Status Page

PROTOCOL 13-309

Permanent
Closed to New Accrual

Closure Effective Date: 04/25/2018
No new subjects may be enrolled in the study as described above. Any questions regarding this closure should be directed to the study's Principal Investigator

Date Submitted:

Alert Page

DF/HCC Protocol #: **[13-309]**

Protocol Clarifications (non-drug related e.g. eligibility criteria, study assessments)

This study is now closed to enrollment at all sites.

Protocol Version Date: v. 19 November 1, 2018

Local Protocol #: 13-309

Title: A Phase II Study of Idelalisib (GS1101, CAL101) + Ofatumumab in Previously Untreated CLL/SLL

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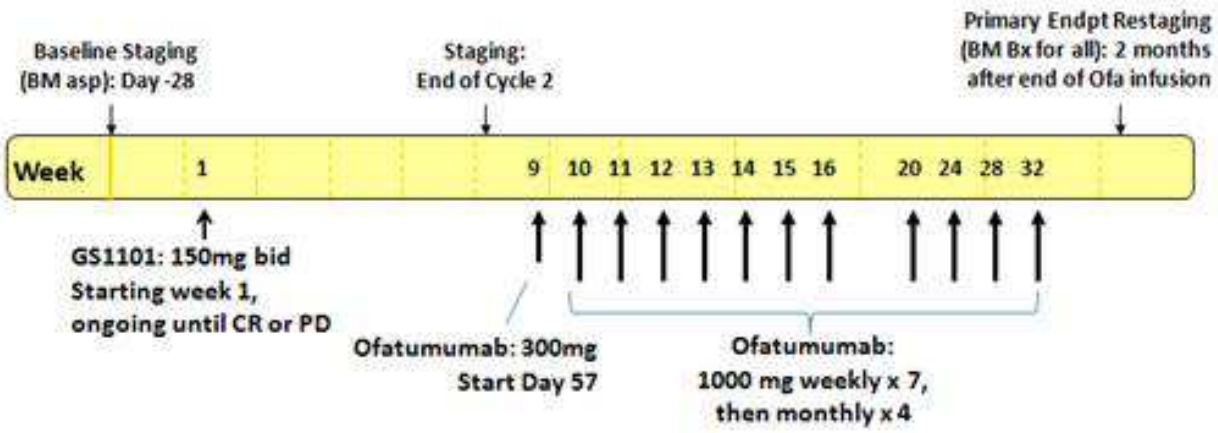
Ofatumumab – Novartis

SCHEMA


Baseline Staging
(BM asp): Day -28
Staging:
End of Cycle 2
Primary Endpt Restaging
(BM Bx for all): 2 months
after end of Ofa infusion
Week
1
9
10
11
12
13
14
15
16
20
24
28
32
GS1101: 150mg bid
Starting week 1,
ongoing until CR or PD
Ofatumumab: 300mg
Start Day 57
Ofatumumab:
1000 mg weekly x 7,
then monthly x 4

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1. OBJECTIVES

1.1 Study Design

This study was designed to enroll 50 subjects with untreated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) who meet IWCLL 2008 criteria for initiation of therapy will initiate single-agent idelalisib (GS1101), a PI3K delta specific inhibitor, daily for the first two months on study, and begin ofatumumab at the start of the 3rd month following a complete response evaluation. The duration of combination therapy will be 8 months. All subjects will receive 8 weekly doses of ofatumumab, following which they will undergo another response evaluation. They will then continue with idelalisib during their 4 monthly doses of ofatumumab. The final primary endpoint response evaluation will occur two months after completion of ofatumumab, at 10 months following start of therapy. Therapy with idelalisib will continue throughout the ofatumumab therapy and after, until development of progressive disease. Once participants are receiving single agent idelalisib therapy they will be seen in clinic every 2 months. After treatment is complete subjects will be followed every 3-6 months at the treating investigator's discretion until initiation of a new therapy or death. Subjects who do not complete cycle 2 are not considered evaluable for the study efficacy objectives and may be replaced. Their data will be included in all toxicity evaluations.

As of 3/11/2016, Gilead has observed an excess of infectious deaths in three trials, one in upfront CLL, and as a result the FDA and Gilead are discontinuing enrollment to upfront CLL trials as well as discontinuing the administration of idelalisib to patients previously enrolled on these trials. All patients on this trial however may receive ofatumumab as planned and continue to be followed per protocol. Correlative analyses will continue as previously planned.

1.2 Primary Objectives

To determine the ORR of ofatumumab and idelalisib in previously untreated CLL/SLL participants in need of therapy

1.3 Secondary Objectives

To determine the CR rate and PFS of ofatumumab and idelalisib.

To determine the ORR, CR rate and rate of nodal PR with lymphocytosis for idelalisib given alone for two months of therapy to previously untreated participants

To determine the rate of lymphocytosis with idelalisib in previously untreated participants

To assess the safety of idelalisib in untreated participants and in combination with ofatumumab.

To determine whether clinical response correlates with known CLL molecular prognostic factors including FISH, *IGHV*, ZAP-70.

To determine whether the use of CT scans in response assessment improves the predictive power of ORR for progression-free survival or time to next treatment.

To determine whether serum ofatumumab and/or idelalisib levels in vivo predict response.

To assess whether initial treatment with idelalisib alters the cell surface marker phenotype of circulating CLL cells.

To assess whether in vivo treatment with idelalisib alters CLL cell sensitivity to therapy with antibodies or other kinase inhibitors.

To assess pharmacodynamic markers of PI3 kinase inhibition including AKT phosphorylation, production of T cell chemokines and response to CXCR 4/5.

To determine whether response or resistance correlates with genetic alterations in PIK3CA or PIK3CD or other genes.

To determine the influence of idelalisib treatment on intrinsic innate immune suppression and on regulatory T cells.

To identify predictors of response and resistance to idelalisib through biochemical and genetic analysis of the PI3K pathway.

To assess the clonal dynamics of CLL in peripheral blood vs bone marrow, and during therapy with idelalisib.

2. BACKGROUND

2.1 Preclinical Characterization of Idelalisib

Nonclinical efficacy pharmacology data in enzyme-based and cell-based systems indicate that idelalisib is a potent inhibitor of PI3Kδ but that its selectivity spares other PI3K isoforms and other kinases. Testing in nonclinical models of lymphoid neoplasia confirm the importance of the PI3Kδ pathway in these tumor types, and document idelalisib activity in suppressing in the growth and survival of these malignancies [1, 2].

In in vitro assays evaluating PI3K enzymatic activity, idelalisib potently inhibited PI3Kδ, with a concentration inducing 50% inhibition (IC_{50}) of 2.5 nM. By contrast, IC_{50} values for the effects of idelalisib on PI3Kα, PI3Kβ, and PI3Kγ were 820, 565, and 89 nM respectively, indicating a selectivity of idelalisib for PI3Kδ that is 40- to 300-fold greater than for other PI3K Class I family members. When assessing IC_{50} values relative to Class II, III, and IV PI3K enzymes, idelalisib showed 400- to 4000-fold greater activity for Class I PI3Kδ inhibition. In vitro selectivity was further demonstrated by evaluation of activity against the comprehensive panel of

402 kinases in the Ambit KinomeScan; idelalisib at 10 μM (0.42 μg/mL) inhibited PI3K enzymes but showed no activity against other enzymes.

Potency and selectivity have been confirmed in cell-based in vitro assays. In human whole blood, idelalisib potently inhibited basophil activation via a PI3Kδ-dependent pathway, with an EC_{50} of 62 nM; by contrast, inhibition of basophil activation via a PI3Kγ-dependent pathway showed an EC_{50} of 4,456 nM. Idelalisib also showed potent *in vitro* inhibition of PI3Kδ-mediated processes in other cell types; activation of human B-cell proliferation via the B-cell receptor, neutrophil degranulation in response to bacterial peptide, and stimulation of human T-cell proliferation via the T-cell receptor were inhibited with respective EC_{50} values of 8 nM, 119 nM, and 932 nM. By contrast, when examining PI3Kα- or PI3Kβ- mediated phosphorylation of AKT in primary mouse fibroblasts, idelalisib showed EC_{50} values of >20 μM and 1900 nM, thus substantiating the lack of idelalisib effect on signaling via these PI3K isoforms.

Consistent with the moderate to high bioavailability seen in nonclinical species, idelalisib shows high permeability across human Caco-2 cell monolayers. At lower concentrations, the reverse permeability at low concentration exceeds forward permeability, indicating efflux driven by transporters (for e.g., human P-glycoprotein (MDR1) and breast cancer resistance protein (BCRP)); idelalisib is a substrate for the efflux transporters MDR1 and BCRP; however, the permeability increases in a concentration-dependent manner, resulting in a lower efflux ratio at higher, clinically relevant concentrations of idelalisib.

Idelalisib exhibits moderately high plasma protein binding in mouse, rat, dog, and human. In dog and human plasma, the protein binding is concentration-independent between 1 and 20 μM. Protein binding in human plasma is slightly higher than in mouse, rat, and dog plasma, which have comparable free fractions. In human plasma, idelalisib and GS-563117 (a metabolite of idelalisib) have an average free fraction of ~16% and ~12%, respectively.

After oral administration of [^{14}C]idelalisib to rats and dogs, radioactivity is widely distributed, but relatively excluded from bone, brain, spinal cord, and eye lens in rats and from brain and eyes in dogs. In rats, the radioactivity declines steadily and most tissues have undetectable levels by 72 hours post dose. In bile duct-cannulated rats and dogs, ≥ 69% of radioactivity is recovered in bile and urine, indicating high absorption of idelalisib in vivo.

In hepatic tissues from nonclinical species, idelalisib is primarily metabolized by aldehyde oxidase, CYP3A, and UGT1A4. In vitro metabolism in dog and human yields 3 primary oxidative metabolites and 5 primary glucuronides. Of these, the oxidative product GS-563117 is the predominant metabolite in vitro and in vivo. In preclinical species, plasma levels of GS-563117 are below those of idelalisib. However, in humans GS-563117 plasma levels significantly exceed those of idelalisib. After oral administration of [^{14}C]idelalisib to rats and dogs, biliary excretion appears to be the major route of elimination of idelalisib and its metabolites as the majority of radioactivity is found in feces or bile and little in urine.

Idelalisib is not a substrate for the renal transporters OCT2, OAT1, and OAT3 or the hepatic uptake transporters OATP1B1 and OATP1B3. GS-563117 is not a substrate for OATP1B1 and OATP1B3.

Idelalisib shows insignificant inhibition of CYP1A, CYP2B6, CYP2C9, and CYP2D6, and modest/moderate inhibition of CYP2C8 (IC_{50} = 13 μM), CYP2C19 (IC_{50} = 76 μM), and CYP3A (IC_{50} = 44 μM). GS-563117 shows insignificant inhibition of CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6, and is a moderate inhibitor of CYP3A (IC_{50} = 3.1 μM).

Idelalisib shows insignificant inhibition of the transporters BCRP, OCT2, OAT1, and OAT3, and modest/moderate inhibition of MDR1 (IC50 = 7.7 μM), OATP1B1 (IC50 = 10.1 μM), OATP1B3 (IC50 = 7.0 μM), and the glucuronosyltransferase UGT1A1 (IC50 = 42.0 μM). GS-563117 shows insignificant inhibition of MDR1, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2, and moderate inhibition of UGT1A1 (IC50 = 16.8 μM).

In support of clinical development in patients with lymphoid cancers, idelalisib has undergone toxicological evaluation in conformance with the International Conference on Harmonisation (ICH) S9 guidance on nonclinical evaluation for anticancer pharmaceuticals

2.1.1.1 General Toxicology

Completed GLP toxicology studies have included 28-day evaluations in both rats and dogs and a study evaluating the hematological effects of co-administration of idelalisib and cyclophosphamide [3]. These studies have shown idelalisib to be tolerated at exposure levels greater than those expected to provide therapeutic activity and have identified signals to be monitored in the clinic. Reversible lymphoid depletion in rats and dogs was consistent with idelalisib-mediated inhibition of PI3Kδ. In rats, partially reversible inflammation of the tongue was noted in idelalisib-treated animals; this may have represented an exaggeration of background effects related to gavage-mediated irritation. Mild congestion or hemorrhage in the large intestine has been seen in dogs receiving high doses of idelalisib. Rats also showed cardiac and hepatic chronic inflammatory infiltrates, although attribution to idelalisib was uncertain because background infiltrates of a similar nature were observed in control recovery animals. In dogs, evidence of hepatocellular injury and chronic inflammation was accompanied by elevations of serum transaminase values (serum alanine aminotransferase [ALT] and serum aspartate aminotransferase [AST]). These hepatic effects appeared dose-related, reversible, and monitorable using standard serum chemistry laboratory parameters. In both rats and dogs, persistent minimal to mild degeneration of the seminiferous tubules and decreased spermatozoa were present in male animals receiving idelalisib. When co-administered with cyclophosphamide in rats, idelalisib did not worsen cyclophosphamide-mediated changes in hematological parameters.

Data from completed 13-week GLP toxicology studies in rats and dogs are available. These data confirm the 28-day toxicology findings. Idelalisib was well tolerated with no notable clinical observation or changes in body weight at exposure levels approximating or exceeding those observed in subjects at the planned clinical starting dose of 150 mg/dose administered twice per day (BID). In both species, dose-dependent lymphoid depletion was observed that was consistent with PI3Kδ inhibition by idelalisib. In dogs, expected transient low-level elevations of serum

ALT in 2 animals receiving the highest idelalisib dose were observed at Day 29 of the study; of note, animals showed spontaneous recovery during continued idelalisib dosing, with no elevations at Day 60 or Day 90. Microscopic review of dog tissues indicated no evidence of persistent or residual liver pathology at the conclusion of the study. Consistent with previous studies, findings of persistent hypospermatogenesis and decreased testicular weight were observed in both species.

In an investigative study, a further characterization of the pattern of serum transaminase changes associated with administration of high-dose of idelalisib to dogs confirmed hepatic adaptation to the effect. In this study, mean serum ALT/AST values peaked at approximately Day 24 to Day 27 and resolved spontaneously as the dogs continued on idelalisib through the end of the study on Day 44.

2.1.1.2 Genotoxicity

Idelalisib was not genotoxic in a standard battery of assays [3]. In the Ames assay, idelalisib did not cause mutagenic effects. In human peripheral blood lymphocytes, the compound induced no chromosomal aberrations. In a rat micronucleus study, idelalisib did not show evidence of clastogenicity.

2.1.1.3 Reproductive Toxicology

A definitive embryo-fetal developmental toxicity study of idelalisib was performed in time-mated pregnant female rats. Maternal toxicity was demonstrated by dose-dependent decreases in the body weight gains of the dams. Dose-dependent developmental findings included decreased fetal viability, greater numbers of early and late fetal resorptions, and reduced fetal weights. Dose-dependent external malformations included short tail or no tail in multiple fetuses, and 1 instance each of hydrocephaly and microphthalmia. The results of this study indicate that oral administration of idelalisib is embryolethal and teratogenic in rats at maternally toxic doses.

As noted in Section 2.1.1.1, 28-day and 13-week general toxicology studies in rats and dogs indicated dose-dependent reductions in testicular weights, with persistent minimal to mild degeneration of the seminiferous tubules and decreased spermatozoa in rats and hypospermatogenesis in dogs. The impact of these testicular changes on fertility, if any, has not been assessed.

2.1.1.4 Phototoxicity

In vitro studies in embryonic murine fibroblasts have yielded equivocal results relating to the phototoxicity of idelalisib but suggest that its major oxidative metabolite, GS-563117, may enhance cytotoxicity when cells are simultaneously exposed to ultraviolet light. While nonclinical findings suggest the hypothetical potential for phototoxicity in humans, available clinical data do not reveal a photosafety concern [3].

2.2 Clinical Experience with Idelalisib

Idelalisib has undergone extensive early clinical evaluation in a series of Phase 1 studies in healthy volunteers and patients. Studies in healthy subjects have provided information on drug safety; pharmacokinetics; food effects; the potential for drug interactions with CYP3A4

inhibitors; and idelalisib absorption, metabolism and excretion[4]. A Phase 1 study in subjects with allergic rhinitis has offered additional safety information and confirmed the expected immunomodulatory pharmacological effects of the drug. A Phase 1 study in patients with lymphoid malignancies has extended safety and pharmacokinetic observations; documented the clinical and pharmacodynamic activity of idelalisib in patients with CLL, iNHL, and MCL; and provided dosing information in support of further development[4-6]. Idelalisib was recently approved by the FDA for the therapy of relapsed CLL in combination with rituximab, as well as for the therapy of relapsed indolent NHL after at least two prior therapies.

2.2.1 **Phase 1 Studies in Healthy Subjects and in Patients with Allergic Rhinitis**

Three studies in healthy subjects (Studies 101-01, 101-04, and 101-05) have provided information regarding drug safety, pharmacokinetics, food effects, and the potential for drug interactions with CYP3A4 inhibitors [3, 4]. One of these trials also included a preliminary evaluation of absorption, metabolism and excretion in healthy volunteers; in this trial, unlabeled idelalisib was co-administered with a trace amount of [^{14}C] idelalisib given either orally or intravenously and biological samples were assessed by accelerator mass spectrometry.

Safety results from these studies indicated that idelalisib was well tolerated when administered to healthy subjects at single doses through 400 mg (the highest dose level tested) and was also generally well tolerated when administered to healthy subjects over 7 days at dose levels through 200 mg/dose BID (the highest dose level tested). Dosing with 200 mg/dose BID for 7 days resulted in a skin rash in 3 out of 6 subjects; histological findings were consistent with a delayed-type hypersensitivity maculopapular exanthema. Rashes have sometimes occurred in patients with hematological malignancies receiving idelalisib, but have not typically proved dose- or treatment-limiting. In placebo-controlled single-dose and multiple-dose trials, repeated ECG evaluations performed in tandem with pharmacokinetic monitoring showed no evidence of drug-, dose-, or exposure-dependent effects on cardiac rhythm or cardiac intervals (eg, QT interval).

Pharmacokinetic results indicated that plasma idelalisib maximum concentration (C_{max}) and area under the concentration-time curve (AUC) values were less-than-dose-proportional with increasing single- and multiple-dose administration. Consistent with mean half-life ($t_{1/2}$) values in the range of 6 to 10 hours, steady state was achieved within 7 days of BID dosing and accumulation was modest.

Idelalisib dosing after a high-fat, high-calorie meal delayed median time of maximum concentration (T_{max}) from 0.75 hours to 3 hours; mean C_{max} was unaffected and mean AUC was ~40% higher. These changes in idelalisib exposures are considered modest/clinically non-relevant; thus, idelalisib may be given with or without food.

Idelalisib is metabolized in humans primarily by aldehyde oxidase, with some involvement of CYP3A4 and UGT1A4. Accordingly, when idelalisib was administered following 4 days of daily dosing with ketoconazole (a potent inhibitor of CYP3A4), modest/moderate increases in mean idelalisib C_{max} and AUC values of ~30% and ~80%-higher, respectively, were observed, indicating that idelalisib is not a sensitive substrate for CYP3A4. Thus, co-administration of

CYP3A4 inhibitors and idelalisib is not contraindicated and does not require special monitoring. GS-563117 is formed from idelalisib primarily via aldehyde oxidase.

The ^{14}C-labeled idelalisib huma mass balance results showed that the drug has moderate to high oral bioavailability Idelalisib is eliminated mainly via hepatic metabolism and biliary excretion in the feces (~78% of dose); recovery in urine was < 15%. GS-563117, was the primary/only circulating metabolite observed in human plasma, and was also observed in urine and feces.

Pharmacodynamic results showed that an idelalisib dose of 200 mg inhibited ex vivo basophil activation via the PI3Kδ-specific, high-affinity immunoglobulin (Ig)E receptor (anti-FCεR1) in basophils collected from healthy volunteers. The findings were confirmed when the drug was assessed over 7 days in a Phase 1b study in subjects with allergic rhinitis. In this study, idelalisib at a dose level of 100 mg/dose BID showed clinical and pharmacodynamic activity (attenuating adverse responses to allergenic challenge and decreasing markers of inflammation) and was well tolerated.

2.2.2 **Phase 1 Study in Patients with Relapsed or Refractory Hematologic Malignancies**

A Phase 1 dose-ranging study (Study 101-02) of single-agent idelalisib extended safety and pharmacokinetic observations; documented the clinical and pharmacodynamic activity of idelalisib in subjects with iNHL, MCL, and CLL; and provided dosing information in support of further development [7]. In this study, idelalisib was administered in cohorts of subjects across a range of dose levels from 50 mg/dose BID to 350 mg/dose BID. Idelalisib administration was continued as long as individual subjects were safely benefitting from therapy. Subjects were evaluated in 4-week cycles; response and progression assessments were based on standard criteria [8].

Altogether, 192 subjects were enrolled to the study, including 55 subjects with CLL. As expected given the demographics of these diseases, subjects were predominantly male and were often elderly, ranging in age to 82 years for the subjects with CLL. The majority (82%) of the subjects with CLL had bulky tumors (≥1 lymph node ≥5 cm in diameter) and 31% had the adverse prognostic factor of a 17p chromosomal deletion (which commonly confers a p53 mutation in the tumors of these subjects). Subjects were heavily pretreated with chemoimmunotherapy; the median number of prior therapies by disease was 5 among subjects with CLL, but ranged up to 15 prior treatments. Among those with CLL, prior rituximab, alkylator, and fludarabine use were nearly universal and 33 percent had received prior alemtuzumab. Considering only rituximab use after initial therapy, 35% had received single-agent rituximab at least once (some patients up to 3 times) and a total of 51/54 (94%) had received rituximab given alone or in combination with other agents. In the estimation of the investigators, a substantial proportion (72%) of these subjects had disease that was refractory to the last prior therapy. In these subjects, therapy was administered for a median of 9 cycles, ranging up to 24 cycles (ie, 96 weeks).

