following three criteria should be met:

- Decrease in number of blood lymphocytes by 50% or more from the value before therapy
- Reduction in lymphadenopathy by physical examination or by imaging as defined by:
- A decrease in lymph node size by 50% or more either in the sum products of up to 6 lymph nodes, or in the largest diameter of the enlarged lymph node(s) detected prior to therapy
- No increase in any lymph node, and no new enlarge lymph node
- In small lymph nodes (< 2 cm), an increase of less than 25% is not considered significant

  A reduction in splenomegaly and hepatomegaly by 50% or more, by physical examination or imaging.

PR with Lymphocytosis

Because of the expected egress of CLL cells into the peripheral blood with BCRi\, lymphocytosis may be encountered with entospletinib. Therefore progressive lymphocytosis without other clinical evidence of disease progression cannot be used to define disease progression. Accordingly, lymphocyte count will be ignored in the evaluations of progression. Of note, this has been an accepted standard in trials using inhibitors of B-cell receptor signaling for the treatment of CLL.

Furthermore, lymphocytosis should not interfere at the time of designation of a PR. PR with lymphocytosis should be based on other measurable aspects of disease other than ALC [45].

Progressive Disease

Includes at least one of the following:

- Appearance of any new lesion, such as enlarged lymph nodes > 1.5 cm, splenomegaly, hepatosplenomegaly, or other organ infiltrates.
- An increase by 50% or more in greatest determined diameter of any previous site including, liver and/or spleen,
- A 50% or greater increase in lymphocyte count.
- Transformation to a more aggressive histology (eg, Richter syndrome). Whenever possible this diagnosis should be established by lymph node biopsy.

Progressive Disease After Treatment

Includes at least one of the following:

- Any progressive disease criteria listed above
- The progression of any cytopenia (unrelated to autoimmune cytopenia) which occurs at least 3 months after treatment as documented by:
  - a decrease in Hb levels by more than 20 g/L (2 g/dL) or to less than 100 g/L (10 g/dL), OR
  - a decrease of platelet counts by more than 500,
- OR
  - a decrease of platelet counts by more than 50% or to less than 100 x 10^9/L (100 000/uL).

Stable Disease

Patient who have not achieved a CR or a PR, and who have not exhibited progressive disease, will be considered to have stable disease (which is equivalent to a nonresponse).

11.2.2. Subjects with Follicular Lymphoma, Marginal Zone Lymphoma and Mantle Cell Lymphoma (enrolled on Phase I portion of the study) – See Appendix G

The determination of MZL and MCL response and progression will be based on standardized response criteria for malignant lymphoma [46].

11.2.3. Subjects with Lymphoplasmacytic Lymphoma (enrolled on Phase I portion of the study) – See Appendix E

11.2.4. Subjects with Hairy cell Leukemia (enrolled on Phase I portion of the study) – See Appendix I

12.0 DATA REPORTING/REGULATORY REQUIREMENTS

12.1 Data Collection and Storage

Study outcome data will be captured in electronic case report forms (eCRFs) using an electronic data capture (EDC) system on OHSU secure servers, which facilitates information being stored in a unified format and location. To further preserve confidentiality, PHI in the EDC system will be limited to just birth date and visit dates. The web-accessible EDC system is password protected and encrypted with role-based security, and administered by designated informatics staff within OHSU or Knight Cancer Institute. All users of the database are assigned a unique ID, username, and password and must complete training appropriate to their role before they are authorized to enter, access, and store data in the database.

Basic accrual tracking information (demographic, consent, visit information) will be captured in OHSU's electronic clinical information research system (eCRIS), hosted on OHSU secure servers and managed by OHSU's information technology group at their data center in downtown Portland, Oregon. Any additional printed documents containing participant identifiers, such as those from the medical record to confirm eligibility, will be filed in binders and kept in a locked, secure location.

Data from correlative studies will be entered into the EDC system by study personnel at OHSU. All other electronic data extracts will be stored only on OHSU computers and restricted drives, limited only to study investigators and staff with authorization to access the data.

Quality assurance will be conducted as outlined in section 12.7 under data safety and monitoring.

12.2 Privacy, Confidentiality, and Data Security

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Participants will sign an authorization that includes the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information

- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

Loss of patient confidentiality is a risk of participation. Study participant identities will be kept confidential except as required by law. Subjects' samples will be identified by code only (i.e. linked, but de-identified). Subject samples will be de-identified at the time and site of collection. Electronic case report forms, participant, and study information will be kept in a password protected database. Additionally, documents containing participant identifiers, such as those from the medical record to confirm eligibility, will be filed in binders and kept in a locked, secure location in the Office of Clinical Research at each center.

Study outcome data will be captured in electronic case report forms (eCRFs) using an electronic data capture (EDC) system stored on REDCap CLOUD secure servers, which facilitates information being stored in a unified format and location. REDCap Cloud is a web-hosted application hosted by nPhase (located in Encinitas, California), and is an approved system that has been reviewed by OHSU Security. To further preserve confidentiality, PHI in the EDC system will be limited to just birth date and dates associated with patient's medical care and life events. The web-accessible EDC system is password protected and encrypted with role-based security, and administered by designated informatics staff within OHSU or Knight Cancer Institute. All users of the database are assigned a unique ID, username, and password and must complete training appropriate to their role before they are authorized to enter, access, and store data in the database.

Each subject who signs consent will be assigned a unique coded identifier consisting of numbers. This identifier will be associated with the subject throughout the duration of their participation in the trial. The coded identifier will used to identify subject specific samples that are received both at OHSU and other sites. Blood and tissue samples collected for the purposes of this protocol will be stored until they can be analyzed and will then be destroyed.

12.3 Protocol Review

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU Knight Cancer Institute Clinical Research Review Committee and the appropriate Institutional Review Board prior to any subject being consented on this study at OHSU.

Other participating sites must have IRB approvals of the protocol by the IRB of record before consenting any subjects.

