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Minimal Residual Disease Eradication With Ibrutinib Therapy (MERIT) in Patients With Chronic Lymphocytic Leukemia After Frontline Therapy

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Mayo Clinic Cancer Center

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Drug Availability
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*Study contributor(s) not responsible for patient care.

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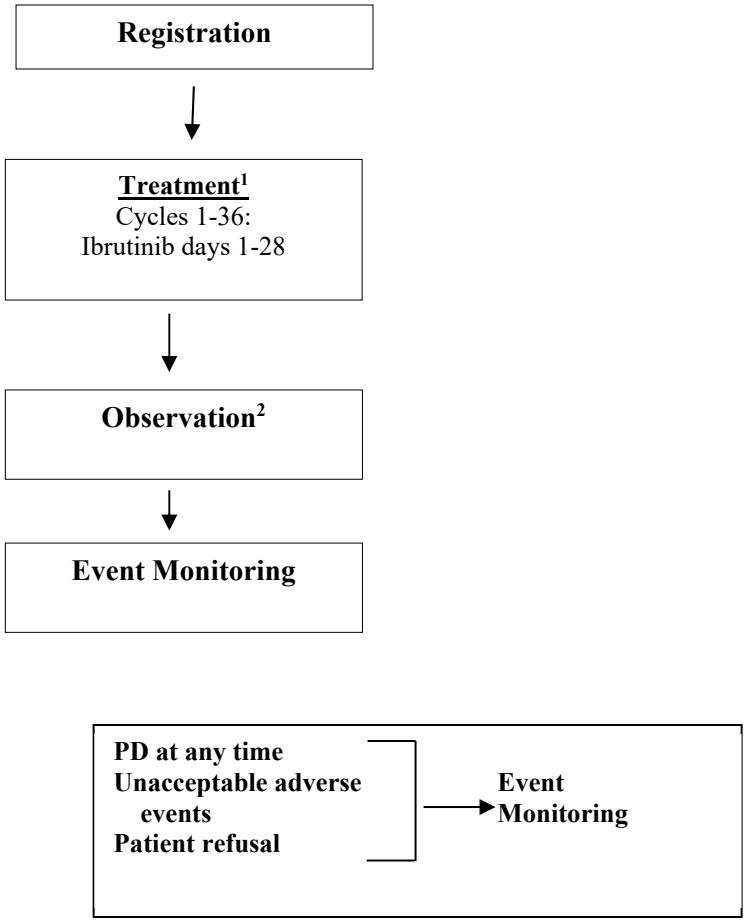
Schema



1. Cycle length = 28 days Last cycle may be up to 56 days to accommodate the Study Drug Discontinuation visit.
2. Q 3 months x 2 years

Generic name: Ibrutinib Brand name(s): Mayo Abbreviation: PCI-32765 Availability: Provided by Pharmacyclics

1.0 Background and Scientific Rationale

1.1 **Overview on CLL:** CLL is a lymphoproliferative malignant disorder that remains incurable in the majority of the patients when using standard therapeutic approaches. It is manifested by the progressive accumulation of functionally-incompetent, mature-looking lymphocytes in the blood, bone marrow and lymphoid tissues. It is a heterogeneous disease with a variable clinical spectrum ranging from an indolent variety (Rai Stage 0), where the patients enjoy a long-term survival of over 12 years, vs. advance-stage disease (Stage III/IV), where the median survival is about 2.5 years.[1] Treatment options have included alkylating agents (Chlorambucil, Cyclophosphamide) or purine analogues (fludarabine, pentostatin) and/or monoclonal antibodies (rituximab, alemtuzumab, ofatumumab). These agents are often used in combination regimens with variable responses. Treatment of this disease remains palliative as the clinical course is punctuated with frequent relapses and the eventual death of the patient from progressive disease. New agents and novel therapeutic strategies are thus needed for the treatment of CLL[2] to cure the disease, induce a prolonged remission, or maintain remission. In reviewing the natural history of this disease, it is clear that these aims are unlikely until complete remission can be achieved in higher proportions of this patient population. Most recently, it has been further reported that eradication of minimal residual disease or MRD, which can be detected by flow cytometry or by polymerase chain reaction (PCR) is associated with more prolonged disease control and is an important end point that determines longer disease free interval.[3-5]

1.2 **Treatment:** Due to the incurable nature of the disease and limited therapeutic options, treatment of CLL is often only instituted when patients develop symptomatic or persistently progressive disease. The criteria for treatment interventions are outlined in the IWCLL/Hallek, December 2008 formulation (see Appendix IV).[6]

(A) Chemotherapy in CLL: Traditionally, the initial treatment for CLL patients that require therapy[7] included either (a) a single agent alkylating agent (chlorambucil) or a (b) purine analogue (fludarabine or pentostatin). Compared to chlorambucil, higher overall response rate (ORR) and complete remission (CR) rate were observed with fludarabine, but there was no superiority in overall survival (OS) or progression-free survival (PFS) noted in randomized studies.[8,9] Kanti Rai reported on the CALGB randomized Chlorambucil vs. Fludarabine vs. the combination of Fludarabine and Chlorambucil.[8] Among the 170 patients treated with fludarabine, 20% achieved a CR, while 43% achieved a partial remission (PR). The median duration of remission and the median PFS in this group were 25 and 20 months, respectively. Despite improvement in the ORR, no survival benefit was reported. Thus, up until very recently, the standard of care for this disease remained the use of single agent oral chlorambucil or fludarabine with a CR rate of 4% and 20%, respectively.

Combining these agents with steroids and/or other chemotherapy agents (such as vincristine or an anthracycline) also did not result in improvement in survival.[10-12] Importantly, even early disease stage patients treated with these agents did not alter the overall clinical outcome. Despite evaluation of various combination regimens, purine analogues remained the most active agents in patients with CLL, yielding higher overall and complete response rates.[8,13,14] Eventually all patients with CLL will relapse. Although retreatment with fludarabine can result again in response, especially in those with an initial clinical response lasting for more than 1 year, continued treatment with

fludarabine is difficult due to cumulative marrow toxicity resulting in prolong cytopenia and inability to further treat the patient. Patients who do not achieve durable remission after first fludarabine therapy have only a modest response with a second round of fludarabine.[15] For these patients, the combination of this drug with alkylating agents (cyclophosphamide) has been used with improved outcome.[13,16,17] Various investigators reported combination of fludarabine with cyclophosphamide as salvage regimen in patients with CLL.[17,18]

(B) Monoclonal antibodies and chemoimmunotherapy
The development of monoclonal antibodies heralded a new era and modified the therapeutic approach to treatment of CLL.

Rituximab is a chimeric humanized monoclonal antibody that showed an ORR of approximately 50-60% in patients with relapsed and refractory low-grade non-Hodgkin's lymphoma.[19-21] Because CLL is a B-cell lymphoproliferative disease with expression of CD20, rituximab was investigated for the treatment of CLL. Interestingly, despite expression of CD20 on the CLL cells, single agent rituximab (on standard dosing schedule) failed to demonstrate any meaningful clinical response. However, more frequent dosing e.g., three times weekly for 4 weeks (at 375 mg/m^2 per dose) showed a better response rate 45% (3% CR, 42% PR) with a median duration of response of 10 months .[22] Higher doses may have more anti-tumor efficacy but are cost prohibitive, and the true long-term benefit remains undetermined.[23]

While results of single agent rituximab in CLL were disappointing, the results of the combination with fludarabine (chemoimmunotherapy) were impressive.[24,25] Clinical experience of combination of rituximab with fludarabine or fludarabine and cyclophosphamide demonstrated higher CR rates.[17,22,23,26-30] ORR of fludarabine + rituximab combination are in the range of 90% with 47% CR.[27,31] In another clinical investigation the FC (Fludarabine/Cyclophosphamide) regimen was also combined with rituximab. Phase III randomized clinical trial of FC vs. FCR confirmed superiority of the chemoimmunotherapy approach in survival outcomes for patients.[32] This strategy of chemoimmunotherapy, although yielding higher response rates, is often associated with significant toxicity and morbidity to the patients. Thus these regimens are often preferred for younger patients with good performance statuses. Despite the higher response rates and increase rates of reported CR, all patients eventually relapse and die of progressive disease or its complications. Nevertheless, the chemoimmunotherapy approach is now the most commonly used front-line treatment approach in CLL.

Obinutuzumab: is a novel CD20 targeting monoclonal antibody that recently received approval for the treatment of elderly patients with CLL. Prior studies of rituximab in combination with chlorambucil showed higher ORR and CR rates, and this led to the clinical trial comparing Obinutuzumab/chlorambucil vs. rituximab/chlorambucil vs. chlorambucil alone. This study demonstrated a higher ORR in favor of chemoimmunotherapy; 77% vs. 65% vs. 31%, respectively. PFS was also significantly improved with Obinutuzumab/chlorambucil combination vs. the other arms.[33]

Despite these high ORR and CR rates noted with the chemoimmunotherapy approach, all patients eventually relapse and develop resistance to therapy. Up until very recently, the only approved treatments for these patients were alemtuzumab (monoclonal antibody targeting CD52) and ofatumumab (monoclonal antibody targeting CD20).

Alemtuzumab: is a humanized monoclonal antibody that targets CD52 and has demonstrated a clinical response in over 30% of CLL patients with relapsed or refractory disease. Notably, the CR rate remains low (<5%). An important and limiting adverse event of alemtuzumab has been severe immunodeficiency resulting from depletion of both T and NK cells along with B cells. This often results in infectious complications and has limited its use in the community.[34,35]

Ofatumumab: Ofatumumab is another monoclonal antibody that targets CD20, and it is one of the three currently available. It has demonstrated efficacy and is approved in patients with relapsed or refractory CLL; however, similar to the experience with other CD20 monoclonal antibodies, by itself the drug has very low CR rates.[36] Currently ofatumumab is approved for the treatment of CLL patients who are refractory to fludarabine and alemtuzumab.[37]

(C) Tyrosine kinase inhibitors:
Ibrutinib (also referred to as PCI-32765 or JNJ54179060) is a first-in-class, potent, orally administered covalent inhibitor of Brutons tyrosine kinase (BTK). BTK is a mediator of critical B-cell signaling pathways implicated in the pathogenesis of B-cell cancers. In vitro studies have shown that ibrutinib binds covalently to a cysteine residue (Cys-481) in the BTK active site, leading to potent inhibition of BTK enzymatic activity. In cellular signal transduction assays with a B-cell lymphoma cell line, ibrutinib inhibited auto-phosphorylation of BTK, phosphorylation of BTK's physiological substrate, phospholipase-Cγ (PLCγ). It also inhibited the phosphorylation of a further downstream kinase, extracellular-regulated kinase (ERK). Ibrutinib inhibited the proliferation of cell lines derived from diffuse large B-cell lymphoma (DLBCL) patients with a median effective concentration, EC50, of 1 or 2 nM. In primary chronic lymphocytic leukemia (CLL) cells, ibrutinib reduced proliferation at concentrations of 500 and 1000 nM. Preclinical studies have also shown that ibrutinib inhibits numerous processes, e.g., NFκB deoxyribonucleic acid (DNA) binding, CpG-mediated CLL cell proliferation, and tumor cell migration and adhesions. At concentrations relevant to exposure levels in patients, ibrutinib has remarkable selectivity for inhibition of B-cell receptor (BCR) signaling over T-cell receptor (TCR) signaling.[38-41]

Clinical efficacy: The clinical benefit of ibrutinib was first shown in the initial clinical study PCYC-04753, which was a Phase 1, multicenter, open-label, dose-escalation study of ibrutinib in subjects with recurrent B-cell lymphoma, including chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), DLBCL, and follicular lymphoma (FL), or Waldenströms macroglobulinemia (WM). It was initiated in February 2009. Thirty-three of the 66 subjects enrolled responded to treatment with ibrutinib monotherapy, including 10 CR. Responses were observed at each dose level and across all included histologic types, with highest response rate observed in subjects with MCL and CLL/SLL (85.7% each). The maximum tolerated dose (MTD) of ibrutinib was not reached using intermittent dosing cohorts up to 12.5 mg/kg/day and continuous dosing cohorts at 560 mg. However, it was noticed that subjects treated on the lowest dosing cohort of 1.25 mg/kg/day, which did not reach full BTK occupancy, reported the lowest overall response rate (25.0%) compared with all other tested dose levels.[42]

The favorable overall safety profile of ibrutinib and the high incidence of objective responses observed in these subjects with advanced and heavily pretreated B-cell lymphomas and CLL support the role of BTK as a crucial mediator of growth and

survival in B-cell malignancies and was further demonstrated in subsequent Phase 2 studies in relapsed or refractory MCL and relapsed or refractory CLL/SLL.
(a) In Study PCYC-1104-CA, 111 subjects with relapsed and/or refractory MCL were treated with 560 mg daily continuously until disease progression or until the subject could no longer tolerate the treatment. The overall response rate was 68%, and complete response (CR) rate was 21%. The median duration of response (DOR) was 17.5 months, and the median progression-free survival (PFS) was 13.9 months. Based on these data, 560 mg daily dosing was chosen for further development in MCL, FL, and DLBCL.[43]

In Study PCYC-1102-CA, subjects with relapsed or refractory or treatment-naïve CLL/SLL were treated with 420 mg or 840 mg daily continuously until disease progression or until the subject could no longer tolerate the treatment. A total of 85 patients (mostly with high risk CLL) were included in this study (51 received 420mg and 34 received 840mg dose). Ibrutinib produced an overall response rate of 71 % in both the groups. Objective responses appeared independent of poor-risk factors, including adverse cytogenetic characteristics. The median overall survival was 83% and at 26 month the progression-free survival was recorded as 75%. The 840 mg dose level did not appear to improve efficacy. Therefore, 420 mg daily dose was chosen as the recommended dose for further development in CLL/SLL.[44] The subsequent section will provide more detail on some of the important safety aspects of ibrutinib.