In this single-agent experience, idelalisib was generally well tolerated at dose levels through 350 mg BID (the highest dose tested). No maximum tolerated dose (MTD) was apparent within the tested dose range. Furthermore, subjects typically found the drug tolerable over periods extending to >2 years; there was no profile suggestive of bothersome chronic events such as

headache, nausea, diarrhea, or fatigue. No subject had tumor lysis syndrome. No overt pattern of myelosuppression was associated with idelalisib treatment. The data also did not suggest drug-related reductions in circulating CD4+ cells or serum Igs.

Among Grade 3-4 nonhematological adverse events, pneumonia/pneumonitis was observed most frequently, occurring in 24% of subjects with CLL. In most instances, these cases were considered bacterial in origin, based either on culture results or on response to conventional antibiotics. Subjects with CLL have occasionally been diagnosed with *Pneumocystis (carinii) jiroveci* pneumonia; the specific causal role of idelalisib has been difficult to elucidate because infection was sometimes present before starting idelalisib or the patients had other pre-existing risk factors. Such subjects were not receiving pneumocystis prophylaxis. The rate of pneumonia over time (0.045 events/subject/month) with idelalisib was not worse than the expected rate (0.06 events/patient/month) reported historically in comparable patients with recurrent CLL [9] .

Monitorable, reversible elevations of hepatic transaminases were observed in some subjects; ~5% of subjects with previously treated CLL had Grade 3-4 increases in serum ALT or AST. The onset of changes was time-dependent; among those with serum ALT/AST abnormalities, onset typically occurred 2 to 8 weeks after idelalisib initiation. In subjects with Grade 1-2 events, serum ALT/AST elevations resolved despite continued idelalisib dosing. In subjects with Grade 3-4 events, idelalisib was temporarily interrupted. Upon resolution of serum ALT/AST abnormalities, resumption of idelalisib at a reduced dose did not result in recurrence of serum transaminase increases in the majority (>70%) of subjects who were rechallenged. This pattern suggests an adaptation to the effect similar to that observed in dogs receiving idelalisib. Such an adaptive response is commonly observed with other drugs that induce transaminase elevations.

Idelalisib proved highly active in subjects with CLL, iNHL, and MCL. Among subjects with CLL, idelalisib reduced lymphadenopathy in all 51 (100%) of those with ≥1 post-treatment tumor assessment. In subjects with CLL tumors having a known 17p chromosomal deletion, substantial antitumor activity was observed, although PFS appeared shorter in these subjects relative to other trial participants without such a deletion or in whom the 17p chromosomal deletion status was unknown.

The pattern of changes in CLL was particularly notable. Rapid and substantial reductions in lymph node size were observed in subjects with CLL with >80% of subjects showing a lymph node response (≥50% reductions in index nodal lesions). Among subjects who entered the trial with baseline thrombocytopenia or anemia, idelalisib induced sustained increases in mean platelet counts and hemoglobin levels. In study participants who entered the study with enlarged spleens due to CLL, >70% showed a resolution in splenomegaly. The median PFS was 14 months, with some subjects having tumor control for durations exceeding 2 years. Antitumor activity and tumor control were longest in subjects starting idelalisib at doses of ≥150 mg/dose BID.

A characteristic finding in the single-agent experience was that the majority of subjects had an initial increase in peripheral absolute lymphocyte count (ALC) from baseline. The increase was maximal during the first 2 cycles and generally decreased thereafter but could be persistent in

some subjects or could be seen repeatedly in subjects who had interruption and resumption of drug therapy (eg, due to intercurrent illness). The characteristics of this lymphocytosis indicated a mobilization of CLL cells from tissues rather than a proliferative event or a disease flair. The effect was evident within 4 hours of initiating treatment, was asymptomatic, and was associated with quiescence of CLL cells as indicated by reductions in AKT phosphorylation and decreases in circulating levels of disease-associated chemokines, CCL3 and CCL4, and the stroma-derived chemokine, CXCL13. The lymphocyte mobilization phenomenon is consistent with in vitro data showing that idelalisib depresses chemokine-mediated signaling between CLL cells and stromal cells [10]. These preclinical data support the concept that drug-mediated PI3Kδ inhibition releases CLL cells from sanctuary sites in lymph nodes and bone marrow. This action is not unique to idelalisib alone. Drugs that inhibit spleen tyrosine kinase (SYK) [11], Bruton tyrosine kinase (BTK) [12], or mTOR [13] cause a CLL cell redistribution from tissue sites to the peripheral blood. Because of the occurrence of this type of pattern, investigators working with idelalisib or inhibitors of these other pathways now rely upon measures of disease control other than peripheral blood lymphocyte count in determining whether a patient's disease has progressed.

An analysis of steady-state idelalisib plasma concentrations (Day 28 C_{max}, $AUC_{0\text{-}6h}$, or C_{trough}) relative to dose in subjects with both NHL and CLL showed increases in these parameters through the dose level of 150 mg/dose BID. At higher doses, flattening of the mean dose-plasma exposure curve was observed, resulting in smaller incremental increases in exposure. Considering all safety, efficacy, and pharmacokinetic findings together, the data supported 150 mg/dose BID as an appropriate idelalisib monotherapy starting dose for future studies in patients with CLL and other lymphoid malignancies.

2.2.3 **Phase 1 Combination Study in Patients with Hematological Malignancies**

A separate Phase 1 trial (Study 101-07) has evaluated the safety and preliminary activity of idelalisib given in combination with ofatumumab to subjects with recurrent CLL [14].

In this study, idelalisib (150 mg BID) was co-administered with a total of 12 infusions of ofatumumab given over 24 weeks (300-mg initial dose followed 1 week later by 1,000 mg weekly for 7 doses, followed 4 weeks later by 1,000 mg every 4 weeks for 4 doses). Thereafter, subjects continued to receive single-agent idelalisib as long as the subject was safely benefiting from therapy. Subjects were evaluated in 4-week cycles; response and progression assessments were based on standard criteria [8].

At the time of the data analysis, accrual of the cohorts was complete with 21 subjects enrolled and evaluable. Median [range] age was 66 [43-79] years. The majority (14/21; 67%) of patients had bulky adenopathy (≥1 lymph node ≥5 cm in diameter). The median [range] number of prior therapies was 3 [1-6], including prior exposure to alkylating agents (18/21; 86%), rituximab (20/21; 95%), purine analogs (16/21; 76%), alemtuzumab (4/21; 19%), and/or ofatumumab (3/21; 14%). The median [range] ofatumumab treatment duration was 36+ [0-48+] week.

No idelalisib-related dose-limiting toxicities were observed within the tested subject cohorts. Ofatumumab infusion reactions were manageable. One patient developed corticosteroid-related hyperglycemia and sepsis. No clinically significant myelosuppression was observed.

Almost all subjects (17/21, 84%) experienced marked and rapid reductions in lymphadenopathy within the first 2 cycles**.** The lymphocyte mobilization that is expected with PI3Kδ inhibition was significantly reduced in magnitude and duration and persisted past Cycle 1 in only 1 patient. The ORR was 16/21 (76%) with 2/21 (10%) subjects showing evidence of complete response (CR), as reported by the investigators. Elevated baseline levels of CCL3, CCL4, CXCL13, and TNFα were significantly reduced after 28 days of treatment. At the time of the data analysis, overall PFS through 48 weeks was >75% and a median PFS had not yet been observed.

Collectively, the emerging data from this study support further evaluation of idelalisib together with ofatumumab in subjects with CLL and indicate that co-administration of idelalisib with ofatumumab is tolerable when using idelalisib at full dose, ie, at a starting dose level of 150 mg/dose BID.

2.2.4. Updated Data on Early Treatment Trials, 3/11/16

As of 3/11/16, Gilead terminated enrollment on all upfront trials in CLL. This was because an excess of mortality was observed on the idelalisib containing arms in three trials: GS-US_312-0123, A Phase 3 Randomized Double Blind Placebo Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS1101) in Combination with Bendamustine and Rituximab for Previously Untreated CLL; GS-US-313-0124, A Phase 3 Randomized Double Blind Placebo Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Rituximab for Previously Treated Indolent NHLs; and GS-US-313-0125, A Phase 3 Randomized Double-Blind Placebo Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS1101) in Combination with BR for Previously Treated Indolent NHL. In total, of 664 patients on idelalisib containing arms, 7.4% had died, compared to 3.5% of 402 patients on the control arm. Most deaths were due to infections including opportunistic infections, and prophylaxis had not been mandated.

2.3 Ofatumumab

Ofatumumab is a human novel anti-CD20 antibody which binds to a different CD20 epitope than rituximab, and induces potent complement–dependent cytotoxicity against cells that express CD20 dimly, including CLL.

2.3.1 **Nonclinical Pharmacology**

Binding of ofatumumab causes clustering of CD20 on the cell surface and cell death through the induction of complement mediated cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC). In vitro studies showed that ofatumumab is able to kill tumor B cells including those with low CD20 expression, such as primary chronic lymphocytic leukaemia (CLL) cells, and cells with high expression of complement defense molecules. The anti-tumor effects of ofatumumab were confirmed in human B cell tumor xenograft models in mice.

Statins were found to reduce the in vitro ability of ofatumumab to induce CDC or ADCC mediated cell lysis. Compared to rituximab, ofatumumab showed potential in nonclinical studies to be more potent at inducing CDC, especially in cells with low CD20 expression. Furthermore, as a fully human antibody, ofatumumab is predicted to be less immunogenic than rituximab, which is a chimeric monoclonal antibody.

2.3.2 **Effects in Humans**

2.3.2.1 **Pharmacokinetics and pharmacodynamics**

Pharmacokinetic data are available from four completed studies (Study Hx-CD20-001, Study Hx-CD20-402, Study Hx-CD20-403, and Study OMB111148), three concluded studies (Study Hx-CD20-405, Study Hx-CD20-407, and Study GEN414/OMS115102 (48-week interim analysis completed)), and four ongoing studies (Study Hx-CD20-406, Study Hx-CD20-409, Study GEN410/OFA110635 (completed to 24 weeks), and Study OFA110867 (Day 169 analysis completed)). Ofatumumab was administered by IV infusion in all studies except Study OFA110867, in which it was given by SC injection. After repeated IV administration, clearance and volume of distribution values were low and half-life values were long for ofatumumab, as seen with other monoclonal antibodies. Statistically significant increases in AUC, Cmax, and t½ values and decreases in clearance (CL) values were found between the first and last infusions. These findings are likely due to the rapid and sustained depletion of CD20+ B cells after first infusion, leaving a reduced number of B cells available for the antibody to bind at subsequent infusions. Subcutaneous administration of a single dose of ofatumumab ≥30 mg in subjects with rheumatoid arthritis similarly resulted in rapid and sustained B-cell depletion.

2.3.2.2 **Summary of safety data**

Infusion reactions in the IV program are common adverse events (AEs) that are generally mild to moderate in severity, and have been mitigated by premedication and slower IV administration. Severe infusion reactions have been reported, and have occasionally led to temporary interruption or withdrawal of ofatumumab. Adverse events in the SC program to date have also shown severe reactions, but overall, most AEs have been generally mild to moderate, and have been considered as post-injection systemic reactions (PISRs). Infectious events including lower respiratory tract infections and cytopenias that include neutropenia, anemia, and thrombocytopenia have been observed in oncology trials with ofatumumab, but these events are commonly reported with the diseases under study and/or other concomitant therapies. Neutropenia and serious infections have also been reported in RA studies, but these generally occurred at a similar frequency between the ofatumumab and placebo groups.

2.3.2.3 **Efficacy in chronic lymphocytic leukemia (CLL)**

As of 21 December 2010, efficacy results are available from two completed studies (Study Hx-CD20-402, Study 148) and 2 concluded studies in CLL (Study 406, Study 407). In Study 402 (N=33), ofatumumab treatment in subjects with relapsed or refractory CLL led to a 48% ORR in the highest dose group, Group C (n=27; 1st dose: 500 mg; 2nd, 3rd, and 4th dose: 2000 mg) and

included 12 (44%) subjects with PR and 1 (4%) subject with nodular partial response (nPR). One of the subjects showed all features of an nPR at Week 19 except that residual lymphadenopathy was identified by computed tomography (CT). For Group C, the median TTP was 15.6 weeks in the full analysis population and 23 weeks in the subgroup of responders. The median duration of response was 16 weeks and the median time to next CLL therapy was 52.4 weeks. In Study 406 (N=154 as of the interim data cutoff of 19 May 2008 and updated results as of cut off of 15 July 2010), the results demonstrated that ofatumumab monotherapy is effective in subjects with CLL who are either refractory to both fludarabine and alemtuzumab (i.e., double refractory [DR]) or who are refractory to fludarabine and considered inappropriate for alemtuzumab treatment due to the presence of bulky (>5cm) lymphadenopathy (i.e., bulky fludarabine refractory [BFR]). Additionally, ofatumumab showed activity in "Other" subjects who failed fludarabine but were enrolled in the study prior to Amendment 3 and did not meet the classification criteria of either DR or BFR defined in the amendment.

The interim results of Study 406 were submitted as the basis for a BLA to the FDA for the use of ofatumumab for the treatment of CLL refractory to fludarabine and alemtuzumab (DR), or refractory to fludararabine but considered inappropriate for alemtuzumab treatment due to bulky (>5 cm) lymphadenopathy (BFR). The FDA reviewed the application and subsequently granted accelerated approval for ofatumumab for the treatment of subjects with CLL refractory to fludarabine and alemtuzumab (DR population). The Arzerra Prescribing Information describes the data presented to the FDA for accelerated approval. As of the 15 July 2010 clinical efficacy cut-off date, updated results of preliminary data for Study 406 are summarized. The primary endpoint analysis in 223 subjects included subjects in the DR (N= 95), BFR (N= 111), and Other (N=17) groups. The ORR was 51% (48/95) in the DR group, 44% (49/111) in the BFR group, and 59% (10/17) in the Other group. Among the 107 responders, 2 subjects in the BFR group achieved CR, 48 subjects in the DR group achieved PR, 47 subjects in the BFR group achieved PR, and 9 subjects in the Other group achieved PR. An additional 33 subjects in the DR group, 49 subjects in the BFR group, and 5 subjects in the Other group achieved SD. The median duration of response was 5.7 months, 6.0 months, and 7.4 months in the DR, BFR, and Other groups, respectively. The median PFS was 5.5 months in both the DR and BFR groups and 8.9 months in the Other group. The median Overall survival (OS) was 14.2 months in the DR group, 17.4 months in the BFR group, and 28.3 months in the Other group. Additional data and analyses are ongoing.

In Study 407 (N=61), subjects with previously untreated CLL were randomized to two dose levels of ofatumumab in combination with FC (fludarabine and cyclophosphamide): 300 mg of ofatumumab (cycle 1) followed by 500 or 1000 mg of ofatumumab (cycles 2-6), in combination with FC, every 4 weeks for 6 cycles. The overall response rate in the 500 mg group was 77% and in the 1000 mg group was 73%. Complete responses were observed in 32% of subjects (10/31) in the 500 mg group and in 50% of subjects (15/30) in the 1000 mg group. Overall, across both dose groups 25 subjects had CR, 19 subjects had PR, 2 subjects had nPR, 5 subjects had SD, and 7 subjects had PD. With the preliminary data, short median follow-up time of 8.2 months did not permit analysis of time to event endpoints.

2.4 Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia is the most common leukemia of adults and remains incurable. Although a subset of patients have very indolent disease and may never require therapy, others have steadily progressive or aggressive disease. These patients tend to experience shorter and shorter remissions, as well as cumulative effects of chemotherapy, which has significant toxicity to their normal bone marrow and immune system. Over time the disease may become more aggressive, acquiring adverse prognostic markers including 11q and 17p deletions. For this reason a highly effective novel therapy which does not induce the myelosuppressive and immunosuppressive effects of chemoimmunotherapy would be ideal. Such a therapy which patients can remain on indefinitely for maintenance is even better. The idelalisib ofatumumab combination studied here has the potential to be such a therapy.

2.5 Rationale

The advent of chemoimmunotherapy has been very effective in the initial treatment of CLL, resulting in long remissions. Increasing evidence suggests however that patients who relapse after chemoimmunotherapy often do not respond well to further chemotherapy. Furthermore, there is an increasing awareness of the long term complications of chemoimmunotherapy, including delayed infections, pancytopenia and MDS/AML. Novel agents that do not have these side effects, including antibodies and small targeted inhibitors, can be quite effective even in refractory disease, and it is of interest to determine their efficacy in previously untreated patients, who may be able to attain prolonged remissions without the side effects of chemoimmunotherapy. Ofatumumab has a 51% response rate in patients refractory to fludarabine and alemtuzumab, and has been recently approved by the FDA for this indication. Ofatumumab clears CLL from peripheral blood very effectively. Its activity in previously untreated CLL has only recently been described, and the ORR is 55%[15].

The investigational drug idelalisib is a specific inhibitor of the delta isoform of PI3 kinase, which is expressed in hematopoietic cells and appears to be functionally critical in B cells. Approximately 190 patients with hematologic malignancies have been treated on the Phase I study of idelalisib. At IWCLL and ASH 2009 and 2010, response rates of 60% in indolent lymphomas were reported. Interestingly, in CLL, all patients have reductions in lymphadenopathy, with 80% of patients reaching >50% reduction, often within 1-2 weeks, and apparently independent of high risk 17p or 11q deletions. However, concomitant with this marked decrease in adenopathy is an increase in lymphocytosis. This lymphocytosis appears to represent a redistribution of lymphocytes from lymph nodes and possibly bone marrow to peripheral blood. Because of the response criteria for CLL, however, this lymphocytosis has prevented a response from being called, even in a patient with marked improvement in bulky lymphadenopathy. A recent revision to the response criteria supports that this lymphocytosis is not progressive disease, and that patients with nodal response with lymphocytosis may be considered as PRs with lymphocytosis. However, this pattern of response suggests that combining idelalisib's activity in nodal disease with another drug which would effectively clear the lymphocytosis should result in excellent and frequent clinical responses. In fact, in previously untreated patients this may represent a potential paradigm for achieving excellent disease control without the side effects of chemotherapy. Thus the combination of idelalisib to

mobilize CLL from lymph nodes, combined with ofatumumab to clear the disease from peripheral blood, should be highly effective in CLL. We have therefore chosen to combine these two drugs in a phase 2 study in which all patients will start idelalisib two months prior to ofatumumab. It is possible that mobilization of cells from sanctuary sites with idelalisib prior to initiation of ofatumumab may enhance response to the combination but this is unclear, as is the rate of lymphocytosis in previously untreated patients. This study design will allow us to address these questions. This study will be run as a multicenter study of the CLL Research Consortium.

Rationale for Prior Amendments in 2014-2015

This study activated for enrollment on June 16, 2014, and since then 15 patients have initiated on therapy. Among the first 8 patients to reach cycle 2, two patients developed grade 4 transaminitis. Transaminitis is a well-known side effect of idelalisib, and included as a black box warning in the FDA approved label. In these two cases the onset was rapid, and continued to increase after discontinuation of the drug. We have therefore previously amended the protocol to significantly increase the frequency of LFT monitoring during the high risk period. Additional observation has shown that this transaminitis appears to be inflammatory, based on the results of two liver biopsies showing a CD8 T cell infiltrate and the response of these patients to steroids and/or mycophenolate mofetil. We have developed an algorithm for the early initiation of steroids with the first signs of transaminitis which together with the frequent monitoring has resulted in predictable safety and much shorter drug interruptions. This amendment served to further refine that treatment algorithm.

An amendment was submitted in January 2015 to add correlative studies, in particular sequencing analysis of the clonal composition of CLL in PB vs BM at baseline, mid treatment and at final restaging. This analysis will still occur.

Rationale for Current Amendment 3/14/16

This amendment will take all patients off idelalisib, but allow them to receive ofatumumab and be followed per protocol assessments. All patients had discontinued idelalisib as of 3/11/16. They will undergo a full disease restaging with correlative samples within 30 days and be followed per protocol until further therapy, and after that just for overall survival.