12.4 Informed Consent

Written informed consent will be obtained from all subjects, or the legally authorized representative of the subject, participating in this trial, as stated in the Informed Consent section of the case of Federal Regulations, Title 21, Part 50. If a subject's signature cannot be obtained, and for all subjects under the age of 18, the investigator must ensure that the informed consent is signed by the subject's legally authorized representative. Documentation of the consent process and a copy of the signed consent shall be maintained in the subject's medical record. All participating sites must have IRB approval of ICF by the IRB of records before consenting any subjects.

12.5 Changes to Protocol

Any modification of this protocol must be documented in the form of a protocol revision or amendment signed by the principal investigator and approved by the CRRC and IRB before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the subject. In that event, the investigator must notify the CRRC and IRB in writing within 10 working days after the implementation. Investigators holding the IND must notify FDA of substantive changes to the protocol.

Other participating sites must submit any proposed changes to protocol to the OHSU Coordinating Center for review and endorsement before submitting or implementing changes.

12.6 Maintenance of Records

If the investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed upon designee, such as another institution, another investigator, or to OHSU Knight Cancer Institute Clinical Trials Office. Records must be maintained according to sponsor or FDA requirements.

Following closure of the study, the investigator will maintain all site study records in a safe and secure location. The records are maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection) and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Upon completion of study analysis, research information is stored in Records Management off-site storage. Documents are shredded on site after 50 years of storage.

Electronic case report forms, participant, and study information will be kept in an electronic password protected database indefinitely.

12.7 OHSU IRB Reporting of Unanticipated Problems and Adverse Events

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.8 OHSU Knight Cancer Institute Data and Safety Monitoring Plan

In addition to complete study and pharmacy files, complete records must be maintained on each subject treated on this protocol. OHSU Knight Cancer Institute, through the auditing function of the Knight Clinical Trials Office, is responsible for ensuring that all member investigators and affiliate investigators conduct clinical research studies in compliance with local IRB standards, FDA regulations and NIH policies and in accordance with the Data and Safety Monitoring Plan policies and procedures here.

Locally initiated studies will be audited by OHSU Knight CI Auditor. Newly approved studies may be audited any time after enrollment has been initiated. Each OHSU Knight approved treatment protocol will be audited on an annual basis in accordance with the Knight Data and Safety Monitoring Plan.

It is the responsibility of each participating site's principal investigator to ensure that the study is being conducted in compliance with local IRB standards, FDA regulations, and NIH policies. It is also the responsibility of each site's principal investigator to ensure that quality assurance audits at their site are conducted according to their institution's policies and procedures. The quality assurance audit process provides assurance that reported data accurately reflects the data in the primary subject record.

Study monitoring will be performed by OHSU and will include periodic assessment of the regulatory compliance, data quality, pharmacy records and study integrity. Study records will be reviewed and directly compared to source documents and the conduct of the study will be discussed with the Lead PI. Monitors may request access to all regulatory documents, source documents, CRFs, and other study documentation for on-site inspection. Direct access to these documents is guaranteed by the investigator, who must provide support at all times for these activities.

12.9 Inclusion of Women, Minorities and Children

12.9.1 Inclusion of Women and Minorities

No OHSU Knight Cancer Institute study will focus on any particular gender, racial or ethnic subset. No subject will be excluded from the study on the basis of gender, racial or ethnic origin. Male, female and minority volunteers will be recruited for this study from the general population.

CLL occurs with higher frequency in males. CLL is also more common among the Caucasians. It is less common among African Americans and much less common among the Hispanics, Asians and American Indians. We anticipate a distribution of gender in this study that is comparable to the disease incidence. However fewer than 25% of individuals in our catchment area are designated as racial or ethnic minorities, and rarely have these individuals appeared as cancer patients. Table 11 below reflects the projected accrual for the study based on the abovementioned factors.

Table 11: Population Demographics - Oregon (%)

Ethnic Category	**Sex/Gender**		
	Females	Males	Total
Hispanic or Latino	5.9	5.8	11.7
Not Hispanic or Latino	44.5	43.8	88.3
Ethnic Category: Total of all subjects*	50.4	49.3	100*
Racial Category			
American Indian or Alaskan Native	0.7	0.7	1.4
Asian	1.9	1.8	3.7
Black or African American	0.9	0.9	1.8
Native Hawaiian or other Pacific Islander	0.2	0.1	0.3
White	42.1	41.5	83.6
More than one race	1.9	1.9	3.8
Unknown/Other	2.7	2.6	5.3
Racial Category: Total of all subjects*	50.4	49.5	100*
TOTALS	50.4	49.6	100*

Source: Adapted from U.S. Census Bureau, 2010 *Totals may not equal 100 due to rounding

Table 12: Projected Accrual for the Present Study

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	0-1	1	0-1	1
Not Hispanic or Latino	8	12	0-1	20
Unknown	0-1	0-1	0-1	0-1
Ethnic Category: Total of all subjects*	13	16	0-1	30*
Racial Category				
American Indian or Alaskan Native	0-1	0-1	0-1	0-1
Asian	0-1	2	0-1	2
Black or African American	0-1	0-1	0-1	0-1
Native Hawaiian or other Pacific Islander	0-1	0-1	0-1	0-1
White	13	14	0-1	27
More than one race	0-1	0-1	0-1	0-1
Unknown	0-1	0-1	0-1	0-1
Racial Category: Total of all subjects*	14	16	0-1	30*

12.9.2 Inclusion of Children

This protocol does not include children for the following reason: the number of children with CLL and NHL is limited. The most common form in children is acute lymphoblastic leukemia which has a very different biology. We plan to survey only the adult forms of these diseases and do not plan to accrue children (under 18 years of age).

12.10 Publication Plan

The results of the study will be submitted as a manuscript to a peer-reviewed scientific journal in the field of oncology for publication.