Safety: Over 736 subjects have been treated with either single agent use of ibrutinib (506 subjects plus 100 healthy volunteers) or in combination with immunotherapy and/or chemotherapy (130 subjects) in nonrandomized studies. In addition, approximately 537 subjects have been treated with either ibrutinib or placebo in five randomized (controlled and open-label) studies. In the absence of an established MTD, responses have been observed in all histologic subtypes treated to date. Ibrutinib has been well tolerated across various dose levels. The most commonly reported treatment-emergent adverse events (AEs) in studies where ibrutinib was administered as monotherapy (n=506) were diarrhea (42.1%), fatigue (33.8%), and nausea (26.1%). The majority of the adverse events were of Grade 1 or 2 in severity. The most commonly reported adverse events considered related to ibrutinib were diarrhea (30.2%), fatigue (17.8%), nausea (15.0%), and thrombocytopenia (9.9%). The majority of these adverse events were of Grade 1 or 2 in severity. Adverse events of Grade 3 or higher in severity were not common and were primarily hematologic in nature including neutropenia (9.7%), thrombocytopenia (6.5%), and anemia (4.9%). Grade 3 or higher pneumonia occurred in 7.7% of subjects. Serious adverse events (SAEs) in the monotherapy studies were commensurate with patient population, the disease state or its complications, the most common being pneumonia (7.9%) and atrial fibrillation (3.2%). Adverse events of ibrutinib on cardiac, hepatic, or renal function have not been apparent.

Treatment related Lymphocytosis:
Similar to other agents targeting B-cell receptor signaling, transient lymphocytosis is a pharmacodynamic effect of ibrutinib, in which the inhibition of BTK-mediated cellular homing and adhesion results in a mobilization of tumor cells to the peripheral blood (Stevenson 2011).

A reversible increase in lymphocyte counts (ie, ≥50% increase from baseline and above absolute count 5000/mcL), often associated with reduction of lymphadenopathy, has been observed in most subjects (approximately 69% to 75%) with CLL/SLL treated with single agent ibrutinib. This effect has also been observed in some subjects (33%) with

MCL treated with single agent ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few weeks of ibrutinib therapy (median time 1.1 weeks) and typically resolves within a median of 8.0 weeks in subjects with MCL and 18.7 weeks in subjects with CLL/SLL.

Lymphocytosis appeared to occur in lower incidence and at lesser magnitude in subjects with CLL/SLL receiving ibrutinib in combination with chemoimmunotherapy (ie, 27% of subjects receiving ibrutinib + BR in Study 1108) or immunotherapy (ie, 55% of subjects receiving ibrutinib + ofatumumab in Group 2 of Study 1109).

A substantial increase in the number of circulating lymphocytes (e.g., >400,000/µL) has been observed in a subset of subjects. There have been isolated cases of leukostasis reported in subjects treated with ibrutinib. Bleeding-related events: There have been reports of hemorrhagic events in subjects treated with ibrutinib both with and without thrombocytopenia. These include primarily minor hemorrhagic events such as contusion, epistaxis, and petechiae; and some major hemorrhagic events including gastrointestinal bleeding, intracranial hemorrhage and hematuria.

Rash: Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. In a randomized Phase 3 study (PCYC-1112-CA), rash occurred at a higher rate in the ibrutinib arm than in the control arm. Most rashes were mild to moderate in severity. One case of Stevens-Johnson Syndrome (SJS), with a fatal outcome, was reported in a subject with CLL. The subject received ibrutinib (420 mg/day) and was also receiving various antibiotics and antigout medication (allopurinol) known to be associated with SJS.

Cardiac: Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. In particular subjects with a history of cardiac arrhythmias should be monitored closely.

Other Malignancies: Other malignancies, most frequently skin cancers, have occurred in subjects treated with ibrutinib. Across the MCL (PCYC-1104-CA) and CLL/SLL studies (PCYC-1112-CA and PCYC-1102-CA)), skin cancers and non-skin cancers were reported in 5.0% (18/357) and 2.5% (9/357) of subjects who received ibrutinib, respectively.

Infection: Fatal and non-fatal infections have occurred with ibrutinib therapy. At least 25% of subjects with MCL and 35% of subjects with CLL had Grade 3 or greater infections per NCI Common Terminology Criteria for Adverse Events (CTCAE). The most commonly reported infections include pneumonia, cellulitis, urinary tract infection and sepsis. Isolated cases of JC virus reactivation resulting in progressive multifocal leukoencephalopathy (PML) have been observed and resulted in death. Two cases in relapsed CLL subjects have been reported. One case occurred after multiple prior rituximab regimens and less than one year after the last dose of rituximab and high dose steroid administration. The second case occurred during concomitant administration of rituximab, bendamustine and ibrutinib.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib.

Diarrhea: Approximately one-third of subjects treated with ibrutinib monotherapy and two-thirds treated with combination therapy reported diarrhea. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe, with only a small number of Grade 3 events, and no Grade 4 events reported to date.

Summary:
Pooled safety data for subjects treated with ibrutinib monotherapy in 11 nonrandomized studies (PCYC-1102-CA, PCYC-1117-CA, PCYC-1112-CA [crossover only], PCYC-1104-CA, PCI-32765MCL2001, PCI-32765MCL4001, PCYC-1106-CA, PCYC-1111-CA, PCI-32765FLR2002, PCYC-04753, and PCI-32765-JPN-101) has been evaluated (ibrutinib Investigator's Brochure [IB], version 8.0, dated 24 June 2014).
The most frequently reported treatment-emergent adverse events in more than 10% of subjects receiving ibrutinib as monotherapy in nonrandomized studies (N=1061) were diarrhea (35.9%), fatigue (28.6%), nausea (20.2%), cough (17.5%), and anemia (15.2%).
The most commonly reported Grade 3 or 4 adverse events that were hematologic in nature were neutropenia (10.7%), thrombocytopenia (6.2%), and anemia (5.5%).
Pneumonia (5.7%), fatigue (2.9%), hypertension (2.7%), and atrial fibrillation (2.6%) were the most frequently reported nonhematologic Grade 3 or 4 adverse events.
The incidence of treatment-emergent SAEs reported was 41.3% (N=1061); pneumonia (7.0%), atrial fibrillation (2.8%), and febrile neutropenia (2.3%) were the most commonly reported treatment-emergent SAEs .

In a randomized Phase 3 study in subjects with CLL/SLL (PCYC-1112-CA), the most frequently reported treatment-emergent adverse events in the ibrutinib arm were diarrhea (47.7%), fatigue (27.7%), nausea (26.2%), pyrexia (23.6%), anemia (22.6%), and neutropenia (21.5%). Adverse events reported at a higher incidence (> 10% difference) in the ibrutinib arm than in the ofatumumab arm included diarrhea (ibrutinib: 47.7%, ofatumumab: 17.8%), arthralgia (17.4%, 6.8%), and petechiae (13.8%, 1.0%).
The most commonly reported Grade 3 or 4 adverse events in more than 2% of ibrutinib treated subjects that were hematologic in nature were neutropenia (16.4%), thrombocytopenia (5.6%), and anemia (4.6%). Pneumonia (6.7%) was the most frequently reported nonhematologic Grade 3 or 4 adverse event. The most frequently reported SAEs in ibrutinib subjects were pneumonia (8.7%), atrial fibrillation (3.1%), pyrexia (3.1%), lung infection (2.6%), lower respiratory tract infection (2.1%) and urinary tract infection (2.1%).
For more detailed information refer to the current version of the IB.

Long-term use and safety: Analysis of adverse events over a 3-year follow-up period is now available (*see Investigator Brochure for details, Item 5.3.1.4; IB-v8_24June2014_v1.2*) and shows that most AEs of clinical interest, including hematological and non-hematological AEs, either decreased or stayed the same overtime.

1.3 **Rationale for the study**

MRD: Over 25 clinical trial evaluations have been completed and established the importance of minimal residual disease (MRD). Analyses of these clinical studies have demonstrated a significant PFS benefit among patients who have achieved MRD-negative (MRD^-) state. Patients who are in CR and are MRD^- tend to have up to 2 years advantage in PFS vs. those who are in CR and maintain residual detectable disease. Data from Dr. Peter Hillmen (Leeds, UK)[47,48] shows that (a) level of MRD (<0.01% vs. 0.01-1% vs. >1%) in marrow is predictive of overall survival outcome in CLL patients, (b) patients who achieve MRD^- state after first-line therapy have a better PFS and OS than those who achieve MRD^- after >1 with prior therapies and (c) patients who achieve an MRD^- state after initial induction therapy have a better PFS and OS than those who remain MRD^+.[49] In a multivariate analysis Kwok et al reported that MRD response of <0.01% was the most significant independent predictor of clinical outcome (PFS and OS) along with prior therapies. **Collectively, these data suggest that attainment of MRD^- disease after first-line therapy may have an important impact on the clinical outcome of patients with CLL.** Thus strategies that can be employed to achieve this goal are highly desirable but remain undefined. The Hillmen data is a retrospective analysis and provided additional important insight that the type of prior therapy may not be significant as long as patients achieve MRD^- post induction therapy. In a clinical study of alemtuzumab consolidation Hillmen et al showed that 83% of the patients can be converted to MRD^- state (NCRI CLL207 study), and this resulted in significant improvement in PFS and OS.[50] They further reported that MRD^+ patients after FCR induction when converted to MRD^- post-consolidation with alemtuzumab benefited from improvement in PFS, validating the critical importance of eradicating MRD post induction therapy.[50] Similar observations were made by the CLL group at MD Anderson.[47] These results have prompted investigation of MRD in 2 phase III clinical trials; in UK NCRI-CLL8 study MRD eradication is attempted in previously treated CLL patients (1-3 prior therapies) with obinutuzumab (GA-101) given for a finite period of 3-6 months. In the UK NCRI-CLL10 study FCR will be evaluated against IR (ibrutinib/rituximab) and MRD will be used to determine the duration of therapy. While these clinical trials will answer the important question on the eradication of MRD using either a consolidation strategy (with GA-101) or upfront induction treatment with a defined regimen, it remains to be determined what **is the most optimal agent that can be *universally* employed for MRD eradication independent of the frontline induction regimen utilized.** Furthermore, can a *primary* maintenance (instead of consolidation) strategy be used to achieve MRD^- after frontline therapy has failed to achieve this?

In this clinical trial we will prospectively evaluate these questions. The design of this clinical trial allows enrollment of all patients who have completed their initial induction regimen independent of the type of regimen (therapy) given to them as long as they are MRD^+. Thus this study will be able to determine prospectively if attainment of MRD^- post-induction can potentially be possible with the novel agent ibrutinib given in a *primary* maintenance setting. Thus this study is unique in the following manner (**a**) it will evaluate the role of single agent ibrutinib in eradication of MRD (**b**) it will evaluate whether the attainment of MRD negativity is possible with ibrutinib and is it independent of the frontline therapy given (**c**) the role and benefit of continuous therapy independent of attainment of MRD negativity and the impact of this in durability of MRD^- status.