2.6 Correlative Studies Background and Rationale

a) **Prognostic correlates**- Prognosis in CLL is widely variable and well-correlated with several key biologic prognostic factors. We will therefore determine standard CLL prognostic markers including FISH, *IGHV* and ZAP-70 (by flow cytometry and methylation) in all patients in order to determine if a particular subgroup shows better response to idelalisib-ofa than others, as well as to define the response rate in each subgroup. We will employ CT scans in order to compare response rates determined with and without CT scans, and a bone marrow biopsy will be incorporated at the end of single agent lead-in, and combination therapy even for patients not in CR, in order to gain information on the effectiveness of bone marrow clearance with these two drugs. The bone marrow biopsy at two months on therapy will allow comparison of the features

of CLL cells that redistribute to peripheral blood with the features of those that remain alive in the bone marrow. Serum ofatumumab levels and serum idelalisib levels will be determined by Covance, in order to correlate response with drug levels. It will be of interest to determine how long ofatumumab will remain detectable following completion of the course of therapy. We will also assess whether CD20 expression levels are altered with ofatumumab therapy.

b) **Activation studies of CLL B cells**- CLL cells generally express markers of activation on their cell surface. This may be related to the degree of activation of the BCR pathway, which is inhibited by idelalisib. We will therefore use flow cytometry to determine whether activation markers are altered by idelalisib as a single agent or in combination with ofatumumab. We further hypothesize that idelalisib will potently inhibit downstream signaling triggered by the BCR and other survival pathways in CLL cells, and we will therefore assess the effects of in vivo inhibition of the PI3K delta pathway by idelalisib on those targets. Other pharmacodynamic markers of PI3 kinase inhibition will also be assessed, including for example production of T cell chemokines, to see if these correlate with degree of response.

c) **CLL B cells and their microenvironment**- CLL B-cells are shifted out of the microenvironment by idelalisib. We will compare the biologic features of CLL cells in PB and BM at baseline and again on idelalisib therapy, to see if these features shift in the two compartments over time. We will look at markers of activation and proliferation in both compartments. We will look at whether in vivo therapy with idelalisib alters in vitro susceptibility to antibody therapy and to therapy with other BCR pathway inhibitors.

d) **Predictors of response to idelalisib** - Little is known about predictors of response to idelalisib, or mechanisms of resistance. Dr. Amy Johnson will explore the baseline activity of the PI3K pathway and the degree of observed inhibition in this regard, and will also look for upregulation of alternative signaling pathways in resistant cells. In addition, we will bank CLL cells from prior to all therapy, for assessment of copy number, somatic mutation, gene expression and mRNA and miRNA profiling. Dr Brown has recently completed a large integrative analysis in CLL in which she identified amplifications of PIK3CA as associated with poor outcome, and found that CLLs with PIK3CA amplification had a higher fraction of PI3K activity dependent on alpha vs delta. We therefore hypothesize that these amplifications may be associated with idelalisib resistance, or may be acquired in patients who progress on therapy, and we plan to assess for them in patients with persistently elevated white counts, or who develop recurrent lymphocytosis on therapy. Although we have not yet identified a significant rate of somatic mutations in PI3K genes in CLL, we have identified somatic RAS, MAPK and mTOR mutations which could confer resistance, and we will plan to perform whole exome sequencing to assess for such mutations.

e) **Immune suppression correlative studies**- CLL progression is associated with hypogammaglobulinemia [16-18], expanded T-regs [19, 20], and increased soluble immunosuppressive cytokines (TGF-β [21-23], IL-6 [24-26], IL-10 [24, 27-29]) derived from the primary tumor cells that can promote both survival of the malignant clone and also potential systemic innate immune suppression. Similar to these well-characterized cytokines, expression of PD1 and PD1-L1 on activated CLL cells has the potential for suppression of the innate

immune system as demonstrated in other types of lymphoma [30, 31] and multiple myeloma [32]. The consequence of such innate immune suppression in CLL relative to antibody therapy is likely significant as exemplified by data with rituximab. While rituximab has significant activity in NHL (reviewed in [33, 34]), success as monotherapy in CLL has been modest (reviewed in [35, 36]). Furthermore, unlike NHL and other cancers where specific FcγR SNPs predict for increased effectiveness of antibody therapy, work [37, 38] of John Byrd and colleagues and confirmed by others [39] showed no such relationship in CLL for rituximab. Several groups [40],[41] have documented that one possible reason for innate immune dysfunction could be suppressive cytokines released by the tumor. Reversal of tumor immunosuppressive properties with respect to cytokine release represents a new potential way to augment antibody treatment that has not been approached to this point. Preliminary data from John Byrd's laboratory demonstrate that idelalisib can diminish expression of many of these immunosuppressive cytokines and ligands in vitro. As part of this proposal he will test the ability of the BCR signaling antagonist molecule idelalisib to diminish these cytokines and improve innate immune therapy.

f) Autoimmune toxicity: The early phases of this study have identified a rapid transaminitis sometimes with fever or pneumonitis, and a later colitis, in a pattern very reminiscent of that seen in mice and humans with genetic defects in T regulatory cells. In this study we are therefore going to investigate the changes in T regulatory cells that occur in patients during idelalisib therapy, and attempt to identify findings that correlate with toxicity. This is still possible as samples have already been banked on the patients previously enrolled.

g) CLL subclonal composition and evolution, with outgrowth of resistance. The last several years have seen an explosion of genomic information in CLL, including the identification of SF3B1 and NOTCH1 as recurrently mutated in CLL[42-44] and the proposal that subclonal driver mutations are associated with shorter time to treatment and shorter overall survival, both results from our group at DFCI[45]. Despite these advances, very little is known about the subclonal architecture over time in CLL and between compartments, including peripheral blood and bone marrow. In particular, nothing is yet known about whether the redistribution lymphocytosis[46-48] associated with BCR inhibitors like idelalisib and ibrutinib changes the clonal architecture of the disease in the blood. Some studies have been initiated with ibrutinib but to date no studies have been initiated with idelalisib. Furthermore, nothing is yet known about the genetic characteristics of the residual or persistent disease in blood and bone marrow after treatment with BCR inhibitors, and whether this residual disease eventually gives rise to the relapse clone. We will therefore perform exome sequencing on selected patients at baseline and after idelalisib therapy in order to assess changes in subclonal architecture, and will subsequently collect relapsed samples for comparison purposes. Similarly these studies will still be done as samples have already been banked.

3. Participant SELECTION: Study is closed to enrollment

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Subjects must have CLL / SLL, as documented by a history at some point in time of an absolute peripheral blood B cell count > 5000 / μl, with a monoclonal B cell population co-expressing CD19, CD5, and CD23, or if CD23 negative, then documentation of the absence of t(11;14) or cyclin D1 overexpression. Alternatively patients with lymphadenopathy in the absence of circulating disease will also be eligible for this study if lymph node biopsy or bone marrow biopsy establishes the diagnosis of CLL with the above immunophenotype.

3.1.2 Participants must have measurable disease (lymphocytosis > 5,000 / μl, or palpable or CT measurable lymphadenopathy > 1.5 cm, or bone marrow involvement >30%).

3.1.3 Subjects must not have received any prior systemic therapy for CLL and currently have an indication for treatment as defined by the IWCLL 2008 Guidelines:

- Massive or progressive splenomegaly; OR
- Massive lymph nodes, nodal clusters, or progressive lymphadenopathy; OR
- Grade 2 or 3 fatigue; OR
- Fever ≥ 100.5°F or night sweats for greater than 2 weeks without documented infection; OR
- Presence of weight loss ≥ 10% over the preceding 6 months; OR
- Progressive lymphocytosis with an increase of ≥ 50% over a 2-month period or an anticipated doubling time of less than 6 months; OR
- Evidence of progressive marrow failure as manifested by the development of or worsening of anemia and or thrombocytopenia.

3.1.4 ECOG performance status ≤2 (see Appendix A).

3.1.5 Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of idelalisib or ofatumumab in participants <18 years of age, children are excluded from this study.

3.1.6 Participants must have normal organ and marrow function as defined below:

- creatinine <2.0 times institutional upper normal limit
- total bilirubin <1.5 times institutional upper normal limit (unless due to disease involvement of liver, hemolysis or a known history of Gilbert's disease)
- ALT <institutional upper normal limit
- alkaline phosphatase <2.5 times institutional upper normal limit (unless due to disease involvement of the liver or bone marrow)

3.1.1 The effects of idelalisib and ofatumumab on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Females of childbearing potential must agree to use a

protocol-recommended method of contraception during heterosexual intercourse from the screening visit throughout the study and for 30 days from the last dose of idelalisib. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

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

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.2.1 Participants who have had any prior systemic therapy for CLL, or chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) for some other indication prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

3.2.2 Participants may not be receiving any other study agents.

3.2.3 Participants with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.4 History of severe allergic reactions attributed to compounds of similar chemical or biologic composition to ofatumumab or idelalisib.

3.2.5 Subjects who have current active hepatic or biliary disease (with exception of participants with Gilbert's syndrome, asymptomatic gallstones, liver metastases or stable chronic liver disease per investigator assessment)

3.2.6 Treatment with any known non-marketed drug substance or experimental therapy within 5 terminal half lives or 4 weeks prior to enrollment, whichever is longer, or currently participating in any other interventional clinical study

3.2.7 Other past or current malignancy that could interfere with the interpretation of outcome. Subjects who have been free of active malignancy for at least 2 years, or have a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma, or whose malignancy will not interfere with the interpretation of study results, are eligible.

3.2.8 Chronic or current infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment such as, but not limited to, chronic renal infection, chronic chest infection with bronchiectasis, tuberculosis and active Hepatitis C.

3.2.9 History of significant cerebrovascular disease in the past 6 months or ongoing event with active symptoms or sequelae

3.2.10 Confirmed HIV positive whether or not on antiretroviral therapy.

3.2.11 Clinically significant cardiac disease including unstable angina, acute myocardial infarction within six months prior to randomization, congestive heart failure (NYHA III-IV), and arrhythmia unless controlled by therapy, with the exception of extra systoles or minor conduction abnormalities.

3.2.12 Significant concurrent, uncontrolled medical condition including, but not limited to, renal, hepatic, gastrointestinal, endocrine, pulmonary, neurological, cerebral or psychiatric disease which in the opinion of the investigator may represent a risk for the participant.

3.2.13 Positive serology for Hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive (regardless of HBsAb status), a HB DNA test will be performed and if positive the subject will be excluded.

*If HBV DNA is negative, subject may be included but must undergo HBV DNA PCR testing at least every 2 months from the start of treatment until 12 months post treatment. Prophylactic antiviral therapy may be initiated at the discretion of the investigator.

3.2.14 Positive serology for hepatitis C (HC) defined as a positive test for HepC Ab, in which case reflexively perform an HC RIBA immunoblot assay or hepatitis C viral load to confirm the result. If the confirmatory test is negative the subject will be eligible.

3.2.15 Pregnant or lactating women. Women of childbearing potential must have a negative pregnancy test at screening. Pregnant women are excluded from this study because idelalisib and ofatumumab are anti-neoplastic agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother, breastfeeding should be discontinued if the mother is treated on this study with idelalisib and ofatumumab.

3.2.16 Women of childbearing potential, including women whose last menstrual period was less than one year prior to screening, unable or unwilling to use adequate contraception from study start to 30 days after the last dose of protocol therapy. Adequate contraception is defined as hormonal birth control, intrauterine device, double barrier method or total abstinence.

3.2.17 Male subjects unable or unwilling to use adequate contraception methods from study start to 30 days after the last dose of protocol therapy.

3.2.18 Participants using concomitant corticosteroids are allowed as long as the subject is on the equivalent of 20mg/day or less of prednisone and has been on a stable dose for at least two weeks prior to initiating therapy.

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

CLL is approximately twice as common in men as women, but women have generally been well represented on our CLL protocols at DFCI and the CRC. The eligibility criteria will not have a

negative impact on enrollment of women, particularly since most women with CLL are postmenopausal. We will make every effort to enroll minorities on this study although few are seen in our clinic.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied. All subjects should also be registered to the CLL Research Consortium tissue bank but this enrollment will be through a separate protocol at each institution.

An investigator will confirm eligibility criteria and a member of the study team will complete the QACT protocol-specific eligibility checklist. Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive any protocol therapy following registration, the participant's registration on the study may be canceled. Notify the QACT Registrar of registration cancellations as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the QACT protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. **To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.**

   Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.

4. The QACT Registrar will (a) review the eligibility checklist, and (b) register the participant on the protocol.

5. An email confirmation of the registration will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration.

4.3 General Guidelines for Other Participating Institutions

Eligible participants will be entered on study centrally at the DFCI by the Study Coordinator. All sites should call the Study Coordinator to verify treatment availability. The required Eligibility Checklist can be found in Appendix B.

Following registration, participants should begin protocol treatment within 5 days. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study may be canceled. The DFCI study team should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Participating Institutions

To register a participant, the following documents should be completed by the research nurse or data manager and faxed or emailed to the DFCI central email (DFCI13309@partners.org), Project Manager and Study Coordinator:

- Copy of all screening test results, CT scan, BM report
- Signed study consent form
- HIPAA authorization form
- Signed eligibility checklist

The research nurse or data manager at the participating site will then call the Project Manager or email the DFCI central email (DFCI13309@partners.org) to verify eligibility. To complete the registration process, the Project Manager will:

- Register the participant on the study with QACT
- Fax or e-mail the participant study number, and if applicable the dose treatment level, to the participating site
- Call the research nurse or data manager at the participating site and verbally confirm registration

Note: Registration with the QACT can only be conducted during the business hours of 8am – 5pm EST Monday through Friday. Same day treatment registrations will only be accepted with prior notice and discussion with DFCI.

5. TREATMENT PLAN

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for ofatumumab are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modification). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Idelalisib lead-in followed by ofatumumab 8 wks later

All therapy with idelalisib has been discontinued. Patients on drug stopped as of 3/11/16. Those currently receiving ofatumumab may complete the planned course and evaluations as below. Those who have not yet reached day 57 may initiate ofatumumab at present. On day 57, ofatumumab will begin with the 300 mg dose. Ofatumumab will then be administered at 1000 mg weekly to complete 8 weeks (days 64, 71, 78, 85, 92, 99, 106) throughout Cycles 3 and 4. Cycle 4 will last 49 days (7 weeks) to accommodate the Ofatumumab dosing schedule. This will be followed by monthly ofatumumab on weeks 20, 24, 28, 32 to complete 4 additional cycles (5-8). The overall induction treatment period will then be up to 8 months, including whatever idelalisib was received prior to March 11, 2016. Restaging with CT scans will happen after Cycle 2, on cycle 4 day 22, and a final restage will occur 2 months after the completion of ofatumumab. There will be a tumor response assessment done via physical exam after Cycle 8.

Table 1: Treatment Description

Agent	Pre-medications; Precautions	Dose	Route	Schedule	Cycle Length
Idelalisib	None	150 mg BID	Oral	Discontinued	28 days (4 weeks) (Except cycle 4- 49 days, 7 weeks)
Ofatumumab	Pre-medication before each ofatumumab infusion must be given within 30 minutes to 2 hours prior to the treatment: Acetaminophen 1000 mg po Benadryl 50 mg IV or po Methylprednisolone 50 mg IV*	300 mg at 0.3 mg/ml in NS; followed one week later by 1000 mg at 1 mg/ml in NS	IV after administration of Idelalisib and premeds	Weekly x 8 doses, then monthly x 4 doses	

* If the 2nd infusion has been completed without the subject experiencing any grade = 3 AEs, pre-medication with glucocorticoid may be reduced or omitted before the 3rd to Nth infusion at the discretion of the investigator.

5.1 Pre-treatment Criteria

5.1.1 Cycle 1, Day 1

Subjects must continue to meet the laboratory eligibility criteria for creatinine and LFTs. Subjects must have initiated infectious prophylaxis; they also must be monitored and/or receive prophylaxis against tumor lysis syndrome as needed at the discretion of the treating physician. See section 5.3.2 and 5.3.6 for additional details.

5.1.2 Subsequent Cycles

Liver function tests, creatinine, and complete blood count with differential must be reviewed prior to administration of ofatumumab therapy and managed as below under toxicity management. Premedication for ofatumumab during cycles 3-8 must be given as per Table 1 above.

5.2 Agent Administration

5.2.1 Idelalisib will not be given

5.2.2 Ofatumumab

The dosing of ofatumumab in CLL should consist of an infusion of 300 mg on Day 1, an infusion of 1000 mg weekly for 7 additional doses, and then infusions of 1000 mg monthly for up to 4 doses. The monthly ofatumumab doses should be given on Day 1 of the cycles.

First Infusion of 300 mg Ofatumumab (CLL)
The first dose administered of ofatumumab in CLL should be 300 mg to minimize infusion reactions. The initial rate of the first infusion of 300 mg ofatumumab (0.3 mg/mL) should be 12 mL/h. If no infusion reactions occur the infusion rate should be increased every 30 minutes, to a maximum of 400 mL/h, according to Table 2. If this schedule is followed, the infusion duration will be approximately 4.6 hours. If the ofatumumab dose cannot be completed on day 1 in clinic, the remaining dose may be completed the following day with the same premedications.

Table 2: Infusion rate at 1st ofatumumab infusion (300 mg)

Time	mL/hour
0 – 30 minutes	12
31 – 60 minutes	25
61 – 90 minutes	50
91 – 120 minutes	100
121 - 150 minutes	200
151 - 180 minutes	300
181+ minutes	400

If an infusion reaction develops, the infusion should be temporarily slowed or interrupted. Upon restart, the infusion rate should be half of the infusion rate at the time the infusion was paused. If, however, the infusion rate was 12 mL/hour before the pause, the infusion should be restarted at 12 mL/hour. Thereafter, the infusion rate may be increased according to the judgment of the investigator, in the manner described in this section. If the infusion is not completed on day 1, the remaining infusion may be completed on day 2 at the starting infusion rate used on day 1.

First Infusion of 1000 mg Ofatumumab
The initial rate of the first infusion of 1000 mg ofatumumab (1 mg/mL) should be 12 mL/h. If no infusion reactions occur the infusion rate should be increased every 30 minutes, to a maximum of 400 mL/h, according to Table 3. If this schedule is followed, the infusion duration will be approximately 4.6 hours. If the ofatumumab dose cannot be completed on day 1 in clinic, the remaining dose may be completed the following day with the same premedications.

Table 3: Infusion rate at 1st ofatumumab infusion (1000 mg)

Time	mL/hour
0 – 30 minutes	12
31 – 60 minutes	25
61 – 90 minutes	50
91 – 120 minutes	100
121 - 150 minutes	200
151 - 180 minutes	300
181+ minutes	400

If an infusion reaction develops, the infusion should be temporarily slowed or interrupted. Upon restart, the infusion rate should be half of the infusion rate at the time the infusion was paused. If, however, the infusion rate was 12 mL/hour before the pause, the infusion should be restarted at 12 mL/hour. Thereafter, the infusion rate may be increased according to the judgment of the investigator, in the manner described in this section. If the infusion is not completed on day 1, the remaining infusion may be completed on day 2 at the starting infusion rate used on day 1.

Subsequent Infusions of 1000 mg Ofatumumab
If the previous infusion has been completed without grade ≥ 3 infusion-associated AEs, the subsequent infusion of the 1000 mg ofatumumab (1 mg/mL) can start at a rate of 25 mL/hour and should be doubled every 30 minutes up to a maximum of 400 mL/h, according to Table 4. Duration of the infusion will be approximately 4 hours if this schedule is followed. If the previous infusion has been completed with grade ≥ 3 infusion-associated AEs, the subsequent infusion should start at a rate of 12 mL/hour according to Table 3 for CLL.

Table 4: Infusion rate at subsequent ofatumumab infusion

Time	mL/hour
0 – 30 minutes	25
31 – 60 minutes	50

61 – 90 minutes	100
91 – 120 minutes	200
121+ minutes	400

During infusion the participant should be monitored closely and appropriate measurements should be performed whenever judged necessary. If the ofatumumab dose cannot be completed on day 1 in clinic, the remaining dose may be completed the following day with the same premedications. If the infusion is not completed on day 1, the remaining infusion may be completed on day 2 at the starting infusion rate used on day 1.

5.3 General Concomitant Medication and Supportive Care Guidelines

To the extent possible, administration of any prescription or over-the-counter drug products other than study medication should be minimized during the study period. Participants should be discouraged from use of recreational drugs, herbal remedies, self-prescribed drugs, tobacco products, Tylenol or excessive alcohol at any time during the clinical study.

If considered necessary for the participant's well-being, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the investigator. The decision to authorize the use of any drug other than study drug should take into account participant safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more significant underlying event, and whether use of the drug will compromise the outcome or integrity of the study

Participants should be instructed about the importance of the need to inform the clinic staff of the use of any drugs or remedies (whether prescribed, over-the-counter, or illicit) before and during the course of the study. Any concomitant drugs taken by a participant during the course of the study and the reason for use should be recorded on the CRFs.

Information regarding use or restrictions on specific concomitant medications, dietary measures, or other interventions is provided below.

5.3.1 **Antiemetics**

Nausea and/or vomiting have not been commonly observed with ofatumumab in prior studies. However, participants who experience nausea or vomiting while on study therapy may receive antiemetics based on the judgment of the treating physician and local institutional practices. At the occurrence of persistent nausea or vomiting of severity grade ≥ 1, it is suggested that the participant receive an oral or transdermal serotonin antagonist (eg, dolasetron, granisetron, ondansetron, tropisetron, palonosetron). The neurokinin receptor antagonist, aprepitant, may be considered but is a mild inhibitor of CYP3A4 and so may modestly increase idelalisib plasma exposures. Other classes of antiemetic medications that may be employed include dopamine antagonists or benzodiazepines. If possible, systemic corticosteroids should be avoided other than as premedication for ofatumumab.

5.3.2 **Tumor Lysis Prophylaxis**

Subjects initiating each study drug should be given allopurinol 300 mg daily for approximately 10 days unless contra-indicated, and tumor lysis laboratory testing should be done at the discretion of the treating investigator. Allopurinol therapy should continue through ofatumumab therapy. If allopurinol is contra-indicated another uric acid reducing agent may be substituted or alternative plans may be discussed with the overall principal investigator. Intravenous fluid prophylaxis may also be given at the discretion of the treating investigator and is recommended at the time of initiating therapy with both idelalisib and again with ofatumumab initiation at cycle 3 day 1.

5.3.3 **Granulocyte Colony-Stimulating Factors and Erythropoietin**

Granulocyte-macrophage colony-stimulating factor (GM-CSF) should not be administered given the potential for GM-CSF-related inflammatory symptoms. Granulocyte colony-stimulating factor (G-CSF) agents including pegfilgrastim if desired and erythropoietic agents (eg, erythropoietin or darbepoetin) may be administered in response to Grade ≥3 neutropenia or anemia, respectively. Such use should be particularly considered if providing hematopoietic support might help to maintain idelalisib-ofatumumab therapy. Reference should be made to the American Society of Clinical Oncology guidelines [49, 50].