12.11 ClinicalTrials.Gov Requirements

As an applicable clinical trial (ACT) under FDAAA (FDA Amendments Act of 2007, US Public Law 110-85, Section 801), this study requires mandatory registration and results reporting into a clinical trial registry. As per Knight SOP, this trial will be registered both in NIH ClinicalTrials.gov (http://clinicaltrials.gov) under the OHSU Knight Cancer Institute's centrally managed organizational account. It will also be registered under the NCI's Clinical Trial Reporting Program (https://trials.nci.nih.gov) prior to enrollment of the first subject. Once complete, primary outcome results will be posted to ClinicalTrials.gov within 12 months of the primary completion date. This process is facilitated and monitored by Knight Clinical Trial Registration Administrator (CTRP-Admin@ohsu.edu) within the Knight Clinical Trials Office with consultation and assistance from the Knight Biostatistics Shared Resource.

13. STATISTICAL CONSIDERATIONS

The Knight Cancer Institute Biostatistics Shared Resource at OHSU will provide statistical support for

this trial.

13.1 Study Design

Phase I Study Design

This is an open-label, phase I/II, dose-finding study in which safety and tolerability of escalating doses SYK inhibitor entospletinib (GS-9973) in combination with obinutuzumab in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and NHL (FL, MCL, LPL, MZL). Since best responses for both entospletinib and obinutuzumab have been documented in CLL/SLL, the Phase II portion of the study will be limited to those patients, however additional expansion cohorts may be considered at a later date.

For the dose finding part of the study, Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined in the section 5.2. The starting dose of entospletinib will be 200 mg po bid daily with and one dose escalation (dose level 2) and 1 dose de-escalation. Entospletinib will be administered as a single agent for 7 days prior to C1D1 to allow for assessment of biomarkers.

Table 13. Dose levels planned for dose escalation phase of the study

Dose Level	Entospletinib (Cycles 1-12)	Obinutuzumab (Cycles 1-6) IV
-1*	200 mg daily	C1D1 – 100 mg; C1D2 – 900 mg C1D8 & 15 – 1000 mg C2-6 – 1000 mg on day 1
1	200 mg BID	
2	400 mg BID	

*Dose Level -1 will be studied only if more than one patient develops a DLT in Dose Level 1

Determination of MTD

The dosage will follow the 3+3 traditional escalation rules, starts with 3 cohorts at a planned dose level. If 0 out of 3 patients experiences DLT, dose will be escalated to the next higher level at which 3 cohort will be enrolled. If 1 out of 3 patients experiences DLT, 3 more patients will be enrolled at the same dose level. Escalation will continue if 1 of 6 patients experiences a DLT. If 2 or more patients in any dose level except for the starting dose level experience DLTs, dosing will stop, and previous dose level is determined to be MTD, unless only 3 patients have been treated at that level (the tentative MTD). If 2 or more patients in the starting dose level experience DLT, dose will be de-escalated to the -1 dose levels. A tentative MTD becomes final when a total of 6 patients are treated with less than 2 DLT, or a total of 3 patients are treated with less than 1 DLT.

Phase II Study Design

The phase II study will begin after determination of MTD. The Phase 2 study of the effect of treatment is designed as a single-stage study with a primary endpoint of efficacy (response rate: ORR, CR). The study will go back to the Phase I stage if 2 or more out of the first six subjects (including those treated in the Phase I) receiving the currently identified MTD experience DLT

13.2 Primary and Secondary Endpoints:

13.2.1 Primary Endpoints:

The primary endpoint of the Phase I portion of the study is to determine the maximum tolerated dose (MTD) and/or a recommended Phase II dose (RP2D) of entospletinib in combination with obinutuzumab in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and NHL (FL, MCL, LPL, MZL) as measured by the incidence of dose limiting toxicities (see Section 5.2).

The primary efficacy endpoint of the Phase 2 portion of the study is the CR, defined as the proportion of subjects who achieve CR described in the section 11.2.1

13.2.2 Secondary Endpoints

Secondary endpoints of phase 2 portion of study are the following:

- Objective response rate (ORR)
- Event free survival defined as the interval between the date of first study treatment and the date of objective signs of disease recurrence, subsequent anti-leukemic therapy, or death, whichever is first reported EFS will be censored if entospletinib is discontinued for other reasons (such as drug is no longer available)
- Safety and tolerability of entospletinib in combination with obinutuzumab by AEs

13.2.3 Exploratory Endpoints

- Peripheral blood B-cell depletion and recovery
- Pharmacodynamics effects of *in vivo* administration of entospletinib on NFκB activation and expression of anti-apoptotic proteins in CLL cells.
- Association of established biomarkers (chromosomal abnormalities, immunoglobulin heavy chain [*IGHV*] mutational status, p53 mutational status) with response (ORR and EFS) to ENTO in combination with obinutuzumab in patients with relapsed/refractory CLL

13.3 Analysis Population

Safety analysis set includes all patients who consent and take at least one dose of study drug, regardless of how long they stay on study drug. The end of treatment and early termination visit (see schedule) includes an evaluation of response at that visit. Reason(s) for going off study will be collected on every patient.

The dose-determining set (DDS) consists of a subset of patients in the safety analysis set who either meet the following minimum exposure criterion and have sufficient safety evaluations, during the first 1 cycle of dosing (including the run-in phase) or discontinue earlier due to DLT.

The efficacy-evaluable population will include all intent-to-treat (ITT) subjects who received at least 1 dose of study medication. Per protocol population will include all intent-to-treat (ITT) patients who completed 1 cycle of study treatment. The ITT subjects will include all subjects who are consented and enrolled in the Phase 2 Portion of the study.

13.4 Statistical Analysis Plan

Demographic and baseline data will be summarized descriptively by phase and dose level. For continuous variables, descriptive statistics will include the mean, standard deviation (or standard error), median, range, and interquartile range. For categorical variables, descriptive statistics will include the number and percent.

13.4.1 Analysis of Primary Endpoints

The MTD will be determined according to 3+3 dose escalation design using the dose determining set. Adverse events will be graded and categorized according to the CTCAE v4.03. All adverse events will be tabulated and summarized by major organ category, grade, anticipation, and drug attribution. SAE specific incidence and exact 95% confidence interval will be provided where appropriate.

The CR will be computed and presented together will the exact 95% confidence interval (CI), using the method of Clopper and Pearson. A null hypothesis of a 20% CR will be rejected if at least 7 of 17 patients achieve a CR and a treatment arm will not be considered further if this threshold is not reached.