2.0 Goals

2.1 Primary

2.11 Determine the rate of MRD-negative responses (in both blood and bone marrow) at any time during treatment with ibrutinib maintenance.

2.2 Secondary

2.21 Median time to achieve MRD^- (negative) status (in blood and in bone marrow) after initiation of ibrutinib maintenance treatment.

2.22 Toxicity profile of ibrutinib as maintenance therapy after frontline induction.

2.23 Durability of the MRD^- state (determined from the time of first documentation of MRD^- until the first documentation of MRD^+(or last date shown to be MRD- for a censor).

2.24 Time to requirement of next therapy for patients who achieve confirmed MRD^- vs. those who remain MRD^+ disease at 48 weeks (end of 12 cycles).

2.25 Progression free survival (as determined by the IWCLL criteria) among patients who achieve confirmed MRD vs. those who remain MRD^+ disease at 48 weeks (end of 12 cycles).

2.3 Correlative Research

2.31 To conduct correlative studies for further understanding of the mechanism of antitumor activity of ibrutinib in eradication of the MRD.

2.32 Determine the impact of ibrutinib on depression and anxiety symptoms to better understand toxicity profile of ibrutinib maintenance.

2.33 Determine impact of social support or lack thereof on mood symptoms in CLL patients receiving maintenance treatment.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Understand and voluntarily sign an informed consent form.

3.12 Age ≥ 18 years.

3.13 Able to adhere to the study visit schedule and other protocol requirements including willing to provide blood, baseline bone marrow aspirate, and control DNA samples for correlative research purposes (see Sections 6.2, 4.0, 14.0, and 17.0).

3.14 Diagnosis of B-CLL, confirmed by flow cytometry and as per the criteria outlined by the IWCLL/Hallek December 2008 (Refer to Appendix III).

3.15 Prior frontline therapy for B-CLL must have been discontinued ≥ 56 days but ≤ 365 days prior to registration. **NOTE:** Patients on supportive care therapy due to use of specific induction regimen such as antibiotics may continue on those treatments at the discretion of the treating physician.

3.16 Patient must have completed a frontline induction therapy (minimum of 2 treatment cycles). **NOTE:** Standard Therapies / therapeutic agents are defined as those listed in the NCCN guidelines for treatment of CLL (nccn.org). Also, patients who received induction regimen as part of a clinical trial and is not necessarily mentioned in the NCCN guidelines, will also be eligible as long as the patient has completed at least 2 treatment cycles of induction regimen, achieved a clinical response (PR or CR) and is able to meet all other criteria for the study. However, patients who have previously received ibrutinib or have been randomized to ibrutinib containing arms in a clinical trial will not be eligible for this study.

3.17 Patients must have a sustained clinical response (PR, nPR, CCR, CRi, CR) with documented residual disease (≥1 CLL cell per 10,000 leukocytes or ≥ 0.01% MRD) either in the blood, bone marrow or a lymph node ≥ 3.5 cm by any available techniques.

3.18 ECOG performance status of 0, 1 or 2 at registration (see Appendix I).

3.19 The following laboratory values obtained ≤ 14 days prior to registration:

- Absolute neutrophil count ≥ 1000/mm^3
- Platelet count ≥ 30,000/mm^3
- Serum creatinine ≤ 1.5 x ULN.
- Total bilirubin ≤ 1.5 mg/dL or direct bilirubin ≤ 1.0 mg/dL for patients with Gilbert's syndrome
- SGOT (AST) and SGPT (ALT) ≤ 3.5 x ULN

3.19a Negative pregnancy test done ≤ 7 days prior to registration, for women of childbearing potential only.

3.2 Exclusion Criteria

3.21 Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.

3.22 Since this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown, any of the following will deem the subject ineligible for the study:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.23 Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.

3.24 Use of any other experimental drug or therapy ≤ 28 days prior to registration on this study. NOTE: Patients on low dose prednisone (≤ 10 mg) for treatment of conditions other than CLL are eligible.

3.25 Patients who have received more than 1 prior therapy. NOTE: (Prior therapy is defined as any single agent or combination regimen that is included as treatment for symptomatic CLL. Treatment(s) given prior to the symptomatic phase of the disease (preventive strategy) will not be considered as prior induction therapy. For the purpose of a particular therapy/regimen to be counted towards the number of prior treatments a patient must have received at least 2 cycles of the induction regimen e.g., a patient who change their treatment regimen after only 1 cycle (due to toxicity or any other reason) will not be considered to have "2" prior therapies.

3.26 Patients who have progressive disease or relapse (as defined by the IWCLL criteria see Section 11.23) at or any time before registration on this study.

3.27 . No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer or any other cancer in situ, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for three years.

3.28 Patients who are already MRD^- (both in the blood and the bone marrow) after frontline therapy and have lymph nodes <3.5cm.

3.29a Concomitant use of warfarin or other Vitamin K antagonists [see Section 9.5(d)].

3.29b Requires treatment with a strong cytochrome P450 modulators (CYP3A inhibitor and/or CYP3A inducers) [see Section 9.5(a)]. NOTE: A comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

3.29c Currently active, clinically significant hepatic impairment Child-Pugh class B or C according to the Child Pugh classification (see Appendix VII)

3.29d Major surgery ≤ 4 weeks prior to registration.

3.29e Patients who have active infectious hepatitis.

3.29f Patients with other diseases that in the opinion of the treating physician pose a higher risk for treatment with ibrutinib therapy including active HIV infection and bleeding disorders.

4.0 Test Schedule

All visits ± 4 days unless otherwise stated.

	Active Monitoring Phase					
	Days Prior to Registration		Cycle 1 (Pre)	Prior to subsequent Cycles 2-36	Study Drug Discontinuation	Observation
Tests & Procedures	≤28 days	≤14 days			3-4 weeks from the last day of the last cycle	Every 3 months x 2 years
Complete medical history (including prior treatment regimen)	X					
Adverse event assessment	X			X	X	X
Physical exam, including weight and vital signs, and PS[1]		X	X	X[20]	X	X
Clinical Response assessment (Tumor measurement by physical exam)[2, 3]		X		X	X	X
CT scans (Chest, Abdomen, Pelvis)[4]	X				X	
EKG/ECHO[5]	X					
CBC with differential[6]		X	X	X	X	X
Chemistry group (SGOT [AST], SGPT [ALT], serum creatinine, total bilirubin, LDH, uric acid, phosphorus, alkaline phosphate, serum electrolytes)[6]		X	X	X	X	X
Direct bilirubin[15]		X				
Quantitative Immunoglobulins	X			X[7]	X	
Quantitative T & B cells, peripheral blood		X		X[17]		
Minimal residual disease assesment[8]	X			X	X	X
Flow Cytometry-CLL Panel[9]	X					
Bone marrow biopsy and/or aspirate[10]	X			X	X	X
CLL FISH Panel[11],	X					
Zap 70, CD38, IgHV[12]	X					
Beta 2 microglobulin[12]	X					
Research blood sample collection[13, R]		X		X	X	X
Research bone marrow aspirate collection[14, R]	X			X	X	X
Mandatory DNA sample which can be collected from any one of the 3 sources (buccal swab, skin biopsy or myeloid cells from bone marrow) as noted in Section 17.0		X[18]				
Urine Pregnancy test		X[16]				
PHQ-8; GAD; Living Situation; MOS-SSS-4 Question; QOL		X		X[19]		

1. During the first 2 cycles of treatment, patients will have a focused clinical examination weekly, as necessary, for the monitoring of tumor lysis syndrome (TLS). This can be done in collaboration with local MD/referring physician.
2. The physical exam should measure the spleen and liver, noting the maximal distance below the respective costal margins and should record the bi-dimensional diameter of the largest palpable node in each area of involvement including the following sites: left neck (sub-mandibular, cervical, supra-clavicular), right neck (sub-mandibular, cervical, supra-clavicular), left axillary, right axillary, left groin (inguinal, femoral) and right groin (inguinal, femoral).
3. Clinical response assessment: will be done per IWCLL criteria starting with evaluation of disease state at baseline and for progression of disease only every 3 cycles (for 36 cycles) during study treatment and every cycle (every 3 months) during follow-up without therapy.
4. CT scans should be done as clinically indicated for the management of the patient and in accordance with the IWCLL guidelines. CT scans may be done with patient's primary physician (if outside Mayo Clinic), results of these will be entered in the source document.
5. EKG or ECHO only if clinically indicated.
6. Hematology (CBC) / Serum Chemistry: During cycle 1 and 2, day 8 and 15 labs will be done at the treating physician discretion based on patient's clinical needs and/or can be done based on risk for TLS or for conduct of correlative studies. Monitoring for TLS is considered standard of care. In subsequent cycles CBC/chemistry will be done prior to beginning of each cycle as standard of care and additional testing will only be done as clinically indicated to be determined by treating physician. Laboratory workup may be done with patient's primary physician (if outside Mayo Clinic), results of these will be entered in the source document.
7. Quantitative immunoglobulin will be done at baseline and thereafter can be done every 4 cycles at the discretion of the treating physician and as per standard clinical practice.
8. Minimal residual disease: MRD assessment will be done at baseline, during the treatment phase and then during the observation phase (no treatment). The MRD will be done on peripheral blood and / or bone marrow aspirate using flow cytometry standardized Mayo Clinic panel. In general bone marrow aspirate evaluation will only be required when the peripheral blood is recorded at least twice (at two separate evaluation 3 months apart) to be negative. If blood is positive for MRD assessment, then bone marrow aspirate evaluation for the MRD will not be needed and can be deferred. **MRD assessment in the Blood:** **(a) Baseline:** all patients will have MRD assessed in the peripheral blood prior to initiating the study. **(b) During treatment phase:** all patients will have MRD assessed in the peripheral blood every 3 cycles. If the ibrutinib maintenance treatment is held > 21 days for toxicity or for any other reason(s) then the MRD testing will be delayed to accommodate 3 treatment cycles prior to testing. **(c) During observation period:** all patients will have MRD assessed within 4 weeks of completion of the last treatment cycles and thereafter every 3 months (if they are MRD negative) and every 6 months (if they are MRD+) for a maximum follow-up of 2 years or until initiation of subsequent treatment for relapsed disease (whichever happens first). **MRD assessment in the Bone marrow aspirate:** The schedule of assessment of the bone marrow aspirate for MRD will be different and dependent upon the results of the MRD status in the blood. **(a) Baseline:** If the peripheral blood MRD results are positive then a BM aspirate assessment for MRD will not be needed. If the peripheral blood MRD results are negative, then a BM aspirate assessment for MRD will be needed. (b) **During the treatment phase:** The MRD assessment of the Bone marrow aspirate will only be required once the peripheral blood MRD is recorded to be negative for at least 2 evaluations that are separated at least 3 months apart. If the blood evaluation demonstrates positivity for MRD, then Bone marrow aspirate evaluation will not be required and can be deferred until the peripheral blood is noted to be negative x 2. **(c) During the observation period:** The MRD assessment of the Bone marrow aspirate will only be required if the post treatment peripheral blood assessment (i.e., that done within 4 weeks of the last treatment dose) was noted to be negative. If the post treatment blood evaluation was noted to be positive, then no bone

marrow aspirate evaluation is required. It is possible, though unlikely, that during observation period the peripheral blood (evaluated every 3 months) may convert to negative. If this is observed, then a bone marrow aspirate for MRD will be done only if 2 consecutive blood MRD assessments are recorded to be negative. **Note:** Bone marrow aspirate done solely for MRD will be considered research, however if the procedure is done to assess response to therapy (such as to document complete remission as part of clinical care as required by the IWCLL guidelines) then it will be considered standard of care.

- See detailed section on the MRD (see Section 11.4).