5.3.4 **Contraception**

In the context of this protocol, a female subject is considered to be of child-bearing potential unless she has had a hysterectomy, a bilateral tubal ligation, or a bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and FSH levels within the institutional postmenopausal range and a negative serum or urine βHCG); or is menopausal (age ≥55 years with amenorrhea for ≥6 months).

Sexually active females of child-bearing potential must accept continuous heterosexual abstinence as a lifestyle choice or agree to use a protocol-recommended method of contraception during heterosexual intercourse throughout the study treatment period and for 30 days from the last dose of study drug or 12 months from the last dose of ofatumumab (whichever is later). The investigator should counsel subjects on the most effective methods for avoiding pregnancy during the trial. Protocol-recommended contraceptive methods are described in table below.

Protocol-Recommended Contraceptive Methods

	Combination Methods	
Individual Methods	**Hormonal Methods (One method to be used with a barrier method)**	**Barrier Methods (Both of these methods to be used OR one of these methods to be used with a hormonal method)**
IUD	Estrogen and progesterone	Diaphragm with spermicide
Copper T 380A IUD	Oral contraceptives	Male condom (with spermicide)
LNg 20 IUD	Transdermal patch	
Tubal sterilization	Vaginal ring	
Hysterectomy	Progesterone	
	Injection	
	Implant	

Abbreviation: IUD=intrauterine device

In the context of this protocol, a male subject is considered able to father a child unless he has had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy, or is receiving ongoing testicular suppression with a depot luteinizing hormone-releasing hormone (LH-RH) agonist (eg, goserelin acetate [Zoladex®]), leuprolide acetate [Lupron®]), or triptorelin pamoate [Trelstar®]).

Sexually active male subjects who can father a child must accept continuous heterosexual abstinence as a lifestyle choice; limit intercourse to female partners who are surgically sterile, post-menopausal, or using effective contraception (as noted in table above); or agree to use a protocol-recommended method of contraception during heterosexual intercourse throughout the study treatment period and for 90 days following discontinuation of idelalisib (as noted in table above).

The Gilead Sciences medical monitor should be consulted regarding any questions relating to child-bearing status or contraception.

5.3.5 **Corticosteroids**

Participants may receive topical or inhaled corticosteroids while on study. The use of systemic corticosteroids is discouraged except as needed for prevention or treatment of infusion reactions related to ofatumumab, or as needed for therapy of transaminitis. However, participants who develop severe or life-threatening conditions that may be alleviated by systemic corticosteroid therapy are permitted to receive such drugs and are not required to discontinue study participation.

5.3.6 **Prophylactic Antibiotics**

Because of the observation of two cases of PCP in this study, PCP prophylaxis is required for all participants initiating therapy on study. At the same time antiviral prophylaxis against HSV and VZV is also required, because of the frequency of reactivation of these viruses in CLL participants.

5.3.7 **Immunization**

Because of its actions to inhibit PI3Kδ-dependent B-cell function, high doses of idelalisib can impair primary or secondary responses to immunization in animals. The specific clinical relevance of these nonclinical findings is unknown. However, for participants who are at substantial risk of an infection (eg, influenza) that may be prevented by immunization, consideration should be given to providing the vaccine prior to initiation of treatment with idelalisib if at all possible, and if not, then vaccination should be provided during idelalisib therapy.

5.4 Duration of Therapy

The planned duration of induction therapy is 8 months of induction therapy. For those still in the midst of induction, they may complete the planned 6 months of ofatumumab therapy followed by

observation. Protocol follow-up may continue until achievement of CR, or indefinitely, until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

5.5 Duration of Follow Up

Once participants have completed study treatment they will be followed until initiation of new therapy following removal from study, or until death, whichever occurs first. They will be seen every 3 or 6 months in the follow up phase; this will be decided by their treating physician. Follow up will continue for up to 10 years. Participants removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event, and/or until initiation of new therapy for their disease, whichever is longer.

5.6 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator (or Protocol Chair) Jennifer R Brown MD PhD at 617-632-4894 or page at 617-632-3352 pager 41344.

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using the following recommendations. Toxicity assessments for non-hematologic toxicity will be done using the CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is identified and located on the CTEP website at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Hematologic toxicity will be evaluated according to the IWCLL 2008 guidelines as outlined below and in Appendix C.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.1 Anticipated Toxicities

A list of the adverse events and potential risks associated with the agents administered in this study appear below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting in addition to routine reporting.

Please note that if one study drug is held, the other will also be held. If drugs are held for more than half a week, then the assessment schedule will also be held until drug resumption.

6.1.1 **Adverse Event Lists(s) for Idelalisib**

Symptomatic adverse events are infrequent, usually low-grade, and not clearly idelalisib-related. Among Grade ≥3 nonhematological adverse events occurring in ≥5% of patients, pneumonia was observed most frequently, occurring in 24% of patients with CLL. In most instances, these cases were considered bacterial in origin, based either on culture results or on response to conventional antibiotics; 2 patients with CLL have had pneumocystis pneumonia. The observed rate of pneumonia of any type in patients with CLL receiving idelalisib over 360 patient-months of observation has been 0.04 pneumonias/patient/month; this rate is modestly less than the rate of 0.06 pneumonias/patient/month reported in the literature for a comparable population of CLL patients [9]. There have however also been a few cases of what appears to be a steroid-responsive idelalisib-related pneumonitis. Other nonhematological adverse events in patients with CLL have included diarrhea (4%), and fatigue (4%). Grade ≥ 3 hematological laboratory abnormalities include neutropenia (8%), thrombocytopenia (4%), anemia (2%) and neutropenic fever (7%).

6.1.2 **Adverse Event List(s) for Ofatumumab**

The primary adverse event associated with ofatumumab is infusion reactions during drug administration. The management of those is discussed under drug administration. Other potential concerns include LFT abnormalities, hepatitis B reactivation, and PML, which has been observed with another CD20 antibody, rituximab.

6.2 Toxicity Management

Patients should be followed closely for adverse events or laboratory abnormalities that might indicate idelalisib or ofatumumab-related toxicity. Recommendations for idelalisib dose modification and when to hold and restart drug are provided below. If a patient experiences a idelalisib-related adverse event requiring dose modification during the course of idelalisib therapy, then study drug administration should be held, as necessary, until the adverse event resolves or stabilizes to an acceptable degree. Thereafter, idelalisib may be reinstituted, but the

dose of idelalisib should be reduced by 1 dose level (except for hematologic toxicity or grade 3 infections or grade 3 asymptomatic laboratory abnormalities, when dose may potentially be maintained at the investigator's discretion); dose adjustments may be made. If the patient cannot tolerate idelalisib at Dose Level -1 (100 mg/dose BID) then the patient should be discontinued from study drug therapy.

After a dose is reduced, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the patient tolerates a reduced dose of idelalisib for ≥4 weeks then the idelalisib dose may be increased to the next higher dose level, at the discretion of the investigator. Such re-escalation may be particularly warranted if further evaluation reveals that the adverse event that led to the dose reduction was not study drug-related. Successive adjustments to progressively higher dose levels can be made at 4-week intervals. The starting dose level (150 mg BID) should not be exceeded.

Except as specified below for hematologic and liver toxicity, in most cases of adverse events both study drugs will be held until resolution.

Table 5

Dose Level	Idelalisib Dose
-1	100 mg BID (1 tablet, 100 mg)
0	150 mg BID (1 tablet, 150 mg)

Management of Hepatic Adverse Events in Patients on or soon after discontinuation of Idelalisib

Based on Phase 1 clinical experience with idelalisib, other adverse events potentially attributable to idelalisib have included pneumonias, rash, and colitis/diarrhea. Hepatic laboratory abnormalities deserve particular attention and reversible Grade ≥3 ALT/AST elevations were seen in patients and attributed to idelalisib. Onset has generally occurred 2 to 8 weeks after idelalisib initiation and resolution has usually been seen 2 to 6 weeks after idelalisib interruption. After resolution of ALT/AST changes, the majority of the patients who were rechallenged at the same or a reduced dose of idelalisib were able to resume treatment without recurrence of transaminase elevations. Only 1 (0.9%) patient has had an elevation in bilirubin to >2 times the upper limit of normal; because of a recent history of biliary obstruction requiring endoscopic retrograde cholangiopancreatography for biliary and common bile duct stone removal, a causal relationship to idelalisib could not be established.

In the initial phase of this study, grade 1-2 LFT elevations have been seen beginning in week 3. Given the rapid rate of rise seen in two patients, a comprehensive metabolic panel (electrolytes, BUN, creatinine, glucose, LDH, phosphate, uric acid, LFTs (total bilirubin, direct bilirubin, AST, ALT, alkaline phosphatase) will be obtained twice per week starting in week 3 and continuing up through week 16 in the absence of LFT abnormalities.

First Event of Transaminitis

If a first event of grade 1 AST or ALT elevations are noted (very slight elevation of 1 to 5 points above normal may be repeated within 3-4 days prior to initiating management as follows), dosing may continue with ongoing at least twice per week monitoring of levels and initiation of prednisone 40 mg daily. Patients whose AST or ALT remain grade 0-1 after initiation of steroids will remain on prednisone 40 mg daily until initiation of ofatumumab therapy at which time steroids may be tapered slowly over not less than one month.

If at any point either AST or ALT reaches grade 2 elevation or higher on any test, idelalisib will be held and prednisone will either be started or increased to 1 mg/kg daily, rounded up to the nearest multiple of 10 mg. If direct or total bilirubin is elevated (grade 2 or higher) and not due to an obvious unrelated cause such as hemolysis or gilbert's syndrome, drug should be held. Monitoring will continue twice weekly until LFTs trend towards normalizing, at which point labs may switch to once weekly, based on conversation between the treating investigator and the overall PI. The labs on non-protocol specified treatment days may be obtained locally at the discretion of the site-responsible investigator but must be followed up the same day by the study site. For patients with a grade 2-3 transaminitis, following resolution of AST or ALT to normal (grade 0), consideration may be given to resuming idelalisib at a one dose level reduction, at 100 mg BID. Steroid dose should be held at its prior level for at least one week after idelalisib is restarted, following which if AST / ALT remain within normal limits, prednisone may be tapered at a recommended rate of 10 mg per week. LFTs should be checked weekly for at least twelve weeks after resuming study drug, even while on prednisone

Patients whose AST or ALT reach grade 4 but resolve rapidly with steroids may be reinitiated on idelalisib while on steroids, as per the above protocol for grade 2-3, at the discretion of the treating investigator in consultation with the PI. Patients whose grade 4 AST or ALT continue to rise despite steroids, or fail to improve in 3-5 days after initiation of steroids, should be discussed with the overall PI, with consideration given to initiation of mycophenolate mofetil 2000 mg BID. These patients will also be carefully assessed for the suitability of reinitiation of idelalisib, in consultation with the overall PI. Otherwise subjects who reinitiate at 100 mg BID with stable normal LFTs and who taper off prednisone may be considered for dose re-escalation to 150 mg BID, after they reach cycle 5 or beyond.

Several subjects have had stable minor grade 1 to low grade 2 AST/ALT elevations typically developing in cycle 3-4. If twice weekly monitoring shows stability at this level, , as either an initial event or a subsequent event, initiation of prednisone and holding idelalisib will be discretionary if LFTs remain less than grade 3, with approval of the overall PI.

Subsequent Events of Transaminitis During Cycle 1-4

If AST / ALT go back up to grade 1, idelalisib and prednisone may be continued at current level or prednisone may be resumed or increased to 40 mg daily at the discretion of the treating investigator and PI, but if they rise to grade 3 or higher, follow above recommendations for grade 2 or above (i.e. hold idelalisib and increase steroids back to 1 mg/kg). Monitoring will continue twice weekly until LFTs trend towards normalizing, at which point labs may switch to once weekly, based on conversation between the treating investigator and the overall PI. These additional labs should be continued at least twelve weeks after resuming study drug. The labs on

non-protocol specified treatment days may be obtained locally at the discretion of the site-responsible investigator.

Alternative management plans for hepatotoxicity may be acceptable with prior approval of the overall PI, except in cases of fulminant grade 3/4 events.

Management of Transaminitis Cycle 5 and onward

Several subjects have had stable minor grade 1 to low grade 2 AST/ALT elevations at this point in the study, as either an initial event or a subsequent event. Therefore initiation of prednisone and holding idelalisib will be discretionary if LFTs remain less than grade 3. On initial observation of this finding, LFTs must be repeated twice per week for at least 2 and up to 4 weeks or an alternative monitoring plan should be discussed with the overall principal investigator. Very slight elevations (approximately 1-5 points) may not necessitate repeat labs in the absence of clinical symptoms. If at any point either AST or ALT reaches grade 3, Idelalisib must be held and LFTs re-checked within 2-3 days; prednisone may be started at the discretion of the treating investigator. If either AST or ALT is greater than 10 times the ULN at any time, or if AST or ALT continue to rise after stopping study drug, then Prednisone must be started at 1mg/kg and LFTs must be checked twice per week until resolution to grade 0, at which time Idelalisib may be resumed. If Idelalisib is resumed prednisone should be continued at current dose for at least one week prior to beginning taper as described above. All subjects will continue with at least weekly LFTs for up to 12 weeks while on stable dose of Idelalisib and off prednisone. If at that time LFTs have remained stable grade 1 or within normal limits, the frequency of LFT checks may decrease to every 2-4 weeks at the discretion of the treating investigator with communication with the overall PI. Some variation in these guidelines may be considered upon consultation of the treating investigator with the overall PI.

Ofatumumab has also been associated with LFT abnormalities. Of particular concern in this context is the possibility of reactivated or new hepatitis. In particular, patients enrolled on study who had HBcAb positive with HBsAg negative may be at (low) risk for reactivation. For that reason, those patients were screened prior to enrollment for HBV DNA and required to be negative. If such a patient develops any even grade 1 LFT elevation, HBV DNA must be performed at the time of this occurrence, in addition to the already planned every 2 month HBV DNA PCR testing from the start of treatment throughout the treatment course. Monitoring during the on treatment periods is required at least every 2 months and during follow-up at a minimum of every 2-3 months up to 12 months after the last dose. If the subjects' HBV DNA becomes positive during the study, the investigator should manage the clinical situation as per the standard of care of that institution, likely including holding drug and instituting antiviral therapy. Also, if a subject's HBV DNA becomes positive during the study, notify Novartis (contact information located in 11.4.1). The risks and benefits of continuing or discontinuing ofatumumab should be discussed with the overall PI before treatment decisions are made for that individual subject. Subjects initiated on antiviral therapy who achieve suppression of their HBV DNA viral load may be eligible to continue on the study at the discretion of the treating investigator and the overall PI.

For those patients with at least grade 2 elevations in ALT/AST and in bilirubin (only if direct), drug should be held as noted above, and they should undergo the further workup below as well as the monitoring discussed above. These patients will have ofatumumab held as well as idelalisib, until resolution. Further workup is particularly warranted in patients who first experience a serum ALT/AST elevation 12 weeks from the start of idelalisib therapy, who have an elevation in serum bilirubin concentration, or who have other characteristics that suggest an atypical change in transaminase values. Further workup may include: obtaining a history of recent symptoms/illnesses and of relevant past history (eg, history of hepatitis or of hepatitis A or hepatitis B vaccination); obtaining information regarding concomitant drug use (prescription and nonprescription medications, dietary supplements, alcohol, illicit drugs, special diets); questioning the patient regarding potential exposure to environmental toxins; ruling out viral hepatitis A, B, C, D (if hepatitis B is positive), and E, Epstein-Barr virus, cytomegalovirus, autoimmune hepatitis, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies, alcoholic hepatitis, nonalcoholic steatohepatitis, hypoxic/ischemic hepatopathy, and biliary tract disease; obtaining additional tests to evaluate liver function (eg, imaging as appropriate, and prothrombin time [PT], activated partial thromboplastin time [aPTT], international normalized ratio [INR], albumin); and considering gastroenterology or hepatology consultation [FDA 2009]

PML

Progressive multifocal leukoencephalopathy (PML) is a viral-induced demyelinating disease of the central nervous system usually occurring in the immunocompromised individual. JC virus infection resulting in PML and death has been reported in rituximab-treated subjects with hematologic malignancies or with systemic lupus erythematosus (SLE), an indication for which rituximab has not been approved. In the literature, PML has been reported to occur in 0.52% of CLL subjects and in approximately 5% of fludarabine-treated B-CLL subjects. One case of PML was reported in a very ill CLL subject treated with ofatumumab, previously treated with alemtuzumab and fludarabine and with very low CD4 cell count.

Investigators and nurses should pay careful attention for signs and symptoms consistent with a diagnosis of PML. Signs and symptoms of PML include visual disturbances, ocular movements, ataxia, and changes in mental status such as disorientation or confusion. These symptoms are not an exhaustive list and the investigator should exercise judgment in deciding to report signs and symptoms to the overall PI and Novartis promptly. Please see Appendix D for a symptom screening questionnaire.

If a subject develops neurological signs or symptoms consistent with PML treatment should be halted and the subject referred to a neurologist for evaluation. The investigator will contact the Novartis within 24 hours of being notified of a participant's potential signs and symptoms of PML. At a minimum, blood JCV PCR and/or MRI will be performed and if either is positive perform Cerebrospinal Fluid (CSF) JCV PCR. If blood JCV PCR and MRI are negative, the investigator will contact the Novartis for appropriate action to be taken. If blood JCV PCR and/or MRI are positive, the subject should proceed to the Follow-Up Period. All such subjects will be followed until resolution. Any subject with a diagnosis of PML will be withdrawn from ofatumumab. There are no known tests that can reliably determine who is at increased risk for

developing PML. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs.

Hematologic Toxicities

While myelosuppression is not a prominent toxicity of idelalisib in previous experience, dose modification provisions for patients experiencing neutropenia or thrombocytopenia are provided as a precaution. Recommendations for dose modification based on the type and severity of adverse events or laboratory abnormalities are provided below in Table 6. Whenever possible, any dose adjustment of idelalisib should be discussed between the treating investigator and the overall Principal Investigator prior to implementation. Myelosuppression is also not a prominent complication of ofatumumab therapy, although neutropenia can occur. Ofatumumab will generally not be held for myelosuppression, but appropriate growth factor and transfusion support will be employed as needed.

Either or both drugs may be held for up to six weeks for resolution of toxicity without removing a participant from the study. Longer holds are acceptable in the post-induction phase following discussion with the overall principal investigator.

6.3 Dose Modifications/Delays

No ofatumumab dose modifications are permitted.

7. DRUG FORMULATION AND ADMINISTRATION

Table 6. Recommendations for Dose Modification of Study Drug(s) Based on Type and Severity of Adverse Event or Laboratory Abnormality

Non-Hepatic and Non-Hematological Study Drug-Related Event				
CTCAE Grade	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Idelalisib and Ofa Dosing Recommendation	Maintain dose level	Maintain dose level	Withhold drugs until toxicity is Grade ≤1. May resume idelalisib only at next lower dose level for most toxicities, but may resume at current dose level in the case of grade 3 infections, grade 3 nausea/vomiting/diarrhea that can be symptomatically managed, grade 3 asymptomatic laboratory abnormalities or grade 3 infusion reactions.	
Hepatic Study Drug-Related Event (Elevation in ALT, AST, or Bilirubin)				
CTCAE Grade	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
ALT/AST	**>ULN-3 x ULN**	**>3-5 x ULN**	**>5-20 ULN**	**>20 x ULN**
Bilirubin	**>ULN-1.5 x ULN**	**>1.5-3 x ULN**	**>3-10 x ULN**	**>10 x ULN**
Idelalisib and Ofa Dosing Recommendation	See Section 6.2: Management of Hepatic Events.			
Hematological Idelalisib -Related Event				
IWCLL Grade	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Neutropenia (ANC x 10^9/µL)	**ANC <LLN-1.5**	**ANC <1.5-1.0**	**ANC <1.0-0.5**	**ANC <0.5**
Thrombocytopenia (platelets x 10^9/µL)	**Platelets 11-24% below baseline**	**Platelets 25-49% below baseline**	**Platelets 50-74% below baseline**	**Platelets ≥75% below baseline or <=25K**
Idelalisib Dosing Recommendation	Maintain dose level	Maintain dose level	Maintain dose level; support with g-csf growth factors at investigator discretion	During combination therapy period, consider G-CSF support and maintain current study drug dose level and schedule. During initial and continuing single-agent study drug therapy period, consider G-CSF support and continue study drug at initial or lower dose level at investigator discretion.

***Note: In any case where Idelalisib is held, ofatumumab should also be held. The assessment schedule is also held in cases where study drug is held for greater than half a week.*

Abbreviations: ALP, alkalkine phosphatase; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; LLN, lower limit of normal; ULN, upper limit of normal

7.1 Idelalisib

7.1.1 Drug Substance and Formulation

Idelalisib is a fluorinated quinazolinone with 1 stereogenic center. Idelalisib is the *S* enantiomer. The compound has no known structural similarity to existing drugs. The drug substance is a white to off-white, crystalline powder with a chemical formula of $C_{22}H_{18}FN_7O$, a molecular weight of ~415 Daltons, and low aqueous solubility. Idelalisib is orally bioavailable.

7.1.2 **Description**

Idelalisib is manufactured according to cGMP. The study drug is provided in tablets intended for oral administration. Each tablet contains 100, or 150 mg of the active study drug substance. Inactive excipients present in the formulation are microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, and magnesium stearate. The 100-mg tablets are orange, and the 150-mg tablets are pink. The yellow coating contains yellow iron oxide, polyethylene glycol, talc, polyvinyl alcohol polymer, and titanium dioxide. The orange coating contains Food Drug & Cosmetic Yellow #6/Sunset Yellow Food Cosmetic Formulary Aluminum Lake, polyethylene glycol, talc, polyvinyl alcohol polymer, and titanium dioxide. The pink coating contains red iron oxide, polyethylene glycol, talc, polyvinyl alcohol polymer, and titanium oxide.