13.4.2 Analysis of Secondary Endpoints

- Overall response rate (ORR) will be summarized with 95% confidence intervals.
- Event free survival (EFS) will be summarized descriptively using the Kaplan-Meier estimate.
- Safety and tolerability of entospletinib in combination with obinutuzumab by AEs
  Safety data will be summarized for the safety population separately for phase 1 and phase 2 portions by dose level. All AEs will be coded by system organ class, MedDRA preferred term, and severity grade using NCI CTCAE (v 4.03).

13.4.3 Analysis of Exploratory Endpoints

Pharmacokinetic parameters including peak and trough levels will be determined by non-compartmental method(s) using the pharmacokinetic profile of entospletinib and obinutuzumab. EFS and ORR by status of complete response will be summarized using descriptive statistics.

We hypothesize that subjects with tumors demonstrating unfavorable chromosomal abnormalities (i.e., del(17p) or del(11q)), unmutated immunoglobulin heavy chain [*IGHV*], or mutations in *TP53* will be associated with decreased ORR and EFS compared with subjects without these biomarkers when treated with entospletinib and obinutuzumab combination. Point and interval estimates of ORR and EFS by biomarker outcome will be provided for each patient subgroup.

Similarly, we hypothesize that patients who have previously received targeted therapy with kinase inhibitors (ibrutinib, idelalisib or investigational inhibitors of BTK, PI3K) will demonstrate worse outcomes. Point and interval estimates of ORR and EFS will be provided separately for such patients.

13.4.4 Interim Analyses and Stopping Rules

A 3+3 dose-escalation algorithm will be followed to insure safety. After the completion of the dose-determining part and prior to enrolling on the expansion cohort (phase II), safety and preliminary efficacy interim analysis will be performed.

13.5 Sample Size and Power

Determination of phase I sample size

3+3 dose escalation scheme will be utilized, with 3 to 6 evaluated at each dose level. It is expected that maximum of 12 patients will be enrolled.

Determination of phase II sample size

Entospletinib has been associated with an ORR 61% at the end of study and obinutuzumab in combination with chlorambucil has led to an ORR of 77.3% and CR rate of 20.7% after completion of therapy [22]. The null hypothesis that the true CR rate is 20% will be tested against a one-sided alternative. A sample size of 17 achieves 83% power to detect a difference in complete response of 0.30 (0.2 vs. 0.5) using a one-sided binomial test with the target significance level of 0.05. The actual significance level achieved by this test is 0.0984. If more than equal to 7 patients achieve complete response, then conclude the regimen is effective, and consider a larger/next phase of clinical trial (phase III).

A sample size of 17 subjects treated at the RP2D provides a reasonable probability to detect a rare adverse event, for example, 83% chance of detecting an adverse event with an incidence of 10% (Table 14). Subjects with CLL treated at the RP2D in Phase I will be counted towards Phase II enrollment. Anticipating an attrition rate of 15%, a total of 20 patients per protocol population will need to be enrolled.

Table 14. Probability of detecting an AE with a specified incidence rate at the RP2D

AE incidence	N=17: Probability of detect an AE
0.01	0.16
0.05	0.58
0.10	0.83
0.15	0.94
0.20	0.98

13.6 Randomization Method

Not applicable

13.7 Handling of Missing Data

For missing data, we will evaluate whether or not the other time points can be used to fulfill the primary and secondary data. No missing data will be imputed. Whenever possible, all available data will be included in the analysis. A sample size for each analysis will be clearly stated along with the reason for exclusion, if any subject is excluded from the analysis due to missing data.

Data Monitoring Committee

The Knight Data Safety Monitoring Committee (DSMC) at the OHSU Knight Cancer Institute will be to monitor safety data.

REFERENCES

1. SEER Cancer Statistics Review, 1975-2010 [Internet]. 2013.
2. Zent CS, Kyasa MJ, Evans R, Schichman SA. Chronic lymphocytic leukemia incidence is substantially higher than estimated from tumor registry data. Cancer. 2001;92(5):1325-30. Epub 2001/09/26. PubMed PMID: 11571749.
3. Kristinsson SY, Dickman PW, Wilson WH, Caporaso N, Bjorkholm M, Landgren O. Improved survival in chronic lymphocytic leukemia in the past decade: a population-based study including 11,179 patients diagnosed between 1973-2003 in Sweden. Haematologica. 2009;94(9):1259-65. Epub 2009/09/08. doi: 10.3324/haematol.2009.007849. PubMed PMID: 19734417; PubMed Central PMCID: PMC2738718.