9. Flow cytometry-CLL Panel: The objective of this is to confirm diagnosis as per standard of care (pretreatment). Patients who have a flow cytometry done at any time prior to starting the clinical trial which validates the diagnosis of B-CLL will not be required to have it repeated.
10. **Bone marrow biopsy/aspirate:** At baseline documentation of bone marrow assessment (aspirate and biopsy) will be required to determine the extent of marrow involvement and / or confirmation of presence of MRD. This is standard of care as per the IWCLL guidelines to accurately assess response to treatment. The BM assessment (aspirate and biopsy) will not be required if (1) a bone marrow assessment (aspirate and biopsy) was done post induction treatment and this showed residual disease (or MRD positivity) or (2) if a bone marrow post induction was done (with negative disease, or if there was no MRD information) but the peripheral blood at the time of screening show MRD positivity. If no bone marrow aspirate/biopsy is done post induction therapy, then a bone marrow aspirate and biopsy will be required prior to starting maintenance therapy to assess extent of disease in the marrow and establish appropriate response category post induction (this is consistent with the IWCLL guidelines and is standard of care). During the treatment and observation phase, a repeat bone marrow biopsy will only be required to establish the response of complete remission as recommended by the IWCLL guidelines and this will be at the discretion of the treating physician who will determine the appropriate timing based on clinical response assessment (this is consistent with the IWCLL guidelines and is standard of care). Bone marrow aspirate will be done for assessment of MRD and the timing of this will be followed as noted in detail in foot note 8.
11. FISH (*florescent in situ hybridization*) in blood or bone marrow (if no CLL cells in the blood): May be performed any time prior to initiation of therapy. If already done previously (prior to initial induction therapy), the results will be obtained and recorded, repeat testing will not be needed unless clinically indicated and at the discretion of the treating physician.
12. These tests may be performed any time prior to initiation of therapy. If already done previously (prior to initial induction therapy), the results will be obtained and recorded, repeat testing will not be needed unless clinically indicated and at the discretion of the treating physician.
13. For blood collected for correlative studies, see Section 14.0. Samples will be collected at baseline (pre-treatment), prior to cycle 4, prior to cycle 7, prior to cycle 13 and at time of relapse.
14. Bone marrow aspirate (optional) for correlative studies, see Section 14.0. Samples will be collected only if bone marrow biopsy or aspirate is done as part of routine clinical care of the patient (as outlined in footnote 10) or as part of MRD assessment (as noted in footnote 8).
15. Only for patients with Gilbert's syndrome and the total bilirubin >1.5 mg/dL.
16. For women of childbearing potential only. Must be done ≤ 7 days prior to registration.
17. Should be performed after 3 cycles, 6 cycles, 12 cycles, and at time of relapse.
18. Buccal swab may be collected any time prior to starting treatment. Skin biopsy is only required if DNA cannot be obtained from the buccal swab. Alternate source could be myeloid cells in the marrow (in cases where bone marrow is obtained). This will be at the discretion of the treating physician in consultation with the PI.

19. PHQ-8, GAD-7, Living situation, MOS-SSS-4 Question, and Linear Analogue Self-Assessment: Prior to cycle 4, prior to cycle 7, prior to cycle 13, at time of relapse and thereafter every 3 months x4.
20. After the first 6 cycles, clinical evaluation and blood tests can be obtained per test schedule and mailed/faxed to Mayo Clinic and patient can return at least every 3 cycles for follow up to Mayo. Patient may be seen more frequently, if clinically necessary. NOTE: All forms, including AEs, will need to be filled out every 28 days.

R. Research funded.

5.0 Grouping Factor: None.

6.0 Registration Procedures

6.1 To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at (507) 284-2753 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page (http://hsrwww.mayo.edu/ccs/training) and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office (507) 284-2753. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.2 Registration to the Correlative Research

Mandatory:
A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.13, 4.0, 14.0 and 17.0).

6.3 Prior to accepting the registration, registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.4 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: 507-284-0885). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted, and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.5 At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research of CLL at Mayo Clinic.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.

6.6 Treatment on this protocol must commence at Mayo Clinic under the supervision of a medical oncologist or hematologist.

6.7 Treatment cannot begin prior to registration and must begin ≤ 14 days after registration.

6.8 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.9 All required baseline symptoms (see Section 10.6) must be documented and graded.

6.9a Study drug is available on site.

6.9b **Patient Questionnaire booklets**
Patient questionnaire booklets are available on site. Copies are not acceptable for these submissions. Booklets should be ordered using the Patient Questionnaire Order Form.

7.0 Protocol Treatment

7.1 Treatment Schedule

Agent	Dose	Route	Days	Max. No. of cycles
Ibrutinib	420 mg QD	Oral	1-28	36

Cycle length = 28 days

7.11 **Ibrutinib**

- 420mg PO QD will begin on day one of cycle #1.
- Four weeks will constitute 1 treatment cycle.
- Patients will be evaluated for MRD status every 3 cycles (as discussed previously in Section 4.0, footnote 8, see detailed MRD section 11.4).
- A maximum of 36 cycles of maintenance cycles will be given.
- Treatment will be discontinued if (**a**) patients develop unacceptable side effects, (**b**) if patients develop disease progression while on ibrutinib maintenance (recommended to be confirmed on two independent occasions at least 2 week apart and consistent with the IWCLL guidelines, see Section 11.0), (**c**) if patients have completed the 36 cycles on maintenance therapy, (**d**) if the patient is removed from the study by the treating physician due to concern of overall wellbeing and in the best interest of the patient, (**e**) patients who have residual disease at the end of 36 cycles will continue to event monitoring

7.2 Treatment by Local Medical Doctor (LMD): If patient is tolerating therapy without excessive toxicity at a stable dose level after 1 cycle (can be confirmed through telecommunication and does not need to be physically evaluated at Mayo Clinic) of treatment the patient may be seen by their primary physician (if outside of Mayo Clinic). Results would need to be returned to Mayo Clinic. Patient would need to return to Mayo Clinic every 3 cycles for follow-up at Mayo Clinic.

7.3 After the first 6 months, clinical evaluation and blood tests can be obtained per test schedule and mailed/faxed to Mayo Clinic and patient can return at least every 3 cycles for follow up to Mayo (patient does not need to be seen every cycle). Patient may be seen more frequently, as clinically necessary. All unused study drug must be returned, and all study drug must be accounted for. A 3-month supply of study drug may be provided at each cycle.

8.0 Dosage Modification Based on Adverse Events

8.1 Dose Levels (Based on Adverse Events in the Tables below)

Dose Level	**Ibrutinib**
0*	420 mg daily
-1	280 mg daily
-2	140 mg daily

* Dose level 0 refers to the starting dose.

8.2 Dose Modification

Omit = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time

Hold/Delay = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.

Discontinue = The specified drug(s) are totally stopped.

Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (section 10.1) unless otherwise specified.			
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION
AT TIME OF RETREATMENT			
Investigations	Neutrophil count decreased Grade 4 lasting >7 days	Ibrutinib	Hold (day 1) or omit (days 2-28) Ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose for first occurrence. Each subsequent occurrence may restart at next lower dose after recovery to Grade ≤1 or baseline. If AE occurs at lowest dose discontinue treatment. **NOTE:** Baseline cytopenia: In patients whose baseline (i.e., prior to starting protocol therapy) ANC is 1000/μL, the above Ibrutinib dose modifications, if required, would not be applied until Cycle 3.
Blood and lymphatic system disorders	≥ Grade 3 Febrile neutropenia		Hold (day 1) or omit (days 2-28) Ibrutinib until fever resolves and ANC ≥1000/μL, then resume Ibrutinib at the previous dose.
Gastrointestinal disorders	≥ Grade 3 Nausea (if persistent despite optimal antiemetic therapy)		Hold (day 1) or omit (days 2-28) Ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose for first occurrence. Each subsequent occurrence may restart at next lower dose after recovery to Grade ≤ 1 or baseline. If AE occurs at lowest dose discontinue treatment.
	≥ Grade 3 Vomiting (if persistent despite optimal antiemetic therapy)		
	≥ Grade 3 Diarrhea (if persistent despite optimal anti-diarrheal therapy)		
Other non-hematologic	Any other Grade 4 AE or any unmanageable Grade 3 AE		

- Dose delay: Ibrutinib may be held for toxicity considerations for a maximum of 28 consecutive days. Study medication should be discontinued permanently in the event of a toxicity lasting more than 28 days. If Ibrutinib is interrupted for a reason other than toxicity (e.g. unrelated illness) it must be restarted within 90 days. If interrupted for more than 90 days, study medication should be discontinued permanently and go to event monitoring.
- Dose re-escalation: Patients who require a dose reduction during a given cycle will remain at that dose for at least 2 additional cycles. **At the investigator discretion, the dose of ibrutinib may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to this reduction**. This is particularly reasonable based upon the long-term safety data now available in ibrutinib treated patients that show that most of the hematological or non-hematological AEs either decreased or remained stable (see investigator brochure section 5.3).

- If multiple adverse events are seen, administer dose based on the greatest reduction required by any single adverse event observed.
- Dose modifications are for adverse events attributed to study treatment only. Dose modifications are not required for adverse events if they are deemed unrelated to study treatment.
- Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
- If cough, dyspnea, and other pulmonary symptoms occur, a chest x-ray and high-resolution chest CT scan should be obtained. Incentive spirometry studies (to include DLCO) should be considered. Consider Pneumocystis pneumonia or viral pneumonitis.

8.3 Dose Modification for Hematological Toxicities (Platelet and Hemoglobin only)

Note: hematological toxicity is not based on CTCAE 4.0 except neutrophil but based on CLL specific hematological toxicity (this table and Appendix V).

Dose modification guidelines for drug-related hematological (hemoglobin and platelets) adverse events

Toxicity	Grade [1, 2]	Decrease from pretreatment	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with PI)
CLL/NHL specific Hematological Toxicity (Appendix V)	1	11-24% decrease in HGB or PLT	No	N/A	N/A	N/A
	2	25-49% decrease in HGB or PLT				
	3	50-74% decrease in HGB or PLT	Yes	Toxicity resolves to Grade 0-1 or baseline	Hold (day 1) or omit (days 2-28) Ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose for first occurrence. Each subsequent occurrence may restart at next lower dose after recovery to Grade ≤1 or baseline. If AE occurs at lowest dose, discontinue treatment.	Toxicity does not resolve within 8 weeks of last treatment *Permanent discontinuation should be considered for any severe or life-threatening event.* Go to event monitoring if ≥1 cycle of therapy was given, otherwise go to observation.
	4	≥75% decrease in HGB or PLT	Yes	Toxicity resolves to Grade 0-1 or baseline		

[1] If, at any level of decrease the platelet count is < 20,000/μL, this will be considered grade 4, unless the initial platelet count was ≤ 20,000 μL in which case the patient is inevaluable for toxicity referable to platelet counts.

[2] If, at any level of decrease from the baseline value the platelet and/or hemoglobin counts are within normal limits, this will be considered a grade 0.

8.4 Dose Modification for Hepatic Impaired Subjects

Ibrutinib is metabolized in the liver and therefore subjects with clinically significant hepatic impairment at the time of screening (Child- Pugh class B or C) are excluded from study participation. For subjects who develop mild liver impairment while on study (Child-Pugh class A), the recommended dose reduction for ibrutinib is to a level of 280 mg daily (two capsules). For subjects who develop moderate liver impairment while on study (Child-Pugh class B), the recommended dose reduction is to a level of 140 mg daily (one capsule). Subjects who develop severe hepatic impairment (Child-Pugh class C) must hold study drug until resolved to moderate impairment (Child-Pugh class B) or better. Monitor subjects for signs of toxicity and follow dose modification guidance as needed (Refer to Appendix VII).

9.0 Ancillary Treatment/Supportive Care

9.1 Growth factors

Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is permitted per institutional policy and in accordance with the ASCO guidelines. They should be utilized as clinically warranted and following institutional policies and recommendations. Growth factors can be used during the treatment cycle as clinically indicated. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (42) Update of Recommendations for the Use of Hematopoietic Colony-Stimulating Factors: Evidence-Based, Clinical Practice Guidelines.[51]

9.2 Supportive care

Patients should receive full **supportive care**, including transfusions of blood and blood products, antibiotics, and antiemetics when appropriate. (A) **Any blood transfusions administered must be irradiated blood products to reduce risk of transfusion-mediated graft versus host disease in CLL patients receiving T-cell suppressive therapy. Leukocyte reduction of all blood products for patients on protocol is also required.** All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records. (B) **Antiemetics** may be used at the discretion of the attending physician. (C) **Prophylactic antibiotics and antifungals** may be prescribed at the treating physicians' discretion and as clinically indicated, or as per the institutional guidelines. (D) Treatment for autoimmune cytopenias are permitted for <14 days at doses that do not exceed 100 mg per day of prednisone or equivalent. (E) Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. (F) Short courses (≤14 days) of steroid treatment for non-cancer related medical reasons (e.g., joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 100mg per day of prednisone or equivalent are permitted.