7.1.3 **Packaging**

Idelalisib will be packaged in bottles containing 60 tablets. A label will be affixed to each bottle and will contain the following information in English:

- Manufacturer name and address
- Protocol identifier
- Description of contents, including dose strength and fill count
- Caution statement (includes “keep out of reach of children” statement)
- Storage conditions
- Manufacture date
- Lot number

7.1.4 **Source**

Idelalisib will be supplied free of charge by Gilead Sciences. Biologics has been selected for the provision of supply procurement and distribution services to each investigative site. Any questions or concerns regarding study drug supply should be referred to DFCI team and Biologics for routing to Gilead Sciences clinical project manager.

7.1.5 **Storage and Stability**

Bottles containing tablets of idelalisib will be stored at controlled room temperature (~15 to 30°C). While stability of tablets stored at controlled room temperature has been confirmed, brief excursions to temperatures up to 40°C or down to 5°C will not adversely affect the drug. Freezing must be avoided. Stability data at the start of study will support the use of the drug product for ≥12 months. The clinical site will be updated as more stability data become available.

7.1.6 **Dispensing**

The clinic pharmacist or an alternative qualified person will be responsible for dispensing study medication. It is planned that drug will be dispensed at 4-week intervals through the first 24 weeks of treatment and at 12-week intervals thereafter. A modest overage will be supplied such that patients have sufficient drug in case of loss, spillage, or necessary deviations in scheduling clinic returns (eg, due to inclement weather, holidays, etc). Tablets should be kept in the original bottles provided. However, it is permissible to re-package the quantity of study

medication into standard amber prescription bottles in the case the need arises (e.g. participant requires a lesser quantity of medication due to dose reductions).

7.1.7 **Return**

Patients should return all unused study medication to the study site at each applicable study visit.

7.1.8 **Accountability**

The disposition of all idelalisib study drug should be documented from the time of receipt at the site through patient dispensing and return.

Study personnel must ensure that all study drug is kept in a secure locked area with access limited to authorized personnel. The study drug must not be used outside the context of this protocol. Under no circumstances should the investigator or site personnel supply study drug to other investigators or clinics, or allow the study drug to be used other than as directed by this protocol.

The investigator and/or the responsible site personnel must maintain accurate records of the receipt of all study drug shipped by Gilead Pharmaceuticals or its designee, including, but not limited to, the date received, lot number, amount received, and the disposition of all study drug. Study drug accountability records must also be maintained that include the patient number to whom the study drug was dispensed and the date, quantity and lot number of the study drug dispensed.

The study drug supply should be retrieved from patients at the end of each dosing interval. The quantity of study drug and the date returned by the patient should be recorded in the study drug accountability records.

Remaining unused study drug supply will be destroyed at the clinical site, standard institutional policy should be followed. Records documenting the date of study drug destruction, relevant lot numbers, and destroyed should be maintained.

7.1.9 **Overdose Precautions**

For this protocol, an overdose is defined as administration of >700 mg of idelalisib in a single day. In a patient who experiences an overdose of this magnitude, idelalisib administration should be temporarily interrupted. If the overdose ingestion is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered. Observation for any symptomatic side effects should be instituted, and vital signs and biochemical and hematological parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated.

The Gilead Sciences medical expert should be contacted if an overdose occurs. Under applicable regulations, overdosing may result in a serious adverse event and may require reporting accordingly (see Section 11 below).

7.1.10 **Inadvertent Exposure and Spill Precautions**

Based on available data from nonclinical studies, idelalisib does not appear to be acutely toxic, genotoxic, or irritative at levels that are likely to result from inadvertent exposure to the contents

of broken capsules or tablets. Personnel handling the drug should use reasonable precautions to avoid eye contact, skin contact, inhalation, or ingestion of the study drug product. For further information regarding inadvertent exposure and spill precautions, please consult the idelalisib investigator brochure.

7.2 Ofatumumab

7.2.1 **Medication**

GlaxoSmithKline will supply commercial ofatumumab free of charge. Biologics has been selected for the provision of supply procurement and distribution services to each investigative site as content-labeled Ofatumumab vials presented as either 100 mg – acetate formulation, 20 mg/mL, 5 mL fill vials; or 1000 mg – acetate formulation, 20 mg/mL, 50 mL fill vials.

The medical product, ofatumumab, is a liquid concentrate for solution for infusion presented in glass vials. Ofatumumab will be infused intravenously as specified above in Section 5.2.2.

The ofatumumab infusions will be prepared in 1000 mL NaCl sterile, pyrogen free 0.9% NaCl to yield a 0.3 mg/mL or 1 mg/mL ofatumumab concentration for infusions of 300 mg or 1000 mg, respectively.

Ofatumumab vials must be stored at 2-8°C. Protect from light and do not freeze. No special packaging components, other than the outer white cardboard carton in which the vials are placed, will be used to afford light protection.

Ofatumumab open-labeled product will be for intravenous infusion. The site is responsible for labeling individual vials for investigational use.

All items required for administration of study medication (e.g., infusion bags, etc.) are to be provided by the site. Filters will be supplied with commercial drug.

7.2.2 **Composition of Ofatumumab Injection 20 mg/mL**

The quantitative composition of acetate formulation 20 mg/mL. This is available in two fill volumes, 5 mL / vial (100 mg/vial) and 50 mL/vial (1000 mg/vial).

Ingredient	**Quantity/ mL**
Ofatumumab	20.0 mg
Sodium Acetate, Trihydrate	6.80 mg
Edetate Disodium, Dihydrate (EDTA)	0.019 mg
Polysorbate 80	0.20 mg
L-Arginine	10.0 mg
Sodium Chloride	2.98 mg

Hydrochloric Acid	to give pH 5.5
Water for Injection	*q.s.* to 1.0 mL

7.2.3 **Preparation of Ofatumumab Infusion**

Ofatumumab will be prepared as 1000 mL dilution of ofatumumab in sterile, pyrogen-free 0.9% NaCl. The expiration time which is calculated based on the exact dilution time into the 0.9% NaCl must be written on the label of the infusion bag.

Once diluted into saline, the product is stable for up to 24 hours at ambient temperature. However, the product contains no preservative and should be used as soon as possible after dilution.

Preparation of drug solution for intravenous injection by the site pharmacist or designee will be done in accordance with the protocol, and in these dilution instructions. Ofatumumab intravenous solution will be prepared using standard dilution methods and following general aseptic practice standard to preparation of IV medications. Eyes and hands should be protected when handling ofatumumab.

For intravenous administration, compatibility of the following components for ofatumumab in clinical studies (i.e., not for commercial product) has been established:

Table 7: Dosing Components for Ofatumumab in Clinical Studies

Dosing component	**Material of construction**	**Suggested Vendor**
1L Saline Bags	Polyvinyl Chloride (PVC)	Baxter
	Polyolefin [polyethylene* (PE)/polypropylene (PP)]	Baxter, B. Braun
Administration Set	PVC	Baxter
	PVC lined with Polyethylene	B. Braun

Preparation of the 1000 mL infusion bags should be done on the day of planned infusion.

* polyethylene (IUPAC name: polyethene)

7.2.3.1 **Materials for Preparation and Administration of Infusion**

The following materials are needed when preparing and administering the infusion:

- 1000 mL sterile pyrogen free 0.9% saline (NaCl) infusion bag(s). The solution can be kept at ambient temperature for a maximum of 24 hours after preparation; however, the product does not contain a preservative and dosing should begin as soon as possible after dose preparation.
- Ofatumumab 100 mg and 1000 mg vials (supplied by Novartis)
- Needles and syringes (50 mL sterile syringe) not supplied by Novartis
- Intravenous (IV) cannula (not required if subject has central venous access) [not supplied by Novartis]
- Infusion pump (not supplied by Novartis) and infusion tubing set (supplied by Novartis)

7.2.3.2 **Dilution of Ofatumumab**

- Ensure the correct container number is used.
- Take a 1000 mL infusion bag (sterile pyrogen free 0.9% saline), remove and dispose of the appropriate amount of saline according to Table 8 or Table 9 below
- Draw the required amount of ofatumumab according to Table 2 (100 mg vials) or Table 3 (1000 mg vials) below
- Inject ofatumumab into the saline bag
- Invert the infusion bag slowly 3 times, avoiding formation of any foam
- Label the infusion bag with the completed label

Table 8: Preparation of Ofatumumab Infusion: 100 mg vials

Dose of Ofatumumab	Infusion bag size	Volume of NaCl to be removed from infusion bag	Volume ofatumumab (number of ofatumumab vials)
300 mg	1000 mL	15 mL	15 mL (3 vials, 5 mL/vial)
1000 mg	1000 mL	50 mL	50 mL (10 vials, 5 mL/vial)

Table 9: Preparation of Ofatumumab Infusion: 1000 mg vials

Dose of Ofatumumab	Infusion bag size	Volume of NaCl to be removed from infusion bag	Volume ofatumumab (number of ofatumumab vials)
1000 mg	1000 mL	50 mL	50 mL (1 vial, 50 mL/vial)

7.2.4 **Ofatumumab Infusion Set up**

Ofatumumab must be administered by IV infusion through an in-line filter and through a well-functioning IV catheter (IV cannula) into a vein in the arm (or other venous access) by an infusion pump.

Please Note: It is mandatory to use an in-line low protein binding 0.2 micron polyether sulfone filter for all IV dosing of ofatumumab drug product.

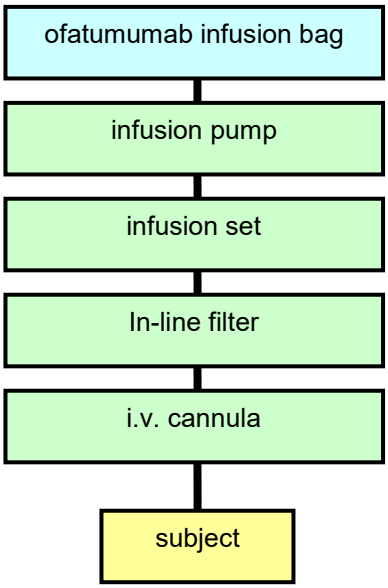
DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.
Ofatumumab should not be mixed with any other medication. The intravenous line should be flushed with normal saline before and after completion of each infusion.

Please note that the infusion site can be used for blood sampling only if there is no risk of contamination of the infusion needle with the saline, infusion solutions, or any other fluid(s). Only a newly inserted needle can be used for the predose blood samples.

- Check subject ID against the label on the infusion bag and ensure the expiry of the solution. The solution must be administered in its entirety to the subject within 24 hours from time of preparation.
- Attach the 1000mL infusion bag to the infusion set (if not done at the pharmacy).
- Attach the in-line filter to the infusion set (closest to the subject; see Figure 1). **Note: The in-line filter must be used during the entire infusion.**
- Prime the infusion set and filter with ofatumumab (if not done at the pharmacy).
- In case of a problem with the filter (i.e. clogging/blockage), please change, re-prime the new filter, and continue the infusion.
- In case of problem with infusion set, follow local procedures.
- Collect the pre-dose blood samples, if required.
- Check the backflow from the IV cannula according to routine practice at site
- Set the pump at the initial infusion rate 12mL/hr for the first infusion and 25mL/hr for the subsequent infusions (if no grade ≥ 3 infusion-associated AEs were observed in the previous infusion)
- Start the infusion using the infusion rates and directions above in section 5.2.2.

No ofatumumab dose modifications are permitted.

Figure 1: Infusion Set-Up Schematic



8. CORRELATIVE/SPECIAL STUDIES

8.1 Pharmacokinetic Studies

Ofatumumab concentrations are determined in EDTA plasma (i.e., one lavender-topped Vacutainer). Samples must be processed in a refrigerated centrifuge (4°C) at 1600g for 15 minutes and frozen at -20°C within 4 hours of collection. The ofatumumab PK samples may be batched at participating sites and/or sent directly to Novartis. The shipping information will be enclosed with the study kits.

Pharmacokinetic sampling for ofatumumab will be as follows:

Cycle 3 Day 1 – Predose, EOI
Cycle 3 Day 8 – Predose
Cycle 3 Day 15 – Predose
Cycle 4 Day 22 (last weekly Ofatumumab dose) – Predose, EOI
Cycle 5 Day 1 (first monthly Ofatumumab dose) – Predose, EOI
Cycle 8 Day 1 (last monthly Ofatumumab dose) – Predose, EOI
2 months after Ofatumumab therapy completed – Predose
6 months after Ofatumumab therapy completed - Predose

Samples will also be obtained for idelalisib pharmacokinetics. These will be determined in K2 EDTA plasma (i.e., one lavender-topped Vacutainer), obtained pre-dose (trough) and 1.5 hours post-dose (peak) with a +/- 10 minute window for post-dose. After drawing invert the tube at

least 8 to 10 times. Keep sample in wet ice prior to centrifugation. It is preferred the sample be centrifuged within 30 minutes and must be centrifuged within 2 hours of blood collection. Centrifuge at a miniumum of 1500 to 2000 x g for 15 minutes until cells and plasma are well separated. Use pipette provided to transfer the plasma equally into four appropriately labeled tubes. Samples will be processed on-site, stored at -70°C, then batched and shipped approximately every 6 months. If your site can only store in a -20 °C freezer, please send the PK sample shipments monthly. The idelalisib PK samples may be batched at participating sites then sent after freezing. Please ship frozen samples on dry ice to Covance Laboratory Inc. at the following address:

Attention: Ujjana Nandihalli
Bioanalytical Principal Investigator
Sample Management—Bioanalytical (Rm 1S 160)
Covance Laboratory Inc.
3301 Kinsman Boulevard
Madison, WI 53704-2523

Pharmacokinetic sampling for idelalisib will be as follows:

Staggered:
Cycle 1 Day 1
Cycle 2 Day 1
Cycle 3 Day 1 (first weekly dose of Ofatumumab)
Cycle 4 Day 22 (last weekly dose of Ofatumumab)
Cycle 8 Day 1 (last monthly dose of Ofatumumab)
2 and 6 months after end of ofatumumab therapy.

8.2 Pharmacodynamic Studies

8.2.1 **Biological Features of the CLLs**

FISH will be determined on either peripheral blood or bone marrow for the common CLL probes (17p, 11q, +12, 13q and t(11;14) to rule out mantle cell lymphoma) at the local institutions prior to enrollment, and this report will be supplied to the Coordinating Center at the time of Registration.

IGHV, CD38 and ZAP70 will be determined by the CLL Research Consortium central tissue bank. All participating CLL Research Consortium sites are required to enroll participants on the above tissue bank, using the dedicated consent form for that study at each institution. Patients already enrolled in the CLL Research Consortium central tissue bank need to provide the results of these tests to the Coordinating Center at the time of registration.

At screening for this study three additional sodium heparin green top tubes of peripheral blood will be submitted to the Tissue Bank for banking if a patient is already enrolled in the CLL Research Consortium

If a site is *not* participating in a CLL Research Consortium tissue bank study, the participant will be required to provide three sodium heparin green top tubes of peripheral blood at screening, cycle 3 day 1 and progressive disease or off study due to toxicity. These samples will then be shipped overnight to Dr. Laura Rassenti at the above CRC address in Section 8.1. In the case of closures of the CRC, a temporary covering or local lab may be designated. Guidance will be provided by correspondence in such cases.

In addition, a saliva sample will be collected at screening using Oragene collection device and shipped to:

Dana Farber Cancer Institute
CLL Center, J. Brown Lab
ATTN: Stacey Fernandes
77 Avenue de Louis Pasteur
HIM 421 (Ref. 13-309)
Boston, MA 02115

CD38 will be determined at screening at the CLL Research Consortium tissue bank.

8.2.2 **DFCI Studies: Genomic Profiling**

Four 10 cc sodium heparin (green top) tubes of peripheral blood will be drawn at screening, and saliva will be collected using Oragene collection devices. Heparinized bone marrow aspirate (5-10 cc) should be sent in addition.

At the time that patients come off study for toxicity or progressive disease, four 10 cc sodium heparin (green top) tubes of peripheral blood should again be drawn and shipped overnight at ambient as below. If a patient coming off study due to progressive disease or toxicity is undergoing a bone marrow biopsy, and in particular if they do not have significant circulating disease, please also send heparinized bone marrow aspirate (5-10 cc).

These samples will then be shipped overnight to Dr. Laura Rassenti at the above CRC address in Section 8.1.

From the blood samples, PBMCs or CLL B-cells will be isolated and viably frozen, for subsequent use in SNP array, gene expression, miRNA profiling and whole exome sequencing. Saliva will be isolated and stored according to the kit directions until DNA is prepared.

8.2.3 **DFCI Studies: Elucidation of subclonal architecture of CLL treated with idelalisib**

The goal of this correlative study is to elucidate the dynamics of CLL subclones during therapy with idelalisib, in particular by comparing blood and bone marrow prior to therapy and after two months of single agent idelalisib. We will also look at the acute alteration in the subclonal architecture in blood after several weeks of idelalisib, in order to explore the effect of redistribution lymphocytosis on the clones present in blood. We will then compare these results

to the features of persistent subclones present in blood and bone marrow at time of final restaging. Eventually, at time of relapse, samples will be banked for comparison to the earlier data on clonal architecture, in order to identify the subclone that has led to relapse and to place it in context of the prior data. We expect that these data will greatly enhance our understanding of the relationship of CLL cells in blood and bone marrow and how that changes with idelalisib therapy, as well as giving us critical information on both primary and acquired resistance to idelalisib.

Experimental Procedures: We propose to perform serial exome sequencing (WES) on a selection of patients from this trial, selected to represent the range of CLL prognostic factors and a range of initial idelalisib responses. We will include roughly half *IGHV* mutated and unmutated patients, and half those who had stable disease (SD) after 2 months of single agent idelalisib vs those with partial response (PR) or partial response with lymphocytosis (PRL) after two months of therapy. Relatively few patients on this study have high risk del 11q or del 17p cytogenetics but we will prioritize those patients for analysis (n=3). The plan will be to perform WES on baseline blood, bone marrow and germline (saliva) samples, on blood and bone marrow from end of single agent cycle 2 restaging, and on blood and bone marrow from final restaging at cycle 10. These samples will allow determination of the relative distribution of clones in blood and bone marrow at the same timepoint, how this is altered by idelalisib, and ultimately which clone(s) persist at the time of low level residual disease. In addition we will sequence peripheral blood at one additional timepoint, week 2-4 on single agent idelalisib, with the goal of assessing the alteration of clonal architecture of CLL in the blood during idelalisib-mediated redistribution. We will study 8 samples for each of 10-15 patients initially, and then follow these patients serially over time and bank them again at relapse, at which time we will sequence them again, for comparison to the initial and residual disease subclones. These studies will continue as sufficient samples have already been banked.

8.2.4 **Flow cytometry for activation markers, adhesion molecules and CD20 levels**

Flow cytometry analysis for cell surface adhesion molecules and activation markers including CXCR4, CXCR5, PD-1, PD-1L, CD38, CD40, CD80, CD86, CD154 and Ki67 will be performed. T cell subsets and immunomodulatory effects on T cells may also be analyzed on these samples. Plasma will be collected for analysis of cytokine levels including CCL3 and CCL4 at the same timepoints.

At the following time points, collect two 10cc sodium heparin green top tubes:
Screening
Cycle 1 Day 8
Cycle 1 Day 15
Cycle 2 Day 1
Cycle 2 Day 22 (two month restaging)
Cycle 3 Day 8
Cycle 3 Day 15
Cycle 4 Day 22
Cycle 10 Day 1 (final restaging)

In addition, the same markers will be assessed on bone marrow aspirates (5-10cc) at the following time points:
Screening
Cycle 2 Day 22 (two month restaging)
Cycle 10 Day 1 (final restaging)

All samples should be sent to Laura Rassenti at the CLL Research Consortium address above in Section 8.1.

8.2.5 **OSU Studies: Assessments of intrinsic innate immune suppression**

These correlative studies propose to confirm that idelalisib can decrease immunosuppressive cytokines (IL-6, IL-10, TGF-β1, and TGF-β2) in vivo in CLL patients from pre-treatment to day 29. Additionally, we will demonstrate by ex vivo evoked stimuli studies from pre-treatment and day 29 that CLL cells treated with idelalisib have less production of IL-6, IL-10 and also expression of CD279 and CD274. Finally, we will assess screening and day 29 monocyte TNF-α production using ofatumumab; NK cell production of IFN-γ and CD107a expression following exposure to immobilized ofatumumab and ofatumumab mediated ADCC against RAJI target cells; MDSC ex vivo and inhibition of T-cell proliferation. We expect this work to demonstrate that idelalisib treatment will inhibit evoked activation of IL-6, IL-10, CD279 and CD274 with innate immune function at day 29 of therapy as compared to pre-treatment. Collectively, this will provide support for idelalisib priming prior to administration of therapeutic antibodies.

For these studies, three 8.5mL ACD (yellow top) tubes and one sodium heparin (green top) tube of peripheral blood should be collected at screening, Cycle 1 Day 1, Cycle 2 Day 1 and cycle 3 day 1 of therapy (prior to ofatumumab)

These blood tubes will be shipped overnight (ambient) to Laura Rassenti at the CLL Research Consortium address above.