4. Brenner H, Gondos A, Pulte D. Trends in long-term survival of patients with chronic lymphocytic leukemia from the 1980s to the early 21st century. Blood. 2008;111(10):4916-21. Epub 2008/03/01. doi: 10.1182/blood-2007-12-129379. PubMed PMID: 18309034.
5. Galton DA, Israels LG, Nabarro JD, Till M. Clinical trials of p-(di-2-chloroethylamino)-phenylbutyric acid (CB 1348) in malignant lymphoma. Br Med J. 1955;2(4949):1172-6. Epub 1955/11/12. PubMed PMID: 13269823; PubMed Central PMCID: PMC1981252.
6. Shaw R.K. BDR, Silberman H.R., and Frei E. III. A Study of prednisone in Chronic Lymphocytic Leukemia. Blood. 1961;17(2):182-95.
7. Keating MJ, O'Brien S, Albitar M, Lerner S, Plunkett W, Giles F, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005;23(18):4079-88. Epub 2005/03/16. doi: 10.1200/JCO.2005.12.051. PubMed PMID: 15767648.
8. Byrd JC, Rai K, Peterson BL, Appelbaum FR, Morrison VA, Kolitz JE, et al. Addition of rituximab to fludarabine may prolong progression-free survival and overall survival in patients with previously untreated chronic lymphocytic leukemia: an updated retrospective comparative analysis of CALGB 9712 and CALGB 9011. Blood. 2005;105(1):49-53. Epub 2004/05/13. doi: 10.1182/blood-2004-03-0796. PubMed PMID: 15138165.
9. Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum KA, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. The New England journal of medicine. 2013;369(1):32-42. Epub 2013/06/21. doi: 10.1056/NEJMoa1215637. PubMed PMID: 23782158; PubMed Central PMCID: PMC3772525.
10. Woyach JA, Furman RR, Liu TM, Ozer HG, Zapatka M, Ruppert AS, et al. Resistance Mechanisms for the Bruton's Tyrosine Kinase Inhibitor Ibrutinib. The New England journal of medicine. 2014. Epub 2014/05/30. doi: 10.1056/NEJMoa1400029. PubMed PMID: 24869598.
11. Jain P, Keating M, Wierda W, Estrov Z, Ferrajoli A, Jain N, et al. Outcomes of patients with chronic lymphocytic leukemia (CLL) after discontinuing ibrutinib. Blood. 2015. doi: 10.1182/blood-2014-09-603670. PubMed PMID: 25573991.
12. Byrd JC, Furman RR, Coutre SE, Burger JA, Blum KA, Coleman M, et al. Three-year follow-up of treatment-naive and previously treated patients with CLL and SLL receiving single-agent ibrutinib. Blood. 2015. doi: 10.1182/blood-2014-10-606038. PubMed PMID: 25700432.
13. Chiron D, Di Liberto M, Martin P, Huang X, Sharman J, Blecua P, et al. Cell-cycle reprogramming for PI3K inhibition overrides a relapse-specific C481S BTK mutation revealed by longitudinal functional genomics in mantle cell lymphoma. Cancer discovery. 2014;4(9):1022-35. doi: 10.1158/2159-8290.CD-14-0098. PubMed PMID: 25082755; PubMed Central PMCID: PMC4155003.
14. Rozovski U, Benjamini O, Jain P, Thompson PA, Wierda WG, O'Brien S, et al. Outcomes of Patients With Chronic Lymphocytic Leukemia and Richter's Transformation After Transplantation Failure. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015;33(14):1557-63. doi: 10.1200/JCO.2014.58.6750. PubMed PMID: 25847930; PubMed Central PMCID: PMC4417727.
15. Turner M, Schweighoffer E, Colucci F, Di Santo JP, Tybulewicz VL. Tyrosine kinase SYK: essential functions for immunoreceptor signalling. Immunol Today. 2000;21(3):148-54. PubMed PMID: 10689303.
16. Braselmann S, Taylor V, Zhao H, Wang S, Sylvain C, Baluom M, et al. R406, an orally available spleen tyrosine kinase inhibitor blocks fc receptor signaling and reduces immune complex-mediated inflammation. The Journal of pharmacology and experimental therapeutics. 2006;319(3):998-1008. Epub 2006/09/02. doi: 10.1124/jpet.106.109058. PubMed PMID: 16946104.
17. Morris DL, O'Neil SP, Devraj RV, Portanova JP, Gilles RW, Gross CJ, et al. Acute lymphoid and gastrointestinal toxicity induced by selective p38alpha map kinase and map kinase-activated protein kinase-2 (MK2) inhibitors in the dog. Toxicol Pathol. 2010;38(4):606-18. doi: 10.1177/0192623310367807. PubMed PMID: 20448081.

18. Barr PM, Saylors GB, Spurgeon SE, Cheson BD, Greenwald DR, O'Brien SM, et al. Phase 2 study of idelalisib and entospletinib: pneumonitis limits combination therapy in relapsed refractory CLL and NHL. Blood. 2016. doi: 10.1182/blood-2015-12-683516. PubMed PMID: 26968534.
19. Mossner E, Brunker P, Moser S, Puntener U, Schmidt C, Herter S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. Blood. 2010;115(22):4393-402. doi: 10.1182/blood-2009-06-225979. PubMed PMID: 20194898; PubMed Central PMCID: PMCPMC2881503.
20. Niederfellner G, Lammens A, Mundigl O, Georges GJ, Schaefer W, Schwaiger M, et al. Epitope characterization and crystal structure of GA101 provide insights into the molecular basis for type I/II distinction of CD20 antibodies. Blood. 2011;118(2):358-67. doi: 10.1182/blood-2010-09-305847. PubMed PMID: 21444918.
21. Herter S, Herting F, Mundigl O, Waldhauer I, Weinzierl T, Fauti T, et al. Preclinical activity of the type II CD20 antibody GA101 (obinutuzumab) compared with rituximab and ofatumumab in vitro and in xenograft models. Molecular cancer therapeutics. 2013;12(10):2031-42. doi: 10.1158/1535-7163.MCT-12-1182. PubMed PMID: 23873847.
22. Goede V, Fischer K, Busch R, Engelke A, Eichhorst B, Wendtner CM, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. The New England journal of medicine. 2014;370(12):1101-10. doi: 10.1056/NEJMoa1313984. PubMed PMID: 24401022.
23. Stilgenbauer S, editor Tumor genomic profiling reveals mechanisms ofresistance to BTK inhibitor ibrutinib in chronic lymphocytic leukemia. International Workshop on Chronic Lymphocytic Leukemia; 2013; Cologne.
24. Iyengar S, Clear A, Bodor C, Maharaj L, Lee A, Calaminici M, et al. P110alpha-mediated constitutive PI3K signaling limits the efficacy of p110delta-selective inhibition in mantle cell lymphoma, particularly with multiple relapse. Blood. 2013;121(12):2274-84. Epub 2013/01/24. doi: 10.1182/blood-2012-10-460832. PubMed PMID: 23341541; PubMed Central PMCID: PMC3606064.
25. Danilov AV, Soderquist RS, Bates DJ, Eastman A. Toward a cure for chronic lymphocytic leukemia: an attack on multiple fronts. Expert Rev Anticancer Ther. 2013;13(9):1009-12. Epub 2013/09/24. doi: 10.1586/14737140.2013.825424. PubMed PMID: 24053199; PubMed Central PMCID: PMC3910377.
26. Kurosaki T. Regulation of B-cell signal transduction by adaptor proteins. Nature reviews Immunology. 2002;2(5):354-63. PubMed PMID: 12033741.
27. Friedberg JW, Sharman J, Sweetenham J, Johnston PB, Vose JM, Lacasce A, et al. Inhibition of Syk with fostamatinib disodium has significant clinical activity in non-Hodgkin lymphoma and chronic lymphocytic leukemia. Blood. 2010;115(13):2578-85. Epub 2009/12/08. doi: 10.1182/blood-2009-08-236471. PubMed PMID: 19965662; PubMed Central PMCID: PMC2852362.
28. Hoellenriegel J, Coffey GP, Sinha U, Pandey A, Sivina M, Ferrajoli A, et al. Selective, novel spleen tyrosine kinase (Syk) inhibitors suppress chronic lymphocytic leukemia B-cell activation and migration. Leukemia. 2012;26(7):1576-83. Epub 2012/03/01. doi: 10.1038/leu.2012.24. PubMed PMID: 22362000.
29. Sharman J, Hawkins M, Kolibaba K, Boxer M, Klein L, Wu M, et al. An open-label phase 2 trial of entospletinib (GS-9973), a selective spleen tyrosine kinase inhibitor, in chronic lymphocytic leukemia. Blood. 2015;125(15):2336-43. doi: 10.1182/blood-2014-08-595934. PubMed PMID: 25696919; PubMed Central PMCID: PMC4401348.
30. Rodig SJ, Shahsafaei A, Li B, Mackay CR, Dorfman DM. BAFF-R, the major B cell-activating factor receptor, is expressed on most mature B cells and B-cell lymphoproliferative disorders. Human pathology. 2005;36(10):1113-9. Epub 2005/10/18. doi: 10.1016/j.humpath.2005.08.005. PubMed PMID: 16226112.
31. Bottcher S, Ritgen M, Fischer K, Stilgenbauer S, Busch RM, Fingerle-Rowson G, et al. Minimal residual disease quantification is an independent predictor of progression-free and overall survival in chronic lymphocytic leukemia: a multivariate analysis from the randomized GCLLSG CLL8 trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(9):980-8. doi: 10.1200/JCO.2011.36.9348. PubMed PMID: 22331940.