9.3 Tumor Lysis Syndrome (TLS) prophylaxis and treatment

Since patient will have received frontline therapy, it is anticipated that they will no longer have bulky disease that pose any risk for TLS. Patients who are still at risk of TLS as determined by the treating physician, may receive Allopurinol 300 mg/day (or an equivalent standard agent for prevention of hyperuricemia) orally for the first two weeks of the first cycle of protocol therapy. Allopurinol may be continued after the first two weeks at the investigator's discretion and as clinically indicated. Subjects should be observed closely for signs and symptoms of TLS during the initial cycle of therapy. Subjects should be encouraged to drink an abundant amount of fluid prior to treatment. Subjects should maintain adequate hydration and urine output.

9.4 Treatment related lymphocytosis

Lymphocytosis has been reported with ibrutinib, however since this is a patient population who are already expected to be in remission post induction therapy it is not known if this lymphocytosis will still happen upon treatment with ibrutinib. Patients who develop this reaction will be monitored as per standard clinical protocol without specific intervention unless other specific symptoms / signs of disease progression is noted (such as increase in lymph node size that is progressive and persist beyond 3 months of

maintenance therapy, worsening of cytopenia from the time of initiation of maintenance therapy that is consistent with the IWCLL guidelines requiring therapeutic intervention, development of B symptoms persisting for more than 2 months while on therapy or other factors such as organomegaly demonstrating disease progression).

9.5 **Medications to be used with caution**

CYP3A-Inhibitors/Inducers: Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong CYP3A4 or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.

If a strong CYP3A inhibitor (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone, or cobicistat) must be used, reduce ibrutinib dose to 140 mg or withhold treatment for the duration of inhibitor use. Subjects should be monitored for signs of ibrutinib toxicity.

If a moderate CYP3A inhibitor (eg, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, or dronedarone) must be used, reduce ibrutinib to 140 mg (for 840 mg/day dose, reduce to 280 mg) for the duration of the inhibitor use. Avoid grapefruit and Seville oranges during ibrutinib/placebo treatment, as these contain moderate inhibitors of CYP3A (see Section 5.3.1.2).

No dose adjustment is required in combination with mild inhibitors.

Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

A comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

For the most comprehensive effect of CYP3A inhibitors or inducers on ibrutinib exposure, please refer to the current version of the IB.

(b) Drugs that may have their plasma concentrations altered by ibrutinib: In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor (with an IC50 of 2.15 μg/mL). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There is no clinical data available; therefore, co-administration of narrow therapeutic index P-gp substrates (e.g., digoxin) with ibrutinib may increase their blood concentration and should be used with caution and monitored closely for toxicity.

(c) QT prolonging agents: Any medications known to cause QT prolongation should be used with caution; periodic ECG and electrolyte monitoring should be considered.

(d) Antiplatelet agents and anticoagulants: Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function.

Subjects requiring the initiation of therapeutic anticoagulation therapy (eg, atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

9.6 **Prohibited concomitant medications:** Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy are prohibited while the subject is receiving ibrutinib treatment. Corticosteroids for the treatment of the underlying disease is prohibited. Corticosteroids for the treatment of non-cancer related reasons for longer than 14 days and/or at doses >100mg of prednisone or its equivalent are prohibited.

9.7 **Guidelines for ibrutinib management with surgeries or procedure:** Ibrutinib may increase the risk of bleeding with invasive procedures or surgery. **Consider the benefit-risk of withholding ibrutinib for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.** The following guidance may be applied to the use of ibrutinib in the perioperative period for patients who require surgical intervention or an invasive procedure while receiving ibrutinib: (a) **Minor surgical procedures -** For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures. **(b) Major surgical procedures** - For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes. **(c) Emergency Procedures** - For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

9.8 **Psychosocial Assessment:** Assessing psychosocial factor is important in cancer patients. The Patient Health Questionnaire 8 (PHQ-8, which is a version of the PHQ-9) will be used to screen for depression symptoms. This is a validated tool in cancer patients when scored as a continuous measure with a cutoff score of 8 or higher. Item 9 on this scale inquiries about "thoughts that you would be better off dead or of hurting yourself in some way". Cancer patients are likely to consider the prospect of death while thinking about their prognosis. This makes this question more ambiguous in this population. Kroenke et al have reported that using PHQ-8 is desirable in conditions where data is collected in settings where real time further follow up questions about response to item 9 on PHQ-9 is not feasible. After comparing the data from PHQ-9 studies they concluded that PHQ-8 is an acceptable alternative to PHQ-9. When using cut off score of 10 or higher, PHQ-8 has 99% sensitivity, 92% specificity and 57% positive predictive value (2) (See appendix VIII)

The GAD-7 (Generalized Anxiety Disorder) self-reported scale will be used to assess anxiety symptoms (See appendix IX).

Subjects will be asked about their living situations by asking:

What best describes your living situation:

- I live with a partner/spouse/family/friends
- I live alone
- I live in a nursing home, hospital, or other long-term care home
- Other

Social support will be assessed by using 4 questions from the Medical Outcomes Study: Social Support Survey (MOS-SSS) (See appendix X).

These will be collected at baseline at the time of study enrollment and will be repeated quarterly.

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Definitions

Adverse Event

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction

Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. 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 web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

a. Identify the grade and severity of the event using the CTCAE version 4.0.
b. Determine whether the event is expected or unexpected (see Section 10.2).

c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).

d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).

e. Determine if other reporting is required (see Section 10.5).

f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in

the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

10.3 Attribution to agent(s) or procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) or procedure, the following attribution categories are utilized:

Definite - The AE *is clearly related* to the agent(s)/procedure.
Probable - The AE *is likely related* to the agent(s)/procedure.
Possible - The AE *may be related* to the agent(s)/procedure.
Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure.

10.4 Expedited Reporting Requirements for IND/IDE Agents

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days			24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		7 Calendar Days	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

The Mayo IND Coordinator will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

10.41 Adverse Events of Special Interest (AESI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities. These events (regardless of seriousness) will be reported to Pharmacyclics Drug Safety per SAE reporting timelines.

Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic adverse events of Grade 3 or higher*. Any treatment-emergent serious adverse events of bleeding of any grade
- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade

*All hemorrhagic events requiring transfusion of red blood cells should be reported as grade 3 or higher AE per CTCAE v4.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 11.4.6 above.

All serious adverse events and AESIs (initial and follow-up information) will be reported on FDA Medwatch (Form 3500A) or Suspect Adverse Event Report (CIOMS Form 1) IRB Reporting Form and sent via email (drugsafety@pcyc.com) or fax ((408) 215-3500) to Pharmacyclics Drug Safety, or designee, within 15 days of the event. Pharmacyclics may request follow-up and other additional information from the Sponsor Investigator.

Regulatory reporting: Reporting an SAE to Pharmacyclics does not relieve the investigator's responsibility of reporting it to FDA or local regulatory authority. Safety reporting responsibility should be clearly stated in the research agreement and the protocol.

Follow up information: Investigators will assist in investigating any SAE/AESI and provide follow-up information as requested by Pharmacyclics. Company staff who frequently interact with the investigators may facilitate the follow-up activity

10.42 Reporting

Use FDA Medwatch (Form 3500A) available in forms packet for Investigational agents or commercial/investigational agents on the same arm. Submit to Pharmacyclics Drug Safety (see contact information above).

Mayo Clinic Cancer Center (MCCC) Institutions:
Submit copies, along with the Event Reporting coversheet, to the following email address: CANCERCROSAFETYIN@mayo.edu. This email will be managed by the SAE, IND and Safety Reporting Coordinators.

10.43 **EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting**

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6). *

CTCAE SOC	Adverse Event	Grade	Attribution	Comments
Investigations	Neutrophil count decreased	Grade 3 or 4	Possible, probable, definite	This frequent event in patients with CLL will be reported through the routine reporting mechanism
	Platelet count decreased	Grade 3 or 4	Possible, probable, definite	This frequent event in patients with CLL will be reported through the routine reporting mechanism
	White blood count	Grade 3 or 4	Possible, probable, definite	This frequent event in patients with CLL will be reported through the routine reporting mechanism
	Lymphocyte count decreased	Grade 3 or 4	Possible, probable, definite	This frequent event in patients with CLL will be reported through the routine reporting mechanism
Blood and lymphatic system disorders	Anemia	Grade 3 or 4	Possible, probable, definite	This frequent event in patients with CLL will be reported through the routine reporting mechanism

*Report any clinically important increase in the **rate** of a serious suspected adverse reaction over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event.

10.5 **Other Required Reporting**

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

Mayo Clinic Cancer Center (MCCC) Institutions:

If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO, provide the Reportable Event coversheet and appropriate documentation to CANCERCROSAFETYIN@mayo.edu. The Mayo Regulatory Affairs Office will review and process the submission to the Mayo Clinic IRB.

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and**

polyps) – Other (Progressive Disease)" under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE will be reported. Three options are available to describe the event:

    - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
    - Myelodysplastic syndrome (MDS)
    - Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

10.55 Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur in a female study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

A female subject must immediately inform the Investigator if she becomes pregnant from the time of consent to 30 days after the last dose of study drug. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of consent to 3 months after the last dose of study drug. Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 30 days after the last dose of study drug must be reported. Any occurrence of pregnancy must be reported to Pharmacyclics

Drug Safety, or designee, per SAE reporting timelines. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. Pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old and this must be reported to Pharmacyclics Drug Safety, or designee, per SAE reporting timelines. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

10.6 **Required Routine Reporting**

10.61 Baseline and Adverse Events Evaluations

Pretreatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation per CTCAE v4.0 grading **unless** otherwise stated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Investigations	Platelet count decreased*	X	X
Blood and lymphatic system disorders	Anemia*	X	X

*** Grading will be performed by the study statisticians at the time of analysis based on the CLL toxicity grading scale for blood counts in Appendix V. Anemia grade per CTCAE will also be recorded for reporting purposes.**

10.62 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

10.621 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.622 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.623 Grade 5 AEs (Deaths)

10.6231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.7 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation

NOTE: Information from CT scans is not considered in the standard classification of response.

Note: Treatment-related lymphocytosis is a known phenomenon with ibrutinib and is not representative of PD. As noted in the Leukemia Research Foundation Workshop report[52]: "Patients with lymphocytosis and no other evidence of PD should continue therapy until they develop other definitive signs of PD (i.e., at least one feature suggesting worsening of the CLL other than lymphocytosis (e.g., anemia, thrombocytopenia, lymphadenopathy, or hepatosplenomegaly) or the occurrence of another reason to discontinue therapy."

PD: "If PD is suspected, clinical examination, computed tomography, and peripheral blood counts should be obtained, and a bone marrow biopsy considered, to provide objective assessment of CLL status. Note: Recommended to be confirmed on two independent occasions at least 2 weeks apart and consistent with the IWCLL guidelines. "

Note: Since this is a maintenance trial in which patients will be enrolled after having a clinical response from induction therapy, a further decrease in disease burden as noted by decrease in lymph node size or hepatosplenomegaly may not be observed. Thus, patients will be recorded with an objective status of "Not PD" as long as they do not demonstrate disease progression (or PD, defined below in section 11.2).

11.1 Overall Schedule of evaluations

(a) **Clinical Response:** Will be evaluated and documented at baseline (this is defined as the response to the induction therapy). Thereafter clinical response will be evaluated for progression of disease only every 3 cycles of study treatment (for 36 cycles) and every cycle (every 3 months) during follow-up period of without therapy for 2 years.

(b) **MRD status:** To be assessed at baseline (document positivity in blood or bone marrow) and then every 3 cycles of treatment (for 36 cycles) and thereafter every 3 months (for MRD-) and every 6 months (for MRD+) during follow-up without therapy for 2 years.

Note: Bone marrow aspirate done solely for MRD will be considered research. As outlined by the IWCLL guidelines a bone marrow biopsy / aspirate is required to document complete remission. Thus, a bone marrow biopsy / aspirate that is done as part of the clinical response to therapy (such as to document complete remission as part of clinical care as required by the IWCLL guidelines) will be considered standard of care. Additionally, if the bone marrow biopsy or aspirate is done as part of the clinical care of the patient (as determined by the treating physician) that procedure will be considered standard of care.

11.2 Evaluation for Progression of Disease

11.21 PROGRESSION (PD): Patients will continue to receive protocol therapy unless they have evidence of disease progression according to the IWCLL criteria[6] as evidenced by:

11.211 ≥ 50% increase in the sum of the products of at least 2 lymph nodes on 2 consecutive determinations 2 weeks apart (at least one node must be ≥2

cm) that persist for > 3 months or the appearance of new palpable lymph nodes >1.5 cm not due to a tumor flare. Enlargements or the appearance of new nodes due to a tumor flare do NOT qualify as progression.