8.2.6 **OSU Studies: Effects of in vivo inhibition of the PI3K delta pathway on CLL cell signaling**

Detailed baseline profiling of tumor cells will be done for expression of PI3K isoforms and activity of downstream B-cell relevant specific kinases targeted by PI3K. In vivo response to PI3K inhibition will be evaluated by measuring phosphorylation of AKT and Novartis 3-beta in CLL cells isolated from two pre-dose 8.5mL ACD (yellow top) tubes of peripheral blood at cycle 1 day 1, day 15, cycle 2 day 1 and two month restaging on idelalisib treatment. During treatment ex vivo response to chemoimmunotherapy will be evaluated by measuring apoptosis (Annexin V/PI staining and flow cytometry) at the same intervals.

These tubes should be sent to the CLL Research Consortium Tissue Bank at the above address, overnight

8.2.7 **Mayo Clinic Microvesicle Studies**

For these studies, a 10 cc sodium heparin green top tube and bone marrow aspirate (a couple ccs if a bone marrow is being performed otherwise) will be drawn at screening (only marrow at screening), cycle 2 day 22(end of single agent idelalisib therapy), cycle 10 day 1(final restaging), every 6 months for the first year in follow-up (if a bone marrow is being performed for clinical reasons) and when a patient comes off study due to progressive disease or toxicity. These samples will be shipped overnight ambient to Laura Rassenti at the above address. On arrival they will be spun in a 15 cc conical tube 3 x 2500g for 20 min at room temperature, and the platelet-free plasma will be carefully decanted into a fresh tube without disturbing the pellet. They can then be aliqouted in 1 ml aliquots in eppendorf tubes and frozen at -80C.

9. STUDY CALENDAR

Screening evaluations are to be conducted within 14 days prior to start of protocol therapy. Scans and Bone Marrow Biopsies must be done $\leq$4 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

All assessments must be performed prior to administration of any study medication. All study assessments and medications should be administered within $\pm$ 3 days of the protocol-specified date during the induction phase and $\pm$ 7 days of the protocol-specified date in the post-induction phase, unless otherwise noted.

Table 10

Procedures	**Screen**	**Treatment Phase**					**Post Induction Phase**		**Long Term Follow-up**	**Survival Follow-up**
		Cycle 1-2 Idelalisib only (Days 1-56)	Cycle 3 & 4 Weekly Ofa + Idelalisib[15]	Cycle 5-8 Monthly Ofa + Idelalisib	Restage Cycle 4 day 22	Cycle 2 day 22 (Restage end of cycle 2), Cycle 10 day 1 (Final Restage 2 months after end of ofa therapy) and off treatment prior to cycle 10	Cycle 9 Day 1	Every 2 mos while on study drug beginning Cycle 10	Every 3 or 6 months[11]	Yearly

Informed Consent	**X**									
Demography	**X**									
Medical History	**X**									
Bone marrow biopsy	**X[1]**					**X[1]**		**X[1]**		
Flow Cytometry by Marrow or blood[16]	**X**				**X**	**X**				
MRD on bone marrow						**X**				
CT (Chest Abdomen Pelvis)	**X[2]**				**X[2]**	**X[2]**		**X[2]**	**X[2]**	
Tumor Assessment by PE	**X**				**X**	**X**	**X**	**X**	**X**	
CLL FISH panel (on bone marrow)	**X**					**X (ON BONE MARROW)**				
Banking at CRC, with Flow Cytometry[3]	**X**	**C1 DAY 8 &15, C2 DAY 1**	**C3 D8 & 15, C4 D22**			**X**				
DFCI Studies: Genomic Profiling[4]	**X**							**End of therapy[4]**		
Banking at Clinical Research Consortium for Sites participating in a CRC study[17]	**X**									
Procedures	**Screen**	**Treatment Phase**					**Post Induction Phase**		**Long Term Follow-up**	**Survival Follow-up**
		Cycle 1-2 Idelalisib only (Days 1-56)	Cycle 3 & 4 Weekly Ofa + Idelalisib[15]	Cycle 5-8 Monthly Ofa + Idelalisib	Restage Cycle 4 day 22	Cycle 2 day 22 (Restage end of cycle 2), Cycle 10 day 1 (Final Restage 2 months after end of ofa therapy) and off treatment prior to cycle 10	Cycle 9 Day 1	Every 2 mos while on study drug beginning Cycle 10	Every 3 or 6 months[11]	Yearly

Banking at Clinical Research Consortium for Sites not participating in a CRC study[18]	**X**		**C 3 D1**						**X**	
PK samples, ofatumumab[5]			**C3 D1, 8, 15; C4 D 22**	**CYCLE 5 D 1 & CYCLE 8 D 1**		**FINAL ONLY**		**6 MOS**		
PK samples, idelalisib [5]		**DAY 1 EACH CYCLE**	**CYCLE 3 DAY 1, CYCLE 4 DAY 22**	**CYCLE 8 DAY 1**		**FINAL ONLY**		**6 MOS**		
OSU Studies[6]	**X**	**CYCLE 1 DAY 1, 15; CYCLE 2 DAY 1**	**CYCLE 3 DAY 1**			**TWO MONTH ONLY**				
Mayo Studies[7]	**X**		**CYCLE 3 DAY 1**			**FINAL ONLY**			**EVERY 6 MONTHS FOR FIRST YEAR; & AT PD**	
Physical Exam	**X**	**WEEKLY**	**CYCLE 3 DAY 1, 8, 15, CYCLE 4 DAY 1, 15**	**MONTHLY**	**X**	**X**	**X**	**X**	**X**	
ECOG	**X**	**WEEKLY**	**WITH PE**	**WITH PE**	**X**	**X**	**X**	**X**		
Height	**X**						**X**			
Weight	**X**		**X**	**X**	**X**	**X**	**X**	**X**		
Vital Signs[12]	**X**	**WEEKLY**	**WEEKLY**	**MONTHLY**	**X**	**X**	**X**	**X**	**X**	
12-lead ECG	**X**									
Procedures	**Screen**	**Treatment Phase**					**Post Induction Phase**		**Long Term Follow-up**	**Survival Follow-up**
		Cycle 1-2 Idelalisib only (Days 1-56)	Cycle 3 & 4 Weekly Ofa + Idelalisib[15]	Cycle 5-8 Monthly Ofa + Idelalisib	Restage Cycle 4 day 22	Cycle 2 day 22 (Restage end of cycle 2), Cycle 10 day 1 (Final Restage 2 months after end of ofa therapy) and off treatment prior to cycle 10	Cycle 9 Day 1	Every 2 mos while on study drug beginning Cycle 10	Every 3 or 6 months[11]	Yearly

Adverse Events	**X**	**WEEKLY**	**WITH PE**	**WITH PE**	**X**	**X**	**X**	**X**	**X[8]**	
Concomitant Therapy	**X**	**WEEKLY**	**WITH PE**	**WITH PE**	**X**	**X**	**X**	**X**		
Chemistry[13]	**X**	**WEEKLY[13]**	**WEEKLY THROUGH C4 D 22[13]**	**MONTHLY**	**X**	**X**	**X**	**X**	**X**	
Hematology[14]	**X**	**WEEKLY**	**WEEKLY THROUGH C4 D 22**	**MONTHLY**	**X**	**X**	**X**	**X**	**X**	
Beta-2-microglobulin	**X**				**X**	**X**		**EVERY 6 MOS**	**EVERY 6 MOS**	
Immunoglobulins (IgG, IgM, IgA)	**X**				**X**	**X**		**EVERY 6 MOS**	**EVERY 6 MOS**	
Serum protein electrophoresis	**X**				**X**	**X**		**EVERY 6 MOS**	**EVERY 6 MOS**	
CD4 count	**X**				**X**	**X**		**EVERY 6 MOS**	**EVERY 6 MOS**	
Direct Coombs test	**X**									
Serum Pregnancy Test[9]	**X**		**MONTHLY**	**X**		**X**		**ONCE 5 MONTHS POST OFA**		
Hepatitis B surface antigen and antibody[10], Hepatitis C antibody, HIV	**X**									
Survival follow-up by telephone or clinic visit note										**X**

1. Bone marrow biopsies are required at screening, cycle 2 day 22 (end of cycle 2 restaging) and cycle 10 day 1 (final restaging). Those patients in clinical CR at any bone marrow restaging should have 4 color MRD flow cytometry performed at the time of their bone marrow evaluation. Bone marrow biopsy can also be done at any subsequent point to confirm a suspected CR. In addition to standard clinical testing, 15 cc bone marrow aspirate will be obtained at each bone marrow biopsy, for flow cytometry immunophenotyping and comparison to PB, as well as studies at OSU and Mayo Clinic. These heparinized aspirate samples will be sent to the CRC for processing and storage. In cases where it is unsafe or not feasible to obtain the appropriate quantity of aspirate, the performing clinician should indicate this in his/her note.
2. CT scan required at screening, cycle 2 day 22 (end of cycle 2), cycle 4 day 22, and cycle 10 day 1 (final restaging). In subsequent follow-up only if clinically indicated at investigator discretion and when a patient comes off treatment due to disease progression or toxicity. A CT scan of the chest, abdomen, pelvis and any other known sites of disease should be completed. Any regions captured at screening such as the neck must be followed by CT throughout subject's participation. <u>All CT scans will be centrally reviewed.</u> These scans should be burned onto CD and sent via FedEx to the Project Manager at DFCI, ATTN: (Project Manager), 450 Brookline Avenue, LG100, Boston, MA 02215. The scan will then be reviewed at the Tumor Imaging Metrics Core at DFCI.

3. Two sodium heparinized tubes (green tops) at screening and at subsequent times. Sodium heparinized bone marrow aspirate (5-10 cc, green top) at screening and cycle 2 day 22 (end of cycle 2 restaging) and cycle 10 day 1 (final restaging).
4. Four sodium heparinized tubes (green tops) and saliva. Sodium heparinized bone marrow aspirate (5-10 cc, green top). Patients who come off treatment for toxicity or progressive disease, four 10 cc sodium heparin (green top) tubes of peripheral blood. If a patient coming off treatment due to progressive disease or toxicity is undergoing a bone marrow biopsy, and does not have significant circulating disease, send sodium heparinized bone marrow aspirate (5-10 cc, green top)
5. For ofatumumab, 2 lavender top tubes. Predose and end of infusion on cycle 3 day 1, cycle 3 day 8, cycle 3 day 15 and cycle 4 day 22 (end of weekly ofa), and cycles 5 and 8 day 1. Note: Predose only for cycle 3 days 8 and 15; and 2 and 6 mos post therapy, no end of infusion.

For idelalisib, one lavender top predose and one lavender top 1.5 hours post-dose, on Cycles 1-3 Day 1, Cycle 4 Day 22, Cycle 8 Day 1 (last monthly dose of Ofatumumab) and 2 and 6 months after end of ofatumumab.

6. OSU: 3 ACD (yellow top) tubes, 8.5 cc each, + one sodium heparin (green top) tube at screen; 5 ACDs and one heparin on day 1 prior to therapy, 2 ACDs on cycle 1 day 15, 5 ACDs and one heparin on cycle 2 day 1, 3 ACDs and 1 sodium heparin (green top) tube at two month restage, and 2 ACDs on cycle 3 day 1.
7. Mayo Clinic: 1 sodium heparinized (10 cc green top) tube. Bone marrow aspirate (a couple ccs) will be obtained at each timepoint. At screening only aspirate should be collected.
8. SAEs and deaths for six months after completion of all therapy.
9. Only in women of childbearing potential
10. For those patients who are hepatitis B core antibody positive but surface antigen and HBV DNA negative, monitoring of HBV DNA or viral load is required during the on treatment period at least every 2 months and during follow-up at a minimum of every 2-3 months up to 12 months after the last dose. This testing is also required in the event of development of grade 1 or more elevation in LFTs.
11. Subjects who discontinue therapy due to an adverse event, but have demonstrated a response of SD or better will enter the follow-up period and be followed every 3 or 6 months until documented relapse or PD, initiation of a new therapy, or for a total of 12 months of follow-up, whichever occurs first.
12. Vitals Signs include: heart rate, respiratory rate, temperature, blood pressure and oxygen saturation.
13. Chemistry: Electrolytes, BUN, creatinine, glucose, LDH, phosphate, uric acid, LFTs (total bilirubin, AST, ALT, alkaline phosphatase). Beginning C1D15 through C4D28 a comprehensive metabolic panel (electrolytes, BUN, creatinine, glucose, LDH, phosphate, uric acid, LFTs (total bilirubin, AST, ALT, alkaline phosphatase) will be obtained twice per week. If grade 1 or higher AST, ALT, or bilirubin elevations are noted please see Section 6.2 "Management of Hepatic AEs."
14. Hematology: CBC, manual differential
15. Weekly Ofatumumab proceeds through Cycle 4 Day 22.
16. Flow Cytometry should assess at minimum the following markers: CD5+CD19+, CD19+, CD 20+, CD19+CD23+, CD19+CD38+, kappa and lambda surface immunoglobulins.

Footnotes 16 & 17 outline the sample collection for sites that are or are not participating in the CLL Research Consortium tissue bank study, (for more information-Section8.2.1):

17. Sites participating in a CLL Research Consortium tissue bank study (Section 8.2.1) provide 3 sodium heparinized (green top) tubes of peripheral blood at screening.
18. Sites *not* participating in a CLL Research Consortium (CRC) tissue bank study (Section 8.2.1) provide 3 sodium heparinized (green top) tubes of peripheral blood at screening, cycle 3 day 1 and coming off study due to disease progression or toxicity. In addition, collect a saliva sample at screening.

Off-Treatment Evaluations

If at all possible, patients going off study should have: hematology, chemistry, beta-2-microglobulin, CD4 count, IgG, IgM, IgA, serum protein electrophoresis, full tumor assessment by CT, bone marrow biopsy and samples for correlative studies. Please obtain the following samples described under genomic and Mayo Microvesicle for correlative studies. If prior to cycle 2 day 22 please obtain any additional studies required for that visit.

10. MEASUREMENT OF EFFECT

10.1 Antitumor Effect – CLL

Definition of response, relapse, and refractory disease
Assessment of response should include a careful physical examination and evaluation of the blood and marrow. CT scanning will be performed as indicated in the table of assessments (required at screening, and at key response assessments).

It is important to note that idelalisib may result in increasing lymphocytosis at the start of the study, which will not be considered evidence of progressive disease. In fact, an isolated increase in lymphocytosis, in the absence of other signs of disease progression including worsening lymphadenopathy, neutropenia, anemia or thrombocytopenia or disease symptoms, will not in this study be sufficient to define progressive disease. This modification to the standard criteria is needed because idelalisib can cause redistribution of CLL lymphocytes from sanctuary sites into peripheral blood, in the absence of progressive disease.

10.1.1 Complete remission (CR)

CR requires all of the following criteria present at one time point and still present when re-assessed at least 2 months after initial documentation:

- **Peripheral blood lymphocytes (evaluated by blood and differential count) below 4 × 10^9/L (4000/µL).**
- **Absence of significant lymphadenopathy (eg, lymph nodes >1.5 cm in diameter) by physical examination.** A CT scan of the chest, abdomen, pelvis will be used to confirm complete response if previously abnormal, and on that CT, lymph nodes should not be larger than 1.5 cm in long axis diameter.
- **No hepatomegaly or splenomegaly by physical examination.**
- **Absence of constitutional symptoms.**
- **Blood counts above the following values:**
  Neutrophils more than 1500/µL without need for exogenous growth factors.
  Platelets more than 100 000/µL without need for exogenous growth factors.
  Hemoglobin more than 11.0 g/dL without red blood cell transfusion or need for exogenous erythropoietin.
- **For patients on this study meeting the above criteria for CR, a marrow aspirate and biopsy must confirm CR.** To define a CR, the marrow sample must be at least normocellular for age, with less than 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. In some cases, lymphoid nodules can be found, which often reflect residual disease.[55,56] These nodules should be recorded as "nodular PR." Moreover, immunohistochemistry should be performed to define whether these nodules are composed primarily of T cells or lymphocytes other than CLL cells or of CLL cells. If the marrow is hypocellular, a repeat determination should be performed after 4 weeks, or not until peripheral blood counts have recovered. However, this time

interval should not exceed 6 months after the last treatment. A marrow biopsy should be compared with that of pretreatment marrow and the quality of the CR should be assessed for MRD by flow cytometry.

Patients who fulfill all the criteria for a CR (including the marrow examinations described above) but who have a persistent anemia or thrombocytopenia or neutropenia apparently unrelated to CLL but related to drug toxicity will be considered CR with incomplete marrow recovery (CRi). For the definition of this category, CRi, the marrow evaluation should be performed with scrutiny and not show any clonal infiltrate.

10.1.2 Partial remission (PR)

PR is defined by the criteria described below if abnormal before therapy, as well as one or more of the blood count requirements. To define a PR, these parameters need to be documented for a minimal duration of 2 months.

- **A decrease in the number of blood lymphocytes by 50% or more from the value before therapy.**
- **Reduction in lymphadenopathy (by CT scans or by physical exam) as defined by the following:** (1) A decrease in lymph node size by 50% or more either in the sum of the bidimensional products of up to 6 lymph nodes, or in the largest diameter of the enlarged lymph node(s) detected prior to therapy AND (2) No increase in any lymph node, and no new enlarged lymph node. In small lymph nodes (< 2 cm), an increase of less than 25% is not considered to be significant.
- **A reduction in the noted pretreatment enlargement of the spleen or liver by 50% or more on physical examination.**
- **The blood count should show one of the following results:** (1) Neutrophils more than 1.5×10^9/L (1500/μL) without need for exogenous growth factors. (2) Platelet counts greater than 100×10^9/L (100 000/μL) or 50% improvement over baseline without need for exogenous growth factors. (3) Hemoglobin greater than 110 g/L (11.0 g/dL) or 50% improvement over baseline without requiring red blood cell transfusions or exogenous erythropoietin.

10.1.3 Progressive disease

Progressive disease during or after therapy is characterized by at least one of the following:

- **Lymphadenopathy.** Progression of lymphadenopathy is often discovered by physical examination and should be recorded. In CLL, the use of CT scans usually does not add much information for the detection of progression or relapse. Therefore, the use of imaging methods to follow CLL progression is at the discretion of the treating physician.
- Disease progression occurs if one of the following events is observed: **(1)** Appearance of any new lesion, such as enlarged lymph nodes (>1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates. **(2)** An increase by 50% or more in greatest determined diameter of any previous site. **(3)** An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.

- **Transformation to a more aggressive histology (eg, Richter syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy.**
- **Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) attributable to CLL.**

  During therapy. Cytopenias may occur as a side effect of many therapies and should be assessed according to Appendix C.

  After treatment. The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels by more than 20 g/L (2 g/dL) or to less than 100 g/L (10 g/dL), or by a decrease of platelet counts by more than 50% or to less than 100×10^9/L (100 000/μL), which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy demonstrates an infiltrate of clonal CLL cells and there is no evidence for an autoimmune process.

10.1.4 Nodal Partial Response with Lymphocytosis

In this study, patients who achieve PR criteria for lymphadenopathy and/or splenomegaly, but have a lymphocyte count which is elevated and/or does not meet PR criteria (and may be significantly above baseline), will be considered to have nodal PR with lymphocytosis.

10.1.5 Stable disease

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

10.1.6 Treatment failure

Responses that should be considered clinically beneficial include CR, PR and nodal PR with lymphocytosis; all others (eg, stable disease, nonresponse, progressive disease, or death from any cause) should be rated as a treatment failure.

10.1.7 Time to progression, progression-free survival, and overall survival

Time to progression (TTP) is defined as the time from study entry until objective disease progression (see above). Progression-free survival (PFS) is defined as the time from study entry until objective disease progression or death. Overall survival is defined as the time from study entry until death from any cause, and is measured in the intent-to-treat population.

10.1.8 Relapse

Relapse is defined as a patient who has previously achieved the above criteria of a CR or PR or nodal response with lymphocytosis, but after a period of 6 or more months, demonstrates evidence of disease progression as described above.

10.1.9 Refractory disease

Refractory disease is defined as treatment failure or disease progression within 6 months to the last antileukemic therapy.

10.1.10 Minimal residual disease

The complete eradication of the leukemia is an obvious desired endpoint. New detection technologies, such as multicolor flow cytometry and real-time quantitative PCR, have determined that many patients who achieved a CR by the 1996 NCI-WG guidelines have detectable MRD. Either 4-color flow cytometry (MRD flow) or allele-specific oligonucleotide PCR is reliably sensitive down to a level of approximately one CLL cell in 10,000 leukocytes. As such, patients will be defined as having a clinical remission in the absence of MRD when they have blood or marrow with less than one CLL cell per 10,000 leukocytes.

Those patients undergoing bone marrow biopsy for evaluation of CR should have a sample sent for 4 color MRD flow.

10.2 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of clinical benefit: The duration of clinical benefit is measured from the time measurement criteria are first met for CR, PR or nodal PR with lymphocytosis, until the first date that recurrent disease is objectively documented.

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started

10.3 Response Review

10.3.1 Central review of the CT scans is required for all scans (screening, cycle 2 day 22, cycle 4 day 22, cycle 10 day 1 (final restaging), and at disease progression). These scans should be burned onto CD and sent via FedEx to the Project Manager at DFCI, ATTN: (Project Manager), 450 Brookline Avenue, LG 100, Boston, MA 02215. The scan will then be reviewed at the Tumor Imaging Metrics Core at DFCI.

11. ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

11.1.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator **are** to be recorded as AEs or SAEs.