32. Herishanu Y, Perez-Galan P, Liu D, Biancotto A, Pittaluga S, Vire B, et al. The lymph node microenvironment promotes B-cell receptor signaling, NF-kappaB activation, and tumor proliferation in chronic lymphocytic leukemia. Blood. 2011;117(2):563-74. Epub 2010/10/14. doi: 10.1182/blood-2010-05-284984. PubMed PMID: 20940416; PubMed Central PMCID: PMC3031480.
33. Hewamana S, Lin TT, Rowntree C, Karunanithi K, Pratt G, Hills R, et al. Rel a is an independent biomarker of clinical outcome in chronic lymphocytic leukemia. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(5):763-9. Epub 2009/01/07. doi: 10.1200/JCO.2008.19.1114. PubMed PMID: 19124804.
34. Burger JA. Nurture versus nature: the microenvironment in chronic lymphocytic leukemia. Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program. 2011;2011:96-103. Epub 2011/12/14. doi: 10.1182/asheducation-2011.1.96. PubMed PMID: 22160019.
35. Burger JA. The CLL Cell Microenvironment. Advances in experimental medicine and biology. 2013;792:25-45. Epub 2013/09/10. doi: 10.1007/978-1-4614-8051-8_2. PubMed PMID: 24014291.
36. Ramsay AD, Rodriguez-Justo M. Chronic lymphocytic leukaemia--the role of the microenvironment pathogenesis and therapy. British journal of haematology. 2013;162(1):15-24. Epub 2013/04/27. doi: 10.1111/bjh.12344. PubMed PMID: 23617880.
37. Godbersen JC, Humphries LA, Danilova OV, Kebbekus PE, Brown JR, Eastman A, et al. The Nedd8-activating enzyme inhibitor MLN4924 thwarts microenvironment-driven NF-kappaB activation and induces apoptosis in chronic lymphocytic leukemia B cells. Clinical cancer research : an official journal of the American Association for Cancer Research. 2014;20(6):1576-89. Epub 2014/03/19. doi: 10.1158/1078-0432.CCR-13-0987. PubMed PMID: 24634471; PubMed Central PMCID: PMC3960291.
38. Godbersen JC, Paiva C, Danilova OV, Berger A, Brown JR, Danilov AV. Targeting neddylation effectively antagonizes nuclear factor-kappaB in chronic lymphocytic leukemia B-cells. Leukemia & lymphoma. 2015;56(5):1566-9. doi: 10.3109/10428194.2014.990901. PubMed PMID: 26086969.
39. Herman SE, Mustafa RZ, Gyamfi JA, Pittaluga S, Chang S, Chang B, et al. Ibrutinib inhibits BCR and NF-kappaB signaling and reduces tumor proliferation in tissue-resident cells of patients with CLL. Blood. 2014;123(21):3286-95. Epub 2014/03/25. doi: 10.1182/blood-2014-02-548610. PubMed PMID: 24659631; PubMed Central PMCID: PMC4046423.
40. Cheson BD, Bennett JM, Grever M, Kay N, Keating MJ, O'Brien S, et al. National Cancer Institute-sponsored Working Group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. Blood. 1996;87(12):4990-7. Epub 1996/06/15. PubMed PMID: 8652811.
41. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, 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(12):5446-56. Epub 2008/01/25. doi: 10.1182/blood-2007-06-093906. PubMed PMID: 18216293; PubMed Central PMCID: PMC2972576.
42. Tosi P, Barosi G, Lazzaro C, Liso V, Marchetti M, Morra E, et al. Consensus conference on the management of tumor lysis syndrome. Haematologica. 2008;93(12):1877-85. Epub 2008/10/08. doi: 10.3324/haematol.13290. PubMed PMID: 18838473.
43. Paiva C, Godbersen JC, Berger A, Brown JR, Danilov AV. Targeting neddylation induces DNA damage and checkpoint activation and sensitizes chronic lymphocytic leukemia B cells to alkylating agents. Cell death & disease. 2015;6:e1807. doi: 10.1038/cddis.2015.161. PubMed PMID: 26158513.
44. Humphries LA, Godbersen JC, Danilova OV, Kaur P, Christensen BC, Danilov AV. Pro-apoptotic TP53 homolog TAp63 is repressed via epigenetic silencing and B-cell receptor signalling in chronic lymphocytic leukaemia. British journal of haematology. 2013;163(5):590-602. Epub 2013/10/15. doi: 10.1111/bjh.12580. PubMed PMID: 24117128.
45. Cheson BD, Byrd JC, Rai KR, Kay NE, O'Brien SM, Flinn IW, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. Journal of clinical oncology : official