11.212 ≥ 50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin on 2 consecutive determinations 2 weeks apart and with a minimum of a ≥ 2 cm increase in size from baseline; or appearance of hepatomegaly or splenomegaly which was not previously present at baseline and not due to a tumor flare.

11.213 Transformation to a more aggressive histology (e.g. Richter's transformation).

Note: If a patient develops DLBCL at any time, it will be considered disease progression. If the patient develops any other hematologic malignancy while on study, it will not be considered progressive disease.

11.214 ≥ 50% increase in the absolute number of circulating lymphocytes NOT due to infection, tumor flare or drug-associated lymphocytosis (taking as reference for progressive disease the smallest absolute lymphocyte count recorded since the treatment started). The absolute lymphocyte count must be at least 5000/mm^3 to qualify as disease progression.

11.215 In the absence of progression as defined by 1, 2, 3, or 4 above, the presence of a ≥ 2 g/dl decrease in HGB, or ≥ 50% decrease in platelet count or absolute neutrophil count will NOT exclude a patient from continuing the study. Work-up of such decreases to exclude auto-immune hemolytic anemia, pure red cell aplasia, or idiopathic thrombocytopenic purpura (ITP) should be considered.

11.216 For patients who achieve a CR or nodular PR, progression will be defined as recurrence of circulating leukemia cell clone and an ALC >5000 or recurrence of adenopathy >1.5 cm not due to a tumor flare.

11.22 Not PD: The patient was evaluated for progression only in this cycle and a formal response evaluation did not occur. The patient did not meet the criteria for progression per section 11.21.

11.3 Minimal Residual Disease (MRD) Response: MRD will be assessed by flow cytometry.

MRD definition
Patients will be considered MRD-negative when they have blood or marrow less than one CLL cell per 10,000 leukocyte (or bone marrow consistent with <0.01% involvement). Patients will be recorded to have either MRD^+ vs. MRD^- disease.

Schedule
(A) Pretreatment All patients will have MRD assessed by flow cytometry at baseline prior to initiation of therapy. This can be done either in the peripheral blood (PB) and/or the bone marrow aspirate (BM). (Note: If blood is positive for MRD, then bone marrow aspirate analysis is not required for the clinical protocol, however, if peripheral blood is positive, then a bone marrow aspirate will be required to document MRD+ status of the patient).

(B) On treatment All patients will have the MRD evaluated by flow cytometry on the peripheral blood **every 3 treatment cycles** while on maintenance therapy. MRD will first be done on the PB. If this is **positive, then** NO BM analysis will be required, but if the PB is **negative (on two consecutive evaluation at least 3 months apart) , then** a BM aspirate analysis for MRD will be done. If the ibrutinib maintenance treatment is held ≥ 21 days for toxicity or for any other reason(s) then the MRD testing will be delayed to accommodate 3 treatment cycles prior to testing.

(C) Observation Patients upon completing maintenance therapy will then be monitored for MRD by flow cytometry in the PB only for a maximum of 24 months after the completion of the last treatment cycle. Monitoring schedule will be in the following manner:

(a) If patient becomes **MRD+** from a previously noted MRD-at any point (or those who never develop MRD^- state) will only be monitored every **6** months for a maximum of 2 year or until initiation of therapy for relapsed disease, whichever comes first.

(b) **MRD-** patients who remain MRD^- at the time of the start of the observation period will be continued to monitor for MRD in the PB every **3** months for a maximum of 2 year or until initiation of therapy for relapsed disease whichever comes first.

Methodology
We will employ Mayo Clinic Standard MRD assay.

Flow cytometry: we will conduct 8 color flow cytometry to assess MRD.

Flow cytometry panel for MRD
(i) CD19/CD5/CD20/CD23/CD38/CD45/kappa/lambda. (8-color panel)

12.0 Descriptive Factors

12.1 Rai Stage: 0 vs. 1 vs. 2 vs. 3 vs. 4. (Appendix II)

12.2 $CD38^+$ expression: Positive (≥30%) vs. negative (<30%).

12.3 Chromosomal anomalies as detected by FISH: 13q- vs. 12+ vs. 11q- vs. 17p- vs. other abnormality vs. normal karyotype.

12.4 IgV_H mutation status: Mutated (≥2%) vs. unmutated (<2%) vs. indeterminate.

12.5 ZAP-70 expression: Positive (≥20%) vs. negative (<20%).

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 If the patient develops PD at any time during active treatment they will go to event monitoring. If the patient develops unacceptable adverse events, if the treating physician feels it is in the patient's best interest, or if the patient refuses all further study participation, study treatment will be discontinued, and the patient will go directly to event monitoring. Patients will then be followed in event monitoring per Section 18.0.

13.2 Patients not progressing on active treatment will continue treatment per protocol up to a maximum of 36 cycles. After the completion of 36 cycles, the patient will go to observation (maximum duration of observation 2 years). After completing observation, patients will enter event monitoring. NOTE: Patients who have residual disease at the end of 36 cycles will continue to event monitoring.

13.3 A patient is deemed ineligible if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns and as long as the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

Note: Due to the nature of the disease, if the patient is diagnosed with DLBCL within the first cycle of treatment, it will be assumed that the DLBCL was present at registration. The patient will be deemed ineligible per Sec 3.27.

13.4 A patient is deemed *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.5 If a patient develops DLBCL at any time, it will be considered progressive disease. The patient will go directly to the event monitoring phase of the study per Section 18.0. If the patient develops any other hematological malignancy while on study, it will not be considered progressive disease.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be Collected for this Protocol

Correlative Study (Section for more information)	**Mandatory or Optional**	**Blood or Body Fluid being Collected**	**Type of Collection Tube (color of tube top)**	**Volume to collect per tube (# of tubes to be collected)**	**Visit 1:**Baseline (pre-tx) **Visit 2:** Prior to Cycle 4 **Visit 3:** Prior to Cycle 7 **Visit 4:** Prior to Cycle 13 **Visit 5:** At time of relapse	**Process at site? (Yes or No)**	**Temperature Conditions for Storage /Shipping**
WES studies and Mate-pair DNA sequencing	Mandatory	Blood	EDTA	5 mL (2)	X	YES	Ambient
		Bone marrow		5 mL (2)	X[1]		
BTK signalosome analysis only for patients with MRD+ disease in blood and/or marrow[2]	Mandatory	Blood	Heparin (green top)	5 mL (2)	X	YES	Ambient
		Bone marrow		5 mL (2)	X[1]		
Immunomodulatory effect analysis	Mandatory	Blood	Heparin (green top)	6 mL (1)	X	YES	Ambient
		Bone marrow		6 mL (1)	X[1]		

1. Only if bone marrow biopsy or aspirate is done as part of routine clinical care of the patient or as part of MRD assessment.
2. Sample should also be collected at the time of first documentation of lymphocytosis >5,000cell/mm^3.

14.2 Collection and Processing

All samples will be collected and stored at Dr. Chanan-Khan's laboratory (Griffin Building, First Floor, Mayo Clinic-Florida, San Pablo Road Jacksonville FL 32224; Telephone 904-953-7291).

14.3 Rationale and Methodology

14.31 Determine the molecular profile predictive of eradication of CLL clone by ibrutinib

Scientific rationale: The current molecular landscape in CLL biology is able to identify patients with high vs. low risk disease in context with standard therapeutics, such as chemoimmunotherapy. However, recent data on ibrutinib seem to demonstrate that the clinical response to ibrutinib is independent of the traditional risk factors such as del(17p). This suggests that molecular markers currently employed may display a differential sensitivity to ibrutinib therapy. Furthermore, certain del(17p) patients upon relapse demonstrate a more aggressive clinical path than other del(17p) patients, hinting at underlying molecular architecture that is directing clinical responsiveness (or lack thereof) to ibrutinib. In this study we expect that ibrutinib treatment of the MRD will result in abrogation of the microenvironmental signaling through the BTK pathway and thus be able to eliminate residual clone. However, we do not expect all patients to be able eradicate MRD with ibrutinib, and this is consistent with the differential clinical response noted in prior studies (21% CR only).

Hypothesis: Therefore, our hypothesis is that it is the primary molecular makeup that directs responsiveness of the malignant clone to BTK inhibition by ibrutinib and that the extent of sensitivity of the clone will be predictive of ability to achieve an MRD-negative disease state.

Methodology & Sample: to address this, we will perform whole genome sequencing and mate-pair DNA sequencing of the malignant clone obtained from patient's blood (2 x 5ml tubes) and / or bone marrow (when available 2 x 5ml tubes). CD19+ cells will be sorted and used for WES. B-CLL cells are known to have two types of mutations: small (site mutations) and large (genomic rearrangements such as translocations, inversions, etc.), and the combination of mate-pair sequencing and WES will enable the detection of both types of lesions. A time series study is ideal for studying clonal evolution, which plays an important role in CLL. This will allow the identification of the sub-clone(s) in the MRD+ patients that were able to survive / eradicate with ibrutinib therapy. The protocol requires to have normal control DNA. This control DNA can be obtained from any one of the samples (which ever is convenient to the patient and preferred by the treating MD). Establishing whether molecular architecture is associated with response or lack of response to ibrutinib therapy will also be attempted by in silico predictive modeling simulation techniques, as previously described (Cellworks Inc.) For this analysis, blinded and de-identified data will be used to derive response from the in silico modeling algorithm. Control: It is important to have controls, which will represent lack of response to ibrutinib (or other anti-CLL therapeutics) to help design in silico algorithms. For this we will collect peripheral blood (2 x 5mL tubes) and/ or bone marrow (when available 2

x 5mL tubes) as well as buccal swab from CLL patients who are not enrolled on trial (and thus not on maintenance therapy for MRD eradication), but who have received ibrutinib with suboptimal clinical response. Possible sources for this DNA identified include either one of the following; 1. buccal swabs, 2. myeloid cells in the marrow (in cases where bone marrow is obtained for clinical reasons) or 3. Skin biopsy (if no other source of germline DNA is available).

Statistical support: WES analysis will be done at Mayo Clinic laboratories, and the data will be analyzed in collaboration with Dr. Asman Yan, PhD.

Sample time: sample will be collected any time prior to starting the ibrutinib therapy and then at time of relapse. Additional samples during treatment will be collected as noted in Table 14.1.

Expected results: This data will help us identify (a) unique molecular patterns of Clone that correlates with highest sensitivity of response to ibrutinib maintenance therapy and achievement of MRD negativity (b) molecular makeup of CLL clone associated with the most expeditious eradication of MRD vs. delayed eradication vs. persistent MRD and (c) molecular profile of the CLL clone associated with the longest durability of MRD negativity and (d) assess for clonal evolution and alteration of molecular profile of the CLL clone post exposure/resistance to ibrutinib therapy.

Clinical implications: these analyses will allow us to determine which patients are exquisitely sensitive to eradication of disease from ibrutinib maintenance therapy and thus will benefit from continued ibrutinib therapy and allow the identification of patients who may harbor a clone that would increase the potential of relapse or development of resistance to ibrutinib maintenance therapy, and thus require more frequent monitoring or perhaps timely use of additional therapeutic(s) to prevent development of ibrutinib resistance.

14.32 **Determine the role of members of the BTK signalosome in eradication of CLL clone by ibrutinib**

Scientific Rationale: It is evident from the clinical data[53,54] that over 70% of the patients will respond to ibrutinib therapy; however, 80% of these "clinically responsive" patients will retain the CLL clone, while approximately 20% will go into CR. This variability in the depth of clinical response may suggest an underlying adaptability of the CLL clone's mediation through components of the BTK signalosome. Woyach et role reported[55] that CLL patients treated with ibrutinib demonstrated upregulation of p-Akt and p-Erk (downstream mediators of BTK) in some (but not all) patients and suggest that these downstream pathways may contribute to the survival of these CLL cells.[56] They also concluded that these cells may not be dependent upon the proximal BTK pathways mediated apoptosis and thus resistant to killing by ibrutinib. While this phenomenon is primarily reported in the displaced CLL cells, we ask the question of whether these pathways play any role in inability to eradicate the disease altogether from the bone marrow?

Hypothesis: Depth of response (i.e., eradication of the MRD) is dependent on the viability of the downstream mediator of the BTK pathway and its response to ibrutinib exposure.

Methodology & Sample: to address this question we will establish the profile of BTK signalosome for each patient through determination of the mRNA (RT-PCR/ nanostring assay) and protein expression (western blot analysis) of members of the BTK signaling pathway. alidation of BTK signaling, and the predictive ability of BTK (and other signaling pathways) for therapy response / or lack of response will be attempted through in silico modeling using a previously published (REF) platform (Cellworks Inc.). For this analysis, blinded and de-identified data will be used to derive response from the in silico modeling algorithm.