- Grade 4 uncomplicated hematologic toxicities that are common in this patient population do NOT need to be reported as SAEs or reported to the DFCI IRB, unless resulting in hospital admission or if the treating investigator deems it appropriate to report.
- All events requiring patients to come off study due to liver toxicity must be recorded as an SAE.
- However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.
- B cell depletion, lymphopenia, IgG below LLN, low CD19+ count, and hypogammaglobulinemia due to treatment with ofatumumab are **not** to be reported as AEs or SAEs.
- Infusion related AEs may lead to a prolonged infusion time. Overnight stay at the hospital due to slow infusion rate is **not** to be reported as a SAE.
- Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as a SAE. Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to Novartis

Not included as SAEs:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs
An event which is part of the natural course of the disease under study (i.e., disease progression) does not need to be reported as a SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, ends in death, or if the investigator considers that there was a causal relationship between treatment with investigational product or protocol design/procedures and the disease progression, then this must be reported as an SAE.

Pregnancy
Any pregnancy that occurs during study participation must be reported to the overall Principal Investigator and to Novartis. To ensure subject safety, each pregnancy must be reported to Novartis within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to Novartis.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to Novartis as described above.

11.1.3 Expectedness

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

11.1.3.1 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 current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of the most common expected adverse events associated with the study agent(s).

11.1.3.2 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 current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

11.1.4 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.

11.2 Procedures for AE and SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting, with the exception of hematologic toxicity, which will be graded according to Appendix C. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

11.3 Reporting Requirements

For multi-site trials where a DF/HCC investigator is serving as the principal investigator, each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the overall PI Dr. Brown and to Novartis and to Gilead as described below.

11.4 Reporting to the Study Sponsor

11.4.1 Serious Adverse Event Reporting to DF/HCC

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 6 months of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator on a MedWatch form. This includes events meeting the criteria outlined in Section 11.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention.
- Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting. See Section 11.1.2 for grade 4 hematological toxicities.
- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator Dr. Brown within 1 business day of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 1 business day after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by email to investigator, Project Manager, and study coordinator (contact information on study contact list):

PI: Jennifer R Brown, MD, PhD
Email: jbrown2@partners.org

Within the following 1-2 business days, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

11.4.2 Reporting to Gilead

In addition to reporting SAEs to the overall principal investigator, SAEs also must be reported to Gilead as follows:

Serious	Within 15 calendar days	Fax or email relevant CRFs (eg, adverse event form, medical history form, concomitant drug/therapy form) and source documents[b] (eg, progress notes, nurses' notes, laboratory and diagnostic test results, discharge summaries) to Gilead Sciences, Inc.[a]

a. The Gilead fax number is 650-522-5477 and email address is Safety_FC@gilead.com. All documents sent to Gilead should have their internal study number included. Gilead internal study number: IN-US-312-1237.
b. Patient name, address, and other personal identifiers should be obscured.
Abbreviations: CRF, case report form; IRB/IEC, Institutional Review Board/Independent Ethics Committee

All SAEs which are reported to Gilead a copy of the report must also be reported to the overall principal investigator, Project Manager and study coordinator (contact information on study contact list):
PI: Jennifer Brown, MD PhD,
Email**: jbrown2@partners.org**

Gilead SAE reporting criteria: See definition of SAE in 11.1.2

All SAEs regardless of relationship to investigational product will be collected from the first dose of investigational product up to 1 month after the last dose of investigational product. SAEs are no longer required to be reported if a subject begins treatment with another therapy.

From the time a subject consents to participate in and completes the study all SAEs assessed **as related to study participation** (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), will be reported promptly to Gilead.

Any SAE brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to investigational product must be reported to Gilead.

11.4.3 Reporting to Novartis

All Serious Adverse Events including life-threatening events resulting in required hospitalization, disability, congenital anomaly, death, or progression of the disease being greater than expected. In the event that the investigator identifies an SAE according to protocol definitions, the SAE will be reported to Novartis within 24 hours of identification of the SAE. SAEs should be reported to Novartis by fax to: U.S. Drug Safety & Epidemiology at fax number: 887-778-9739. . Please use the Novartis SAE Report Fax Coversheet and reference to the Novartis study code provided by the DFCI study team.

All SAEs which are reported to Novartis a copy of the report must also be reported to the overall principal investigator, Project Manager and study coordinator (contact information on study contact list):

PI: Jennifer Brown, MD PhD,
Email: jbrown2@partners.org

11.4.4 Non-Serious Adverse Event Reporting to DF/HCC

Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

11.5 Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).
Other investigative sites should report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to:

Jennifer R Brown MD PhD
Tel 617-632-4564
Fax 617-582-7909
Email jbrown2@partners.org

The DF/HCC Principal Investigator Dr. Brown will submit SAE reports from outside institutions to the DFCI Office for Human Research Studies (OHRS) according to DFCI IRB policies and procedures in reporting adverse events.

11.6 Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA. Please refer to appendix E for FDA reporting guidelines.

11.7 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

11.8 Monitoring of Adverse Events and Period of Observation

All adverse events that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. SAEs and death should be reported for 6 months after the last day of study intervention. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification. For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12. DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Method

The QACT will collect, manage, and perform quality checks on the data for this study.

12.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

Form	Submission Timeline

Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

12.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

13. REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.3 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.4 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13.5 Multi-center Guidelines

This protocol will adhere to the policies and requirements of the Dana-Farber/Harvard Cancer Center. The specific responsibilities of the DF/HCC Overall Principal Investigator (or Protocol Chair), Coordinating Center, and Participating Institutions are presented in the Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (see Appendix D).

- The DF/HCC Overall Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.
- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.
- Except in very unusual circumstances, each participating institution will order the agent(s) directly from the supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

14. STATISTICAL CONSIDERATIONS

14.1 Sample Size/Accrual Rate

Primary Objective:

The primary objective for this phase II study is to estimate the overall response rate or ORR (CR+PR) of ofatumumab and idelalisib in previously untreated CLL/SLL.

Hypothesis:
Null: 0.55 ORR
Alternative: 0.75 ORR

Sample size and power calculation:

A two stage design is used to compute the sample size. A total number of 50 eligible patients is needed in order to detect a 75% response rate, assuming the ORR for the null hypothesis is 55%, with 90% power and 4% type I error. 31 patients will be enrolled initially into the study. The study will stop early if only 17 or fewer responses out of 31 patients are observed and the drug will not be declared promising if less than 34 responses are seen in the total 50 patients. The probability of stopping at the first stage is 0.56 if the null hypothesis is true. For the purposes of the two-stage design and in order to avoid potential closure to enrollment, we will use the four month response evaluation to decide about moving to the second stage.

Primary Analysis:

The overall response rate and a 90% confidence interval will also be calculated, using the

method of Atkinson and Brown for a two stage study. Patients' baseline characteristics will be summarized using descriptive statistics (median, interquartile range, proportions).

Enrollment was discontinued at 27 patients and ORR will be estimated based on the data, with 90% confidence interval.

14.2 Analysis of Secondary Endpoints

Other Secondary Objectives:

- To determine the CR rate and PFS of ofatumumab and idelalisib.
- To determine the ORR, CR and rate of nodal PR with lymphocytosis for idelalisib given alone for 2 months.
- To assess the safety of ofatumumab and idelalisib in combination.
- To determine whether clinical response correlates with known CLL molecular prognostic factors.
- To determine whether the use of CT scans in response assessment improves the predictive power of ORR for progression-free or overall survival.
- To determine whether serum ofatumumab levels in vivo predict response.
- To assess whether idelalisib alters the flow cytometric phenotype of circulating CLL cells.
- To assess whether in vivo treatment with idelalisib alters CLL cell sensitivity to therapy with antibodies or other kinase inhibitors
- To assess pharmacodynamic markers of PI3 kinase inhibition including AKT phosphorylation, production of T cell chemokines and response to CXCR 4/5
- To determine whether response or resistance correlates with genetic alterations in PIK3CA or PIK3CD or other genes
- To assess the clonal dynamics of CLL in peripheral blood vs bone marrow, and during therapy with idelalisib.

Secondary Analysis:

The CR rate of combination therapy, ORR rate, and rate of nodal PR with lymphocytosis for idelalisib given alone for 2 months will be summarized as numbers and percentages. The Kaplan Meier method will be used to estimate the median progression free survival. The number and percent of patients who experience toxicities on combination therapy after at least one dose of treatment will also be summarized. Associations of clinical response rate and known prognostic factors will be assessed using Fisher's exact test.

14.3 Reporting and Exclusions

14.3.1 **Evaluation of toxicity.** All participants who receive one dose of study therapy will be evaluable for toxicity from the time of their first treatment.

14.3.2 **Evaluation of response.** All participants included in the study and who actually receive at least one dose of study therapy will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each participant should be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) nodal response with lymphocytosis; 5) progressive disease, 6) early death from malignant disease, 7) early death from toxicity, 8) early death because of other cause, or 9) unknown (not assessable, insufficient data). By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.

15. PUBLICATION PLAN

The overall Principal Investigator Dr Jennifer Brown will have the responsibility for collecting and analyzing the study data and preparing the manuscript for publication. The data may be presented at a national or international meeting prior to full publication. The manuscript will be written within 6 months of study completion and submitted to Gilead and Novartis for their review prior to journal submission.

16. REFERENCES

1. Herman, S.E., et al., *Phosphatidylinositol 3-kinase-delta inhibitor CAL-101 shows promising preclinical activity in chronic lymphocytic leukemia by antagonizing intrinsic and extrinsic cellular survival signals.* Blood, 2010. **116**(12): p. 2078-88.
2. Lannutti, B.J., et al., *CAL-101, a p110delta selective phosphatidylinositol-3-kinase inhibitor for the treatment of B-cell malignancies, inhibits PI3K signaling and cellular viability.* Blood, 2011. **117**(2): p. 591-4.
3. . Gilead Sciences. GS-1101 (CAL-101) investigator brochure. 2012 July.
4. Webb, H.L., et al., *Clinical Pharmacokinetics of CAL-101, a p110δ Isoform-Selective PI3K Inhibitor, Following Single- and Multiple-Dose Administration In Healthy Volunteers and Patients with Hematological Malignancies* in *Poster Presentation, ASH*. 2010.
5. Furman, R., et al., *CAL-101, an isoform-selective inhibitor of phosphatidylinositol 3 kinase p110δ, demonstrates clinical activity and pharmacodynamic effects in patients with relapsed or refractory chronic lymphocytic leukemia.* Blood, 2010. **116**(21): p. 31.
6. Kahl, B.S., B.D. Cheson, and J.W. Friedberg, *Clinical Roundtable Monograph: current treatment options for NHL patients refractory to standard therapy: recent data in single-agent and combination therapy.* Clin Adv Hematol Oncol, 2010. **8**(5): p. 1-16.
7. Brown, J.R., et al., *Final results of a phase I study of idelalisib (GSE1101) a selective inhibitor of PI3K{delta}, in patients with relapsed or refractory CLL.* ASCO Meeting Abstracts, 2013. **31**(15_suppl): p. 7003.
8. Hallek, M., 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): p. 5446-56.
9. Perkins, J.G., et al., *Frequency and type of serious infections in fludarabine-refractory B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma: implications for clinical trials in this patient population.* Cancer, 2002. **94**(7): p. 2033-9.
10. Hoellenriegel, J., et al., *The phosphoinositide 3'-kinase delta inhibitor, CAL-101, inhibits B-cell receptor signaling and chemokine networks in chronic lymphocytic leukemia.* Blood, 2011. **118**(13): p. 3603-12.
11. Friedberg, J.W., et al., *Inhibition of Syk with fostamatinib disodium has significant clinical activity in non-Hodgkin lymphoma and chronic lymphocytic leukemia.* Blood, 2010. **115**(13): p. 2578-85.
12. Burger, J.A., et al., *The Bruton's Tyrosine Kinase Inhibitor, PCI-32765, Is Well Tolerated and Demonstrates Promising Clinical Activity In Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL): An Update on Ongoing Phase 1 Studies.* ASH Annual Meeting Abstracts, 2010. **116**(21): p. 57-.
13. Zent, C.S., et al., *The treatment of recurrent/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL) with everolimus results in clinical responses and mobilization of CLL cells into the circulation.* Cancer, 2010. **116**(9): p. 2201-7.

14. Furman, R.R., et al., *A phase I/II study of the selective phosphatidylinositol 3-kinase-delta (PI3K{delta}) inhibitor, GS-1101 (CAL-101), with ofatumumab in patients with previously treated chronic lymphocytic leukemia (CLL).* ASCO Meeting Abstracts, 2012. **30**(15_suppl): p. 6518.
15. Flinn, I.W., et al., *Phase II Trial of Ofatumumab for Older Patients and Patients Who Refuse Fludarabine-Based Regimens with Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma.* Blood, 2012. **120**: p. 719.
16. Rozman, C., E. Montserrat, and N. Vinolas, *Serum immunoglobulins in B-chronic lymphocytic leukemia. Natural history and prognostic significance.* Cancer, 1988. **61**(2): p. 279-83.
17. Wadhwa, P.D. and V.A. Morrison, *Infectious complications of chronic lymphocytic leukemia.* Semin Oncol, 2006. **33**(2): p. 240-9.
18. Davey, F.R., et al., *Serum immunoglobulins and lymphocyte subsets in chronic lymphocytic leukemia.* Am J Clin Pathol, 1987. **87**(1): p. 60-5.
19. Giannopoulos, K., et al., *Characterization of regulatory T cells in patients with B-cell chronic lymphocytic leukemia.* Oncol Rep, 2008. **20**(3): p. 677-82.
20. Beyer, M., et al., *Reduced frequencies and suppressive function of CD4+CD25hi regulatory T cells in patients with chronic lymphocytic leukemia after therapy with fludarabine.* Blood, 2005. **106**(6): p. 2018-25.
21. Kremer, J.P., et al., *B-cell chronic lymphocytic leukaemia cells express and release transforming growth factor-beta.* Br J Haematol, 1992. **80**(4): p. 480-7.
22. Schuler, M., et al., *Autocrine transforming growth factor-beta from chronic lymphocytic leukemia-B cells interferes with proliferative T cell signals.* Immunobiology, 1999. **200**(1): p. 128-39.
23. Lagneaux, L., et al., *Excessive production of transforming growth factor-beta by bone marrow stromal cells in B-cell chronic lymphocytic leukemia inhibits growth of hematopoietic precursors and interleukin-6 production.* Blood, 1993. **82**(8): p. 2379-85.
24. Fayad, L., et al., *Interleukin-6 and interleukin-10 levels in chronic lymphocytic leukemia: correlation with phenotypic characteristics and outcome.* Blood, 2001. **97**(1): p. 256-63.
25. Pettersson, T., et al., *Immunoreactive interleukin-6 in serum of patients with B-lymphoproliferative diseases.* J Intern Med, 1992. **232**(5): p. 439-42.
26. Buggins, A.G., et al., *Tumor-derived IL-6 may contribute to the immunological defect in CLL.* Leukemia, 2008. **22**(5): p. 1084-7.
27. Malisan, F., et al., *B-chronic lymphocytic leukemias can undergo isotype switching in vivo and can be induced to differentiate and switch in vitro.* Blood, 1996. **87**(2): p. 717-24.
28. Kitabayashi, A., M. Hirokawa, and A.B. Miura, *The role of interleukin-10 (IL-10) in chronic B-lymphocytic leukemia: IL-10 prevents leukemic cells from apoptotic cell death.* Int J Hematol, 1995. **62**(2): p. 99-106.
29. Jurlander, J., et al., *Characterization of interleukin-10 receptor expression on B-cell chronic lymphocytic leukemia cells.* Blood, 1997. **89**(11): p. 4146-52.
30. Yang, Z.Z., et al., *Intratumoral CD4+CD25+ regulatory T-cell-mediated suppression of infiltrating CD4+ T cells in B-cell non-Hodgkin lymphoma.* Blood, 2006. **107**(9): p. 3639-46.

31. Yamamoto, R., et al., *PD-1-PD-1 ligand interaction contributes to immunosuppressive microenvironment of Hodgkin lymphoma.* Blood, 2008. **111**(6): p. 3220-4.
32. Benson, D.M., Jr., et al., *The PD-1/PD-L1 axis modulates the natural killer cell versus multiple myeloma effect: a therapeutic target for CT-011, a novel monoclonal anti-PD-1 antibody.* Blood. **116**(13): p. 2286-94.
33. Hagemeister, F., *Rituximab for the treatment of non-Hodgkin's lymphoma and chronic lymphocytic leukaemia.* Drugs. **70**(3): p. 261-72.
34. Cheson, B.D. and J.P. Leonard, *Monoclonal antibody therapy for B-cell non-Hodgkin's lymphoma.* N Engl J Med, 2008. **359**(6): p. 613-26.
35. Jaglowski, S.M. and J.C. Byrd, *Rituximab in chronic lymphocytic leukemia.* Semin Hematol. **47**(2): p. 156-69.
36. Jaglowski, S.M., et al., *The clinical application of monoclonal antibodies in chronic lymphocytic leukemia.* Blood. **116**(19): p. 3705-14.
37. Farag, S.S., et al., *Fc gamma RIIIa and Fc gamma RIIa polymorphisms do not predict response to rituximab in B-cell chronic lymphocytic leukemia.* Blood, 2004. **103**(4): p. 1472-4.
38. Woyach, J.A., et al., *A phase I/II study of rituximab and etanercept in patients with chronic lymphocytic leukemia and small lymphocytic lymphoma.* Leukemia, 2009. **23**(5): p. 912-8.
39. Dornan, D., et al., *Effect of FCGR2A and FCGR3A variants on CLL outcome.* Blood. **116**(20): p. 4212-22.
40. Tridandapani, S., et al., *TGF-beta 1 suppresses [correction of supresses] myeloid Fc gamma receptor function by regulating the expression and function of the common gamma-subunit.* J Immunol, 2003. **170**(9): p. 4572-7.
41. Trotta, R., et al., *TGF-beta utilizes SMAD3 to inhibit CD16-mediated IFN-gamma production and antibody-dependent cellular cytotoxicity in human NK cells.* J Immunol, 2008. **181**(6): p. 3784-92.
42. Puente, X.S., et al., *Whole-genome sequencing identifies recurrent mutations in chronic lymphocytic leukaemia.* Nature, 2011. **475**(7354): p. 101-5.
43. Quesada, V., et al., *Exome sequencing identifies recurrent mutations of the splicing factor SF3B1 gene in chronic lymphocytic leukemia.* Nat Genet, 2012. **44**(1): p. 47-52.
44. Wang, L., et al., *SF3B1 and other novel cancer genes in chronic lymphocytic leukemia.* N Engl J Med, 2011. **365**(26): p. 2497-506.
45. Landau, D.A., et al., *Evolution and impact of subclonal mutations in chronic lymphocytic leukemia.* Cell, 2013. **152**(4): p. 714-26.
46. Brown, J.R., et al., *Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110delta, for relapsed/refractory chronic lymphocytic leukemia.* Blood, 2014. **123**(22): p. 3390-7.
47. Byrd, J.C., et al., *Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia.* N Engl J Med, 2014. **371**(3): p. 213-23.
48. Byrd, J.C., et al., *Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia.* N Engl J Med, 2013. **369**(1): p. 32-42.
49. Rizzo, J.D., et al., *Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update.* Blood, 2008. **111**(1): p. 25-41.

50. Smith, T.J., et al., *2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline.* J Clin Oncol, 2006. **24**(19): p. 3187-205.

17. APPENDICES

Appendix A: **Performance Status Criteria**

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Description	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B IWCLL MODIFIED CRITERIA FOR HEMATOLOGIC TOXICITY

Modified Grading Scale for Hematological Toxicity in CLL Studies			
Grade	**Decrease in Plts from Lower Limit of Normal or Pre-Tx Value, whichever is Lower (%)[1]**	**ANC/µl (nadir)[2]**	**Hemoglobin[3]**
0	**No change to 10%**	**≥2000**	**No change to 10%**
1	**11 - 24%**	**≥1500 and <2000**	**11 - 24%**
2	**25 – 49%**	**≥1000 and <1500**	**25 – 49%**
3	**50 – 74%**	**≥500 and <1000**	**50 – 74%**
4	**≥ 75%**	**<500**	**≥ 75%**

[1]Starting platelet counts must be below 100,000/mm^3 to use this chart. If at any level of decrease the platelet count is ≤20,000/mm^3 this will be considered grade 4 toxicity, unless the patient's starting platelet count was ≤20,000/mm^3. In that case, the individual is considered not evaluable for platelet toxicity and will receive study therapy supported with transfusions as needed.
[2] If baseline ANC is <1,000/µL OR chronically dependent on myeloid growth factors, then neutrophil toxicity cannot be evaluated and the patient will be treated on study regardless of neutrophil count and supported by myeloid growth factors as needed.
[3] Hb levels must be below 10 gm/dL to use this table. Baseline and subsequent Hb determinations must be performed before any transfusions.

APPENDIX C PML SCREENING QUESTIONNAIRE

		YES	NO
1.	Does the subject report any new weakness?		
2.	Does the subject report any new difficulty with coordination or walking?		
3.	Does the subject report any new signs of confusion, impaired memory or attention?		
4.	Does the subject appear apathetic compared to previous contacts?		
5.	Does the subject report any new visual disturbances?		
6.	Has the subject had any new trouble speaking, either slurring speech, difficulty getting out words, difficulty understanding words, or difficulty comprehending spoken language:		
7.	Does the subject have any other new neurological symptoms, including but not limited to: New onset seizure New sensory loss New emotional liability		

If any of the above are answered "Yes" at any visit, the investigator will contact the overall PI and the Novartis medical monitor and the patient will be referred to a neurologist.

DFCI IRB Protocol #: *13-309*

APPENDIX D

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

Table of Contents

1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center (DF/HCC) Multi-center protocol will comply with Federal regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

The Multi-Center Data and Safety Monitoring Plan includes the following components:

DF/HCC Multi-center Protocol: A research protocol in which one or more outside institutions collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Children's Hospital Boston (CHB), Brigham and Women's Hospital (BWH)) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies (FDA). The DF/HCC Protocol Chair has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Protocol Chair is the same person as the DF/HCC Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator.