journal of the American Society of Clinical Oncology. 2012;30(23):2820-2. Epub 2012/07/11. doi: 10.1200/JCO.2012.43.3748. PubMed PMID: 22778323; PubMed Central PMCID: PMC3410400.
46. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2014;32(27):3059-68. doi: 10.1200/JCO.2013.54.8800. PubMed PMID: 25113753.
47. Consensus resolution: proposed criteria for evaluation of response to treatment in hairy cell leukemia. Leukemia. 1987;1(4):405. PubMed PMID: 3669765.

APPENDIX A Obinutuzumab Prescribing Information

The most current obinutuzumab prescribing information can be found at the link below.

http://www.gene.com/download/pdf/gazyva_prescribing.pdf

APPENDIX B Creatinine Clearance Formula

CrCL should be calculated using the Cockroft-Gault formula:
CrCL= [(140-age) x Weight (kg) x 0.85 (if female)]/[72 x serum creatinine (in mg/dL)].

APPENDIX C Strong and Moderate Inhibitors and Inducers of CYP Enzymes

CYP Inhibitors

	Strong	Moderate
CYP2C9	- fluvoxamine - ticlopidine	- fluconazole - esomeprazole - fluoxetine - moclobemide - omeprazole - voriconazole
CYP3A	• boceprevir • clarithromycin • conivaptan • grapefruit juice • indinavir • itraconazole • ketoconazole • lopinavir/ritonavir • mibefradil • nefazodone • nelfinavir • posaconazole • ritonavir • saquinavir • telaprevir • telithromycin • voriconazole	- amprenavir - aprepitant - atazanavir - ciprofloxacin - darunavir/ritonavir - diltiazem - erythromycin - fluconazole - fosamprenavir - grapefruit juice - imatinib - verapamil

CYP Inducers

	Strong	Moderate
CYP2C9		• carbamazepine • rifampin
CYP3A	- avasimibe - carbamazepine - phenobarbital	• bosentan • efavirenz • etravirine

	- phenytoin - rifampin - St. John's wort	• modafinil • nafcillin

APPENDIX D ECOG Performance Status*

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

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

APPENDIX E LPL Assessment

Category	Finding
Laboratory	Serum monoclonal IgM > 0.5 g/dL Hemoglobin level < 10 g/dL Platelet count < 100 x 10^9 /L
Laboratory + symptoms	Cryoglobulinemia with symptoms Hyperviscosity with symptoms
Physical Findings	Bulky adenopathy Organomegaly
Symptoms	Recurrent fevers Night sweats Weight loss Fatigue Symptomatic neuropathies
Organ Disease	Nephropathy Amyloidosis
Pathology	Disease Transformation

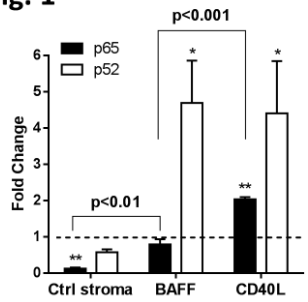
Definitions of Response for Waldenstrom's Macroglobulinemia

- Complete response (CR): Absence of serum monoclonal IgM protein by immunofixation; normal serum IgM level and complete resolution of extramedullary disease, i.e. lymphadenopathy and splenomegaly if present at baseline; morphologically normal bone marrow/aspirate and trephine biopsy.
- Very good partial response: Monoclonal IgM protein is detectable; ≥ 90% reduction in serum IgM level from baseline; complete resolution of extramedullary disease, i.e. lymphadenopathy and splenomegaly if present at baseline; no new signs or symptoms of active disease.
- Partial response (PR): Monoclonal IgM protein is detectable; ≥ 50% but < 90% reduction in serum IgM level from baseline; reduction of extramedullary disease, ie, lymphadenopathy and splenomegaly if present at baseline; no new signs or symptoms of active disease.
- Minor response: Monoclonal IgM protein is detectable; ≥ 25% but < 50% reduction in serum
- IgM level from baseline; no progression in extramedullary disease, i.e. lymphadenopathy/splenomegaly if present at baseline; no new signs or symptoms of active disease.
- Stable disease: Monoclonal IgM protein is detectable; < 25% reduction and < 25% increase in serum IgM level from baseline; no new signs or symptoms of active disease.
- Progressive disease: ≥ 25% increase in serum IgM level from lowest nadir (requires confirmation) and/or progression in clinical features attributable to the disease.

APPENDIX F Pre-clinical data

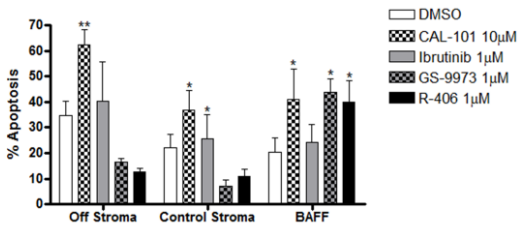
SYK Inhibition abrogates BAFF-mediated CLL survival

Fig. 1



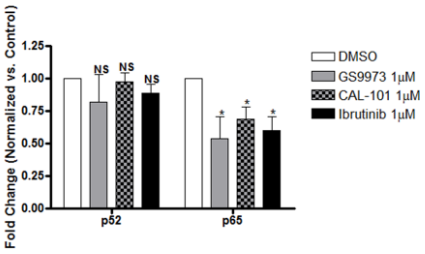
CLL cells were co-cultured with control, BAFF- or CD40L-expressing stroma for 24 h. p65/p52 activity was determined using NFκB TransAm Assay. *-p<0.05, ** - p<0.01 compared to 0 h (prior to co-culture, set at 1, dotted line).