Samples: Blood (2 x 5ml green top tubes) and/or bone marrow samples (when available 2 x 5ml green top tubes) will be collected at anytime prior to initiating the ibrutinib therapy. Serial blood samples (first at the time of first documentation of lymphocytosis >5,000cell/mm^3 and then prior to starting cycles 4, 7, and 13 and then at time of relapse) will be collected if patients are noted to have lymphocytosis as a result of ibrutinib therapy. Bone marrow samples will only be collected when the procedure is performed as part of the clinical care of the patient and will follow the bone marrow biopsy and aspirate schedule noted in section 4. Control: It is important to have controls, which will represent lack of response to ibrutinib (or other CLL therapeutics) to help design in silico algorithms. For this we will collect peripheral blood (2 x 5mL tubes) and/ or bone marrow (when available 2 x5mL tubes) as well as buccal swab from CLL patients who are not enrolled on trial (and thus not on maintenance therapy for MRD eradication), but who have received ibrutinib with suboptimal clinical response.

Expected results: We anticipate (a) a variability in the expression and phosphorylation status of various members of the BTK pathway (Syk, Lyn CD79 FYN) and their targets (ERK, AKT, NFKB and Bcl-2, Mcl-1, XIAP, MYC, CD40 and CFLAR) (b) and predict a correlation of this variability with the ability to eradicate the MRD.

14.33 **Determine the contribution of immunomodulatory effects of ibrutinib in eradication of MRD and maintenance of clinical response**

Scientific rationale: our prior investigation of lenalidomide in CLL demonstrated that while lenalidomide was not directly cytotoxic it mediated its anti-CLL effect through activation of an innate (NK cell dependent) coupled by a CD8+ cytotoxic immune response. This resulted in 18% of the patients achieving MRD-negative disease with lenalidomide alone. Thus immune restoration can effectively deliver deeper responses in CLL. Traditional induction regimen incorporates chemoimmunotherapy (such as fludarabine and cyclophosphamide) causing direct insult to host immunity. Interestingly, many patients demonstrate regeneration of T cell enrich lymphocytic nodules in the bone marrow. In cancer redirection of host immunity from a predominant Th2 to Th1 response can deliver antitumor response. Dubovsky et al[57] recently reported in an elegant paper that ibrutinib can bind to ITK (IL-2 inducible kinase). ITK a member of the TEC-kinase family mediate TCR signaling through PLCγ, NFAT, NFκB and MAPK. This results in activation and proliferation of CD8+ cells. We wonder

whether the eradication of MRD in CLL is perhaps *also* dependent upon its immunomodulatory effects.

Hypothesis: Ibrutinib alters the Th2:Th1 balance in the blood and bone marrow microenvironment, skewing towards a more Th1 profile, and this translates into its effects on the MRD. We further hypothesize that the robustness of the Th1 response will direct ibrutinib's depth of response i.e., MRD negativity post-induction.

Method and samples: Blood and/or bone marrow will be evaluated/quantified for Th1 and Th2 cells by flow cytometry. Changes in the cellular profile as well as respective cytokine levels (such as IL2, IL12, INFα and IL4, IL5, IL13 and IL10, respectively) will be measured (for cytokines we will use a multiplex assay). Blood (1 x 5ml green top tubes) and/or bone marrow samples (when available, 1 x 5ml green top tubes) will be collected at anytime prior to initiating the ibrutinib therapy. Serial blood samples (starting at 0 month and then every 3 cycles at time of MRD/clinical response assessment and then at time of relapse) will be collected. Control samples will be collected from CLL patients who are not enrolled on trial (not on maintenance therapy for MRD eradication), but who received ibrutinib and achieved suboptimal clinical response. Peripheral blood (2 x 5mL tubes) and/ or bone marrow (when available 2 x5mL tubes) as well as buccal swabs will be collected. *Note that the bone marrow sample will only be collected when the procedure is being done for clinical reasons* and will follow the bone marrow biopsy and aspirate schedule noted in section 4. Changes in cytokine levels will also be implemented into the in silico predictive simulation modeling algorithm and resulting effect on tumor cell proliferation as well as correlation with response to therapy will be assessed. Expected results: We anticipate that ibrutinib treatment (a) will result in an increase in Th1 cells both in the blood and the bone marrow with bone marrow demonstrating a higher percentage of Th1 cell activity and that (b) extent of immune cellular response will correlate with the robustness of the MRD eradication and that (c) the cytokine profile will mimic this cellular pattern and can be used to predict immune cellular response to ibrutinib.

Clinical relevance: CLL patients have been reported to have immune dysfunction or restoration of host immunity and immune cellular function with drugs such as lenalidomide, but to date there is no approved agent to address this aspect of CLL therapy. Identification / validation of immune restoration ability of ibrutinib and its correlation with disease eradiation in the maintenance setting will be a highly novel observation and will define a unique role and mechanism of ibrutinib in CLL.

14.4 **Clinical relevance of these correlative studies**

1. Identification of patients who are likely to have the maximum benefit from ibrutinib maintenance therapy.
2. Identification of patients who are likely to have a rapidly vs. delayed response to ibrutinib maintenance therapy.
3. Identification of patients who are likely to have a prolonged vs. a short-lived response.

4. Identification of *additional* targets within the BTK pathway that can be exploited concurrently to optimize the response from ibrutinib in eradication of MRD.
5. Identification of molecular landscape associated with CLL clone resistant to ibrutinib therapy.
6. Potential development of biomarkers of clinical response/resistance.

15.0 Drug Information

15.1 Ibrutinib (Imbruvica™, PCI-32765)

15.11 **Background**: Ibrutinib is an antineoplastic agent that is an inhibitor of Bruton's tyrosine kinase.

15.12 **Formulation**: Ibrutinib comes in a capsule: either size 0, gray. 140 mg capsules or size 2, yellow immediate-release 70 mg capsules. The capsules also contain the following compendial excipients: microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate. Capsules are packaged in high-density polyethylene bottles with an induction seal and a child resistant screw-top cap. The number of capsules in each aclar blister pack or per bottle is indicated on the label.

15.13 **Preparation and storage**: All formulations should be stored according to the storage conditions indicated on the label. Ibrutinib capsules: 70 mg and 140 mg

15.14 **Administration:** Administer orally with water at approximately the same time every day. Ibrutinib can be taken with or without food. Swallow capsules whole; do not open, break, or chew the capsules. Ibrutinib should be held at least 3-7 days pre- and post- surgery depending upon the type of surgery and the risk of bleeding. Hazardous agent; use appropriate precautions for handling and disposal.

15.15 **Pharmacokinetic information**:
a) Absorption – Current data indicates bioavailability is low and displays high inter-subject variability. The median time to reach maximum plasma concentration (T_{max}) is approximately 2 hours. Administration of ibrutinib in a fasted condition resulted in approximately 60% of exposure as compared to administration either in fed condition (30 minutes after a high-fat breakfast), or when drug was taken 30 minutes before or 2 hours after a meal. Based on data for the effects of food, ibrutinib could be taken with or without food at approximately the same time each day.
b) Distribution: The plasma protein binding of ibrutinib and its metabolite PCI 45227 in human plasma is 97.3% and 91%, respectively. The apparent steady state volume of distribution is approximately 10,000 L.
c) Metabolism – Ibrutinib is extensively metabolized by CYP3A4/5 (major) and CYP2D6 (minor). The half-life elimination is 4-6 hours. Ibrutinib is metabolized in the liver.

d) Excretion –The excretion of ibrutinib is predominantly via the feces with approximately 80% recovered mostly within 2 days, whereas ~8% is excreted in urine. Approximately 1% of the ibrutinib is recovered as unchanged drug, all in feces. Overall, these PK characteristics resulted in minimal accumulation of both parent compound and metabolite PCI-45227 on repeated daily dosing of ibrutinib.
e) Special populations: a small increase in bioavailability was estimated with increasing age. Exposure is predicted to increase approximately 14% and decrease approximately 20% in subjects of 81 and 49 years of age, compared to a typical 67-year old subject. No statistically significant effects were observed for the other covariates tested, i.e., sex, race, mild and moderate renal impairment, mild hepatic impairment and B-cell histology. The recommended doses for patients with mild and moderate liver impairment are 280 mg/day and 140 mg/day (Child-Pugh Class A and B, respectively). It is not recommended to administer ibrutinib to subjects with severe hepatic impairment (Child-Pugh Class C).

15.16 **Potential Drug Interactions**: Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A4/5. Voriconazole and posaconazole can be used concomitantly with ibrutinib as per the dosing guidance described in the specific clinical study protocol. All other strong inhibitors of CYP3A (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone, and cobicistat) should be avoided, and an alternative with less CYP3A inhibitory potential should be considered. If the benefit outweighs the risk and a strong CYP3A inhibitor must be used, see the recommended dose modifications described in the specific clinical study protocol.

If a moderate CYP3A inhibitor (eg, fluconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib, verapamil, amiodarone, dronedarone) is indicated in patients with B-cell malignancies, reduce the ibrutinib dose to 280 mg for the duration of the inhibitor use or as per recommended dose modifications described in the specific clinical study protocol. No ibrutinib dose modifications for moderate inhibitors are required in patients with cGVHD dosed with ibrutinib 420 mg.

No dose adjustment is required in combination with mild inhibitors. Monitor patient closely for toxicity and follow dose modification guidance as needed. Avoid grapefruit and Seville oranges during ibrutinib treatment as these contain moderate inhibitors of CYP3A.

Administration of ibrutinib with strong inducers of CYP3A decreases ibrutinib plasma concentrations by up to 90%. Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin and St. John's Wort). Consider alternative agents with less CYP3A induction.

To minimize the potential for an interaction in the GI tract, narrow therapeutic range P-gp or BCRP substrates such as digoxin or methotrexate should be taken at least 6 hours before or after ibrutinib.

Ibrutinib may also inhibit BCRP systemically and increase the exposure of drugs that undergo BCRP-mediated hepatic efflux, such as rosuvastatin.

There have been reports of bleeding-related events in subjects treated with ibrutinib. Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib unless specified in the protocol. Supplements such as fish oil and vitamin E preparations should be avoided.

15.17 **Known potential toxicities**:

- Common(1 to <10%: febrile neutropenia, atrial fibrillation diarrhea, pyrexia, pneumonia,
- Uncommon/Rare (<1%):, leukocytosis, thrombocytopenia, l, vision blurred, stomatitis, gastritis, asthenia, bronchitis, lung infection, sinusitis, urinary tract infection, neutrophil count decreased, platelet count decreased, dehydration, hyperuricemia, myalgia, extremity pain, dizziness, hematuria, epistaxis, erythematous rash, maculo-papular rash, hematoma, hypertension, cellulitis, infection, lower respiratory tract infection, sepsis, skin infection, arthritis, bone pain, flank pain, basil cell carcinoma, squamous cell carcinoma, syncope, acute kidney injury, pleural effusion, respiratory failure, macular rash, hypotension, respiratory tract infection, leukostasis syndrome, pancytopenia, atrial flutter, cardiac failure, myocardial infarction, colitis, intestinal obstruction, oral mucosal blistering, systemic inflammatory response syndrome, atypical pneumonia, bacteremia, infectious enterocolitis, neutropenic sepsis, periorbital cellulitis, pneumonia (pneumocystis jirovecii, bacterial, cryptococcal, fungal, haemophilus, influenzal, viral, pseudomonal klebsiella, legionella, parainfluenzae viral, streptococcal, organising), septic shock, urosepsis, post procedural hemorrhage, subdural hematoma, tumor lysis syndrome, pain (pelvic, groin), hemorrhage intracranial, lung infiltration, pneumonitis, pustular rash, breast cellulitis, bronchopulmonary aspergillosis, Escherichia sepsis, viral lower respiratory tract infection, pneumococcal sepsis, fungal sinusitis, staphylococcal infection, staphylococcal skin infection, interstitial lung disease, angioedema, hypertensive crisis , chronic sinusitis bacteroides bacteremia, orbital cellulitis, staphylococcal cellulitis, Escherichia bacteremia, alveolitis allergic, Stevens-Johnson syndrome, Haemophilus bacteremia/sepsis, pseudomonal lung infection, bacterial sepsis, herpes zoster disseminated, muscle hemorrhage, cerebral hemorrhage, deep vein thrombosis, squamous cell carcinoma of the skin, basosquamous carcinoma of the skin, hepatic failure, ventricular tachyarrhythmia
- Cardiac Arrhythmias: Atrial fibrillation, atrial flutter, and cases of ventricular tachyarrhythmia including some fatal events, have been reported in subjects treated with ibrutinib,

particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmia. Periodically monitor subjects clinically for cardiac arrhythmia. Subjects who develop arrhythmic symptoms (eg, palpitations, lightheadedness, syncope, chest discomfort or new onset of dyspnea) should be evaluated clinically, and if indicated, have an ECG performed. For cardiac arrhythmias which persist, consider the risks and benefits of ibrutinib treatment, and follow the dose modification guidelines

- **Cerebrovascular accidents:** Cases of cerebrovascular accident, transient ischemic attack, and ischemic stroke including fatalities have been reported with the use of ibrutinib in the post-marketing setting, with and without concomitant atrial fibrillation and/or hypertension. Regular monitoring and appropriate treatment of conditions that can contribute to the occurrence of these events is recommended.
- Cutaneous vasculitis has been identified as a new adverse reaction in the postmarketing setting

Please refer to the prescribing information or Investigator's Brochure for a more complete comprehensive list of treatment-emergent adverse events.