The participating institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides the administrative support to the **DF/HCC Sponsor** in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol. Should the DF/HCC Sponsor decide to use a CRO, the CRO will be deemed the Coordinating Center.

DF/HCC Quality Assurance Office for Clinical Trials: A unit within DF/HCC developed to computerize and manage data, and to provide a Quality Control and Quality Assurance function for DF/HCC trials.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, Jennifer R Brown MD, PhD, will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Submit the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Assure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA (investigator-held IND trials) or OBA (gene therapy trials), as applicable. For this study, Dr. Brown will hold the IND and will be responsible for all FDA correspondence.

- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center (Lead Institution DFCI)

The Coordinating Center will assume the following general responsibilities:

- Assist in protocol development
- Maintain copies of Federal Wide Assurance and Institutional Review Board (IRB) approvals from all participating institutions.
- MaintainFDA correspondence, as applicable.
- Maintain updated roster of participants.
- Verify eligibility.
- Verify response.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports submitted by Participating Institutions and submit to DF/HCC Sponsor for timely review.
- Distribute adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all participating investigators.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Monitor Participating Institutions either by on-site or virtual monitoring.
- Maintain Regulatory documents of all Participating Institutions.
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc).
- Maintain documentation of all communications.
- Ensure that each Participating Institution has the appropriate assurance on file with the Office of Human Research Protection (OHRP).

2.3 DF/HCC Quality Assurance Office for Clinical Trials (QACT)

In addition to the Coordinating Center, the DF/HCC QACT provides the following support services to assist the DF/HCC Sponsor:

- Develop protocol specific case report forms (CRF/eCRFS).
- QA/QC data of protocol specific CRFs.
- Provide Central Participant Registration, which includes review of consent and eligibility

- Provide auditing services (funding and QACT approval required).

2.4 Participating Institution

Each Participating Institution is expected to comply with all applicable Federal Regulations and DF/HCC requirements, the protocol and HIPAA requirements. All Participating Institutions will provide a list of personnel assigned to the role for oversight of data management at their site to the Coordinating Center.

The general responsibilities for each participating institution are as follows:

- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain a regulatory binder in accordance with DF/HCC requirements.
- Provide the Coordinating Center with regulatory documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as needed (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center.
- Submit source documents, research records, and CRFs per protocol specific submission guidelines to the Coordinating Center.
- Submit Serious Adverse Event (SAE) reports to local IRB per local requirements, and to the Coordinating Center, in accordance with DF/HCC requirements as well as to Gilead Pharmaceuticals.
- Submit protocol deviations and violations to local IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Secure and store investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- For protocols using investigational agents, the Participating Institution will order their own investigational agents regardless of the supplier (Novartis and Gilead in this case).

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.
- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.
- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent to interventional trials (i.e. drug and/or device trials).

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Approval letter of the Participating Institution's IRB
- Copy of the Informed Consent Form approved by the Participating Institution's IRB
- Participating IRB's approval for all amendments

It is the Participating Institution's responsibility to notify its IRB of protocol amendments. Participating Institutions will have 90 days from receipt to provide the Coordinating Center their IRB approval for amendments to a protocol.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPAA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an Authorization. This Authorization may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, which covered entities (Participating Institutions) must use.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected per NCI requirements. These are the primary reasons why DF/HCC has chosen to use Authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center must have the participant's full name & social security number "blacked out" and the assigned DF/HCC QACT case number (as described below) and DF/HCC protocol number written in (with the

exception of the signed informed consent document). Participant initials may only be included or retained for cross verification of identification

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 **Participant Registration**

Please see protocol section 4.4.

3.7.2 **Initiation of Therapy**

Participants must be registered with the DF/HCC QACT before receiving treatment. Treatment may not be initiated until the Participating Institution receives a faxed or e-mailed copy of the participant's registration confirmation memo from the Coordinating Center. Therapy must be initiated per protocol guidelines. The DF/HCC Sponsor and DFCI IRB must be notified of any exceptions to this policy.

3.7.3 **Eligibility Exceptions**

The DF/HCC QACT will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. The DF/HCC QACT requires each institution to fully comply with this requirement.

3.7.4 **Verification of Registration, Dose Levels, and Arm Designation**

A registration confirmation memo for participants registered to DF/HCC Multi-Center Protocol will be faxed or emailed to the registering institution within one business day of the registration. Treatment may not be initiated until the site receives a faxed or e-mailed copy of the registration confirmation memo.

3.8 DF/HCC Protocol Case Number

Once eligibility has been established and the participant successfully registered, the participant is assigned a five digit protocol case number. This number is unique to the participant on this trial and must be used for QACT CRF/eCRF completion and written on all data and QACT correspondence for the participant.

3.9 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe derivations from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.9.1 **Definitions**

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.9.2 **Reporting Procedures**

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission.

All protocol violations must be sent to the Coordinating Center in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

3.10 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.10.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 11.4.

Participating Institutions must report the AEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB SAE Reporting Requirements.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Investigators will review any distributed AE reports, send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents.

3.10.2 Guidelines for Processing IND Safety Reports

FDA regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any adverse experience associated with the use of the investigational agent that is both serious and unexpected. The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. The Participating Institutions willreview and submit to their IRB according to their institutional policies and procedures.

3.11 Data Management

The DF/HCC QACT develops a set of either paper or electronic case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. The DF/HCC QACT provides a web based training for eCRF users.

Notations concerning adverse events will address relationship to protocol treatment for each adverse event grade. All adverse events encountered during the study will be evaluated according to the NCI Common Toxicity Criteria and CLL specific hematologic criteria in Appendix C, and all adverse events must be noted on the participant's Adverse Event (Toxicity) Forms.

3.11.1 **Data Forms Review**

When data forms arrive at the DF/HCC QACT, they are reviewed for completeness, protocol treatment compliance, adverse events (toxicities) and response. Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following:

Incomplete or Questionable Data
If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC QACT Data Analyst or study monitor. Responses to all queries should be completed and submitted within 14 calendar days. Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

Missing Forms
If study forms are not submitted on schedule, the Participating Institution will receive a Missing Form Report from the Coordinating Center noting the missing forms. These reports are compiled by the DF/HCC QACT and distributed a minimum of four times a year.

4. REQUISITIONING INVESTIGATIONAL DRUG

See main protocol Section 7.

5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the QACT provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions will be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institution may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion.

The participating institutions in this study are experienced CLL Centers who work together in the CLL Research Consortium, which has conference calls every two weeks and a couple meetings per year. The investigators are therefore in close contact on a frequent basis. Furthermore, these are all tertiary care oncology centers with internal audit mechanisms. We therefore anticipate that monitoring will be primarily performed through the submission of source documents to DFCI for review (virtual monitoring) at critical points in the therapy.

At a minimum, the Coordinating Center, or designee, will monitor each participating site once a year while patients are receiving treatment. Should a Participating Institution be monitored once and then not accrue any additional patients, additional monitoring visits may not be necessary.

Virtual Monitoring: Participating Institutions will be required to forward copies of participants' medical record and source documents to the Coordinating Center upon request for remote monitoring purposes. Virtual monitoring may include, but is not limited to, review of the following:

1. Eligibility and registration (diagnostic flow cytometry and when available CT scans, bone marrow biopsy and FISH results)
2. Restaging evaluations (end of cycle 2 (idelalisib alone), end of cycle 4 (weekly ofa))
3. Final restaging evaluation in both arms (two months after monthly ofa, including bone marrow biopsy with MRD analysis and CT scan)
4. At time of off study for progressive disease

If any issues are identified in the course of virtual monitoring, the participating institution may be subject to on-site monitoring conducted by the Coordinating Center or designee.

On-Site Monitoring: On-site monitoring visits will be conducted at the discretion of the sponsor-investigator. The need for on-site monitoring will depend on participant accrual, data compliance, virtual monitoring findings, and other factors. Participating Institutions will be required to provide access to participants' complete medical records and source documents for verification during any on-site monitoring visits. In addition, Participating Institutions should provide access to regulatory documents, pharmacy records, local policies related to the conduct of research, and any other trial-related documentation maintained by the participating site.

5.2 Evaluation of Participating Institution Performance

5.2.1 **Monitoring Reports**

The DF/HCC Sponsor will review all monitoring reports for on-site and virtual monitoring of Participating Institutions to ensure protocol compliance and ability to fulfill responsibilities of participating in the study. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

The minimum accrual requirements are 3-5 patients per site/annually.

6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 DF/HCC Sponsored Trials

Participating institutions will be eligible for one on-site audit, to be scheduled by the QACT, after at least three participants have been treated on protocol at the site. Approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.2 Participating Institution

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates and re-audit dates (if applicable), which involve this protocol. All

institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 DF/HCC Sponsor and Coordinating Center

The DF/HCC Sponsor will review all final audit reports and corrective action plans if applicable. The Coordinating Center, must forward these reports to the DF/HCC QACT per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the DF/HCC Sponsor to implement recommendations or require further follow-up. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Sub-Standard Performance

The DF/HCC Sponsor, DFCI IRB, is charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

6.4.1 **Corrective Actions**

Participating Institutions that fail to meet the performance goals of accrual, submission of timely accurate data, adherence to protocol requirements, and compliance with state and federal regulations, will be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation.

Guidelines for Dana-Farber use ONLY
Other sites should NOT make any submissions to the FDA for this trial

Appendix E:

FDA guidelines for Dana-Farber outlined on Study May Proceed Letter

IND Responsibilities:
The responsibilities of the sponsor-investigator include:
-Reporting any unexpected fatal-life threatening suspected adverse reactions to the FDA no later than 7 days after initial receipt of the information.
-Reporting any

1. serious, unexpected suspected adverse reactions
2. findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and
3. a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting. If your IND is not in eCTD format, you may submit 15-day reports in paper format.

- Submitting annual progress reports within 60 days of the anniversary of the date that the IND became active (the date clinical studies were permitted to begin).

Submission Requirements

Cite the IND number listed above at the top of the first page of any communications concerning this application. Each submission to this IND must be provided in triplicate (original plus two copies). Please include three originals of all illustrations that do not reproduce well. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
Attn: Janet Higgins
5901-B Ammendale Road
Beltsville, MD 20705-1266
Phone Number: (240) 402-0330

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved.

Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http:/ /wvvw.fda.govDrugs/DevelopmentApprovalProcess/FormsSubmissionReguirements/DrugMasterFilesDMFs/ucm073080.htm.

DANA-FARBER CANCER INSTITUTE
Nursing Protocol Education Sheet

Protocol Number:	**13-309**
Protocol Name:	**A Phase II Study of Idelalisib (GS1101, CAL101) + Ofatumumab in Previously Untreated CLL/SLL**
DFCI Site PI:	Jennifer Brown, MD, PhD
DFCI Research Nurse:	Karen Francoeur RN, Karen Polinski RN, Kathleen McDermott, RN

Page the DFCI research nurse or DFCI site PI if there are any questions/concerns about the protocol.
Please also refer to ONC 15: Oncology Nursing Protocol Education Policy
***** Remember to check the ALERT PAGE*****

SPECIAL NURSING CONSIDERATIONS UNIQUE TO THIS PROTOCOL

Study Design	Phosphatidylinositol 3-kinases (PI3Ks) are enzymes that regulate several cellular functions including motility, proliferations and survival. PI3K signaling is mediated by 4 catalytic isoforms of the p110 subunit of the enzyme – α, β, γ and δ. PI3Kδ shows an expression pattern that is particularly prominent in cells of hematopoietic origin. **Idelalisib** can selectively inhibit PI3Kδ function. **Ofatumumab** ia an anti-CD20 antibody that induces potent complement-dependent cytotoxicity against cells tha express CD20 dimly, including CLL. **Study Design** – Section 1.1; **Study Rationale** – Section 2.5. **A cycle is 28 days** – Section 5, Table 1.
Dose Calc.	• **Idelalisib** and **Ofatumumab** are both fixed dosing in mg – Section 5, Table 1
Study Drug Administration	**Idelalisib** *Administration* Guidelines are found in Section 5.0 through 5.2,1 including Table 1 • Dosing will start on Cycle 1, Day 1 • Always administered BEFORE Ofatumumab when given on the same day • Oral, taken twice per day approximately 12 hours apart. • May be taken with or without food; Note: Food consumption should be recorded on PK days – Section 5.2.1 • Tablets must be swallowed whole with 100 – 200 mL of water. Participants must be instructed not to bite or chew the tablets. In case of breakage of tablets in the oral cavity, additional water should be taken as a rinse. • Missed doses may be taken within 6 hours of the scheduled dosing time. • Vomited doses can only be retaken if the tablet is visible in the vomitus. **Ofatumumab** *Administration* Guidelines are found in Sections 5.0 through 5.1; 5.2.2 and 7.2 • Dosing will start on Cycle 3, Day 1 and continue once weekly for 8 weeks (Cycles 3 and 4). This will be followed by monthly dosing for four additional cycles (Cycles 5, 6, 7 and 8) • Administered IV through infusion tubing set supplied by Sponsor. • Please note than infusion time can be up to 4.6 hours. • Do NOT mix with any other meds. IV line must be flushed with NS before and after completion of infusion. • **Premedication regimen** – See Table 1 in Section 5.0 • **Please review Section 5.2.2 and Tables 2 through 4 for specific instructions on the rate of infusion** • **Infusion reactions are an expected risk – monitor patient closely** – Section 6.1.2 • **Please review 7.2.4 and Figure 1 for detailed instructions on the infusion set up for Ofatumumab, including the use of a 0.2 micron polyether sulfone in-line filter.** **NOTE:** Criteria to treat is found in Section 5.1
Dose Mods & Toxicity	*Dose Modifications/Dosing Delay for Toxicity* are outlined in Section 6 • This protocol uses NCI CTCAE criteria, version 4.0 – Section 6 • **Participants must be monitored for s/sx consistent with PML and for Hepatic Adverse Events** – see Table 6 and Section 6.2 for a description of the signs and symptoms. See also Appendix D for a symptom screening questionnaire. • See Section 6.3 and Table 6 for dose modifications and delays.
Con Meds	*Concomitant Therapy* Guidelines are in Section 5.3 • Please review the cited sections for permitted, prohibited, and "use with caution" medications/therapies/foods • See Section 5.3.2 for **required tumor lysis prophylaxis** and recommendation for hydration • See Section 5.3.6 for recommended prophylactic antibiotics and antivirals. • **Tylenol** use is discouraged – Section 5.3

Required Data	*Study Calendar and Assessment Required data* are outlined in Sections 8 and 9 • PKs and Pharmacodynamics: Please see Section 8 for time points • Study calendar is in Section 9
Charting Tips	**All study drugs require documentation of exact administration time.** Please be sure to DOCUMENT study medication **actual** UP/DOWN times in medical record (e.g. LMR, eMAR, nursing notes). **Edit eMAR as needed to match the exact time given**. • If there is a discrepancy in the infusion time, delay in administration, or infusion takes longer than is permitted by the guidelines of the protocol, please **document the reason for the discrepancy in the medical record.** Please be sure to also DOCUMENT any additional V/S, routes of administration, and exact time of PK collections.

OTHER MEDICATIONS TAKEN

If you take a daily medication (prescribed or otherwise), please use one line per drug and indicate the start and stop dates under the "Date(s) Taken" section (i.e., 6/2/09 - 6/5/09).

Drug Name	Dose	Dates Taken	Reason Taken

Study Participant Initials _____ Date _____

FOR STUDY TEAM USE ONLY	
Staff Initials:	
Date Dispensed:	Date Returned:
# pills/caps/tabs dispensed:	# pills/caps/tabs returned:
# pills/caps/tabs that should have been taken:	
Discrepancy Notes:	

Study Participant
Self-Administration
Study Drug Diary
Dana-Farber/Harvard Cancer Center

Participant Identifier: _____
Protocol # : 13-309
Your MD _____ Phone _____
Your RN _____ Phone _____

STUDY DRUG INSTRUCTIONS:

Study Drug: Idelalisib
How Much: 150 mg
How Often: You will take each dose twice daily.
When: You should take your dose at about the same time each day, ideally 12 hours apart.

SPECIAL INSTRUCTIONS:
Swallow each dose whole with about 4-8oz. of water.
Do not bite or chew tablets.
If tablet breaks, additional water should be taken as a rinse.
Drug can be taken with or without food.
Missed doses can be taken up to 6 hours after scheduled dose.
Vomited doses should be retaken only if the tablet is visible in the vomitus.

Please bring an unused study drug, all empty containers, and diary to the next clinic visit.

DOSING LOG

Idelalisib

Cycle: ___

For each AM dose take: 1 tablet

For each PM dose take: 1 tablet

Please indicate the date, time, amount taken and any comments.

	Date	Amount Taken		Comments
		AM dose	PM dose	
Ex:	6/1/2009	8 am - 1	7:30 pm - 1	vomited PM pill
Day 1				
Day 2				
Day 3				
Day 4				
Day 5				
Day 6				
Day 7				
Day 8				
Day 9				
Day 10				
Day 11				
Day 12				
Day 13				
Day 14				
Day 15				
Day 16				
Day 17				
Day 18				
Day 19				
Day 20				
Day 21				
Day 22				
Day 23				
Day 24				
Day 25				
Day 26				
Day 27				
Day 28				

SYMPTOMS/SIDE EFFECTS

Please record any side effects experienced during this cycle. Include the date the particular symptom started and when it ended. Please evaluate the severity of the symptom according to the following scale:

Mild: Awareness of sign or symptom; easily tolerated and did not affect ability to perform normal daily activities. Symptom did not require medication or therapeutic intervention.

Moderate: Significant discomfort which interfered with ability to perform normal daily activities. Symptom was easily resolved with at home medication or simple therapeutic intervention.

Severe: Marked discomfort with an inability to carry out normal daily activities. Symptom required new medication and/or therapeutic intervention in order to resolve.

Please Note: The severity should reflect the most severe level experienced during the time period.

Symptom	Start Date	End Date	Severity

Charting Tips	**All study drugs require documentation of exact administration time.** Please be sure to DOCUMENT study medication **actual** UP/DOWN times in medical record (e.g. LMR, eMAR, nursing notes). **Edit eMAR as needed to match the exact time given**. • If there is a discrepancy in the infusion time, delay in administration, or infusion takes longer than is permitted by the guidelines of the protocol, please **document the reason for the discrepancy in the medical record.** Please be sure to also DOCUMENT any additional V/S, routes of administration, and exact time of PK collections.

DFCI Protocol: 13-309
PI: Jennifer R. Brown, MD, PhD

Acceptable Methods of Contraception

Sexually active women of childbearing potential and sexually active men who are able to father a child must choose from the methods of birth control listed below:

Individual Methods	**Combination Methods**	
	Hormone Methods (choose one and use with a barrier method)	**Barrier Methods** (use both OR choose one with a hormone method)
IUD	**Estrogen and Progesterone**	Diaphragm with spermicide
Copper T 380A IUD	Oral contraceptives	Male condom (with spermicide)
LNg 20 IUD	Transdermal patch	
Tubal Sterilization	Vaginal ring	
Hysterectomy	**Progesterone**	
	Injection	
	Implant	

Abbreviation: IUD = intrauterine device

Women who could become pregnant should always use barrier contraception in combination with other oral or hormonal methods of contraception since it is possible that the study drug might make some oral or hormonal contraceptives less effective. If your partner had a vasectomy you must use a hormone or barrier method as well.

Your study doctor or personal health care provider can discuss the benefits and disadvantages of these birth control options with you.

DFCI Protocol: 13-309
PI: Jennifer R. Brown, MD, PhD

Idelalisib possible interactions with other medications

Idelalisib is a strong inhibitor of CYP3A. Accordingly, coadministration of CYP3A substrates with idelalisib may result in an increase in their systemic exposures (eg, certain antiarrhythmics, calcium channel blockers, benzodiazepines, HMG-CoA reductase inhibitors, phosphodiesterase-5 [PDE5] inhibitors, and warfarin). Particular caution is recommended during coadministration of idelalisib with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events, including narrow therapeutic index CYP3A substrates (eg, alfentanil, cyclosporine, sirolimus, tacrolimus, cisapride, pimozide, fentanyl, quinidine, ergotamine, dihydroergotamine, astemizole, and terfenadine).

When coadministered with rifampin, a highly potent inducer of CYP3A, idelalisib exposures are approximately 75% lower. Coadministration of potent inducers of CYP3A (rifampin, carbamazepine, phenytoin, and St. John's wort) with idelalisib should be avoided.

DANA-FARBER CANCER INSTITUTE

Beth Israel Deaconess Medical Center

MASSACHUSETTS GENERAL HOSPITAL

Jennifer Brown, MD PhD
Principal Investigator
Dana-Farber Cancer Institute
450 Brookline Avenue
Boston, MA 02215

Dear Patient,

July 18, 2018

As a patient of *A Phase II Study of Idelalisib + Ofatumumab in Previously Untreated CLL/SLL*, your study doctor would like to inform you of a clarification made to the study's consent form. In this envelope, you have received a consent form addendum. This is a short version of the full informed consent form that you usually sign during clinic visits. This consent form addendum explains the small change that has been made.

Your study nurse or doctor will call you to go over the consent form addendum together. During this time, you will be able to ask any questions you have. Once all your questions have been answered please make sure to complete the following three tasks:

1. Please indicate your agreement to the changes by checking a box. Then put your initials and the date next to your answer. (Part C, page 2)
2. Please indicate your consent to continue participating in the study by signing and dating the form. (Part E, page 3)
3. Once complete, please mail back the entire consent form to the hospital using the addressed and stamped envelope provided.

Sincerely,

Jennifer Brown, MD PhD