Fig. 2



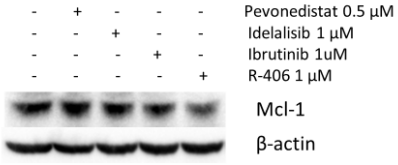
CLL cells were co-cultured with BAFF-expressing stroma for 24 h, incubated with the indicated drugs for 24 h, and assayed for apoptosis using flow cytometry (Annexin V-positive cells shown).

Fig. 3



CLL cells were co-cultured with BAFF-expressing stroma for 24 and incubated with the indicated drugs for 224 hours. p65/p52 activity was determined using NFκB TransAm Assay. *-p<0.05 compared to untreated control.

Fig. 4



CLL cells were co-cultured with BAFF-expressing stroma for 24 h, incubated with the indicated drugs for 24 h and subjected to immunoblotting.

APPENDIX G Response Criteria for FL, MZL and MCL

Response criteria for subjects with Follicular Lymphoma, Marginal Zone Lymphoma and Mantle Cell Lymphoma

Complete Response (CR)

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present prior to therapy. Typically FDG-avid lymphoma: in patients with no pre-treatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative. Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, the designation of CR requires all nodal indicator lesions to regress to the size of normal lymph nodes. Lymph nodes that were > 15 mm in GTD regardless of the short axis diameter at the screening tumor assessment must regress to ≤ 15 mm in GTD regardless of the short axis diameter. Lymph nodes that were 11 to 15 mm in GTD and > 10 mm in the short axis diameter at the screening tumor assessment must regress to ≤ 10 mm in the short axis diameter.

2. The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

3. If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (> 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but demonstrating a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

Partial Remission (PR)

1. ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following: (a) they should be clearly measurable in at least 2 perpendicular dimensions; (b) if possible they should be from disparate regions of the body; (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

2. No increase in the size of the other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.

4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive prior to treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a complete remission by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.

6. No new sites of disease should be observed (e.g., nodes > 1.5 cm in any axis).

7. Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.

8. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used.

9. In patients with follicular lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

Stable Disease (SD)

1. Failing to attain the criteria needed for a CR or PR, but not fulfilling those for progressive disease (see below).

2. Typically FDG-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post- treatment CT or PET.

3. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed Disease (RD; after CR) or Progressive Disease (PD; for Patients with PR or SD)

Progressive/Relapsed Disease

1. Lymph nodes should be considered abnormal if the long axis is > 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1−1.5 cm, it should only be considered abnormal if its short axis is > 1.0. Lymph nodes ≤ 1.0 cm by ≤ 1.0 cm will not be considered as abnormal for relapse or progressive disease.

2. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities

3. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 × 1.5 cm or more than 1.5 cm in the long axis.

4. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

5. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 15 mm in its long axis by CT).

6. Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease.

Notes: Bone marrow status is evaluated as follows:

- Positive: Unequivocal cytological or architectural evidence of malignancy.
- Negative: No aggregates or only a few well-circumscribed lymphoid aggregates.

APPENDIX H Safety Reporting Fax Cover Sheet

Genentech
A Member of the Roche Group

GENENTECH SUPPORTED RESEARCH

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

Alternate Fax No: (650) 225-4630

Page 1 of ___

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

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

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

Appendix I Response criteria for Hairy cell leukemia (determined by the Consensus Resolution response criteria [47])

Complete response (CR)
• A morphological absence of hairy cells in the blood and bone marrow
• A normalization of any organomegaly and cytopenias
Partial response (PR)
• A normalization of cytopenias
• ≥50% reduction in organomegaly and bone marrow hairy cells.
All other responses are considered as no response (NR)
Relapse after CR
• Reappearance of hairy cells in the blood or bone marrow
• Development of cytopenias and/or splenomegaly on physical examination
Relapse after PR
• >50% increase of residual disease

LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this study protocol.

Term	Explanation
AE	Adverse Event
ALC	Absolute lymphocyte count
ALT	Alanine aminotransaminase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BCR	B-cell receptor
BID	Twice daily
BTK	Bruton tyrosine kinase
CBC	Complete blood count
CCRC	Clinical Cancer Review Committee
CIRS	Cumulative Illness Rating Scale
CLL	Chronic lymphocytic leukemia
CPHS	Committee for the Protection of Human Subjects
CR	Complete response
CrCL	(estimated) Creatinine clearance
CRi	Complete response with incomplete marrow recovery
CRMS	Knight Clinical Research Management System
CT	Computed tomography
CTO	Clinical Trials Office
DLT	Dose-limiting toxicity
DSMC	Data and Safety Monitoring Committee
eCRF	Electronic case report form
EFS	Event-free survival
FISH	FISH
FL	Follicular lymphoma
IGHV	Immunoglobulin heavy chain gene
IHC	Immunohistochemistry
IRB	Institutional Review Board
IRR	Infusion-related reaction
IV	Intravenously
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
KCI	Knight Cancer Institute
LPL	Lymphoplasmacytic lymphoma
LVEF	Left Ventricular Ejection Fraction
LDH	Lactate dehydrogenase
MCL	Mantle cell lymphoma
MTD	Maximum tolerated dose
MZL	Marginal zone lymphoma
nPR	Nodular partial response
OHSU	Oregon Health and Science University
ORR	Objective response rate
OS	Overall survival

PD	Pharmacodynamic
PFS	Progression-free survival
PI	Principal investigator
PI-3K	Phosphoinositide-3 kinase
PK	Pharmacokinetic
PO	By mouth
PR	Partial remission
RP2D	Recommended Phase II dose
SAE	SAE
SLL	Small lymphocytic lymphoma
t½ - half-life	Half-life
ULN	Upper limit of normal
USPI	United States prescribing information
WBC	White blood cells
ZAP-70	Zeta chain-associated T-cell receptor protein kinase 70 kDa