15.18 **Drug procurement:** Drug will be provided free of charge to study participants by Pharmacyclics, Inc.

15.19 **Nursing Guidelines:**

- There are numerous drug to drug interactions. Record all of patient's medications including OTC, and herbal use. Avoid concomitant use with agents as listed in section 15.16.
- Patients should be instructed to avoid eating grapefruit (including juice) and Seville oranges while on ibrutinib.
- Peripheral edema is common. Instruct patients to report this to the study team.
- Gastrointestinal side effects are common (diarrhea, nausea, constipation, abdominal pain, vomiting, etc). Treat symptomatically and monitor for effectiveness of intervention.
- Monitor CBC w/diff. Instruct patients in energy conserving lifestyle (anemia) and to report any unusual bruising or bleeding and/or signs or symptoms of infection to study team.
- Arthralgias, Myalgias, and muscle spasm can be seen. Treat symptomatically and monitor for effectiveness.
- Monitor renal function/uric acid levels, especially in patients who may be experiencing dehydration.
- Respiratory symptoms may include, cough, SOB, and URI. Instruct patients to report these symptoms to the study team.
- Rarely patients can experience secondary skin cancers. Instruct patients to report any new skin lesions to the study team.
- Rash can be seen. Instruct patient to report to study team.
- Cardiac arrhythmias have been seen with this agent including a-fib, atrial flutter and ventricular tachyarrhythmia's, some of which have led to death.

Instruct patients who experience any palpitations, lightheadedness, syncope, or SOB to see medical care immediately. This is especially important in patients who have pre-existing cardiac issues.

- Warn patients of the risk of bleeding. Patients should not take warfarin or other vitamin K antagonists while on ibrutinib, unless the protocol allows for it. Additionally, patients should be cautioned to avoid fish oil and Vitamin E supplements.
- Patients who are concurrently on ibrutinib and ventoclax should be monitored closely for excess toxicity.

16.0 Statistical Considerations and Methodology

16.1 Overview:

This is a Phase II study designed to assess the eradication of minimal residual disease (MRD) as well as the toxicity associated with ibrutinib used as maintenance therapy in CLL patients who achieve a PR, nPR, CCR, CRi, or CR post-induction therapy but who have residual disease (i.e. MRD positive).

16.11 Primary Endpoint:

The primary endpoint of this trial is the rate of confirmed MRD-negative response at any time during treatment with ibrutinib maintenance. A confirmed MRD-negative response is defined as an achievement of MRD-negative status in both the blood and the bone marrow on two consecutive evaluations at least three months apart. Confirmed MRD-negative response will be evaluated using all cycles of treatment. Throughout Section 16.0, confirmed MRD-negative response will be considered synonymous with "success" unless specified otherwise. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for confirmed MRD-negative response, with the exception of patients who are determined to be a major treatment schedule violation.

16.2 Statistical Design:

16.21 Decision Rule:

Prior clinical investigations have evaluated eradication of the MRD with consolidation treatment post induction therapy and these suggest the importance of MRD eradication after first-line therapy. None of these studies have investigated primary maintenance after first-line induction treatment. Two ongoing studies (mentioned in the introduction) have been initiated, but no data is available. Therefore, any indication of benefit with ibrutinib maintenance therapy will be considered promising.

The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 5%, representing a response by chance alone. The smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 20%. The following one-stage binomial design uses 32 evaluable patients to test the null

hypothesis that the true success proportion in a given patient population is at most 5%.

16.211 Final Decision Rule: Enter 32 evaluable patients into the study. If 3 or fewer successes are observed in the first 32 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. Otherwise, if the number of successes is at least 4, this will be considered evidence of promising activity and the treatment may be recommended for further testing in subsequent studies.

16.212 Over Accrual: If more than the target number of patients are accrued, then the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section 16.34.

16.22 Sample Size:
The phase II study design to be used is fully described in section 16.21. A maximum of 32 evaluable patients will be accrued onto this phase II study unless undue toxicity is encountered. We anticipate accruing an additional 3 patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Maximum projected accrual is 35 patients.

16.23 Accrual Rate and Study Duration: The anticipated accrual rate is approximately 1-2 patients per month. Therefore, the accrual period for this phase II study is expected to be about 2 years. The final analysis can begin approximately 2.5 years after the trial begins, i.e. as soon as the final patient accrued to this trial has been followed for at least 6 months.

16.24 Power and Significance Level: Assuming that the number of responses is binomially distributed, with a significance level of 7%, the probability of declaring that the regimen warrants further studies (i.e., statistical power) can be tabulated as a function of the true success proportion as shown in the table below.

If the true success proportion is…	0.05	0.10	0.15	0.20
Then the probability of declaring that the regimen is promising and warrants further study is…	0.07	0.40	0.73	0.91

16.25 Other Considerations: Toxicity, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.3 Analysis Plan:

The analysis for this trial will commence at planned time points (see 16.2) and at the time the patients have become evaluable for the primary endpoint. Such a decision will be made by the Statistician and Study Chair in accordance with CCS Standard Operating Procedures, availability of data for secondary endpoints (e.g., laboratory correlates), and the level of data maturity. It is anticipated that the earliest date in which the results will

be made available via manuscript, abstract, or presentation format is when the last patient has been followed for at least 6 months.

16.31 Primary Endpoint:

16.311 Definition: The primary endpoint of this trial is the rate of confirmed MRD-negative response. A confirmed MRD-negative response is defined as an achievement of MRD-negative status in both the blood and the bone marrow on two consecutive evaluations at least 3 months apart. Confirmed MRD-negative response will be evaluated using all cycles of treatment. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response, with the exception of patients who are determined to be a major treatment schedule violation.

16.312 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Ninety-five percent exact binomial confidence intervals for the true success proportion will be calculated.

16.32 Secondary Endpoint:

16.321 Duration of MRD-negative response is defined in patients who have achieved a confirmed MRD-negative response as the time from the earliest date that the patient was noted as having MRD-negative response in both the blood and bone marrow until the first notation of MRD positive disease in the blood or the bone marrow. The distribution of duration of MRD-negative response will be estimated using the method of Kaplan-Meier.[58]

16.322 Time to MRD-negative response is defined in patients who have achieved a confirmed MRD-negative response as the time from the date of registration to the earliest date that the patient was noted as having MRD-negative response in both the blood and bone marrow. Time to MRD-negative response will be summarized descriptively (median, range).

16.323 Time to requirement of next therapy: A landmark analysis will be conducted to evaluate time to requirement of next therapy for patients who achieve a confirmed MRD-negative response in both the blood and bone marrow vs. those who remain MRD-positive, as assessed at 48 weeks (end of 12 cycles; +/- 4 weeks). Patients who discontinue treatment before 48 weeks are excluded from this analysis. Time to requirement of next therapy will be defined as the time from the 48 week MRD evaluation until the time of initiation of subsequent treatment for progressive CLL. The distribution of time to requirement of next therapy will be estimated using the Kaplan-Meier method and log-rank statistics will be utilized to evaluate differences between the two groups.

16.324 Progression-free survival: A landmark analysis will be conducted to evaluate progression-free survival for patients who achieve a confirmed

MRD-negative response in both the blood and bone marrow vs. those who remain MRD-positive, as assessed at 48 weeks (end of 12 cycles; +/- 4 weeks). Patients who discontinue treatment before 48 weeks are excluded from this analysis. Progression-free survival will be defined as the time from the 48 week MRD evaluation until the time of disease progression per the IWCLL criteria or death due to any cause. The distribution of progression-free survival will be estimated using the Kaplan-Meier method and log-rank statistics will be utilized to evaluate differences between the two groups.

16.325 Adverse Events: Platelets and hemoglobin will be graded according to the Grading Scale for Hematologic Adverse Events in CLL Studies in Appendix V. The maximum grade for each type of adverse event, regardless of causality, will be recorded and reported for each patient, and frequency tables will be reviewed to determine adverse event patterns. Adverse events will continue to be recorded and reported up to 30 days after the last day of study drug treatment.

16.33 Correlative Analyses. The reports on the correlative will be descriptive as they are exploratory in nature.

16.332 Study of the impact of ibrutinib treatment on mood is exploratory in nature. Reports of these correlative analyses will be descriptive.

16.34 Over Accrual: If more than the target number of patients are accrued, then the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence intervals.

16.35 Data & Safety Monitoring

16.351 The principal investigator(s) and the study statistician will review the study at least every quarter to identify accrual, adverse events, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.352 Adverse Event Stopping Rule: The stopping rule specified below is based on the knowledge available at study development. We note that the rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatments under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (e.g., an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy either of the following:

- If 3 or more of the first 12 treated patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

- If after the first 12 patients have been treated, 25% of all patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related," to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.4 Results Reporting on ClinicalTrials.gov

At study activation, this study will have been registered within the "ClincialTrials.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 2.5 years after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time the last patient registered has been followed for at least 6 months.

16.5 Inclusion of Women and Minorities

16.51 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.52 There is no information currently available regarding differential effects of this regimen in subsets defined by race or gender, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.53 The geographical region served by Mayo Clinic has a population that includes approximately 3% minorities. Based on prior Mayo Clinic studies involving similar disease sites, we expect about 3-5% of patients will be classified as minorities by race, and about 30% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	1	1
Not Hispanic or Latino	11	23	34
Ethnic Category: Total of all subjects	11	24	35
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	1	1	2
Native Hawaiian or other Pacific Islander	0	0	0
White	10	23	33
Racial Category: Total of all subjects	11	24	35

Ethnic Categories:

Hispanic or Latino - a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native - a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian - a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American - a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander - a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White - a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens:

17.1 Summary Table of Research Tissue Specimens to be Collected for this Protocol

Correlative Study (Section for more information)	Mandatory or Optional	Type of Tissue to Collect	Block, Slides, Core, etc. (# of each to submit)	**Visit 1:** Baseline only	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Control DNA	Mandatory	Patient must be willing to provide one of the following samples:				
		Saliva/buccal swab from oral cavity	NA	X	No	Ambient
		Skin biopsy (only if buccal swab is not able to deliver adequate DNA)	3mm punch biopsy	X	yes	Ambient
		Myeloid cells from the bone marrow (only if buccal swab is not able to deliver adequate DNA and a bone marrow is done as part of routine standard clinical test)	aspirate	X	yes	Ambient

17.2 Correlative Tissue Collection

17.21 Standard 3mm skin biopsy tissue. Kits will not be provided for this protocol.

17.22 Oral buccal swab for normal DNA sample

17.221 The oragene kit will be used for collection saliva/buccal swab.

If slides will be submitted, include thickness of tissue, and type of slide (charged or uncharged). Do not coverslip unstained slides.

17.222 Sample can be shipped overnight at ambient temperature

17.223 samples will be shipped to DR. Chanan-Khan's laboratory in Griffin Building 4500 San Pablo Rd. Jacksonville FL 32224

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
On-Study	≤2 weeks after registration
Adverse Event - Baseline	
Measurement - Baseline	
Research Blood Submission - Baseline (See section 14.0)	
Research Bone Marrow Aspirate Submission - Baseline (See section 14.0)	
Bone Marrow Biopsy	
FISH Results - Baseline	
Quantitative Flow Cytometry	
Pre-induction and pre-registration immunophenotyping/pre-registration MRD reports including CD38 and ZAP-70[1, 2]	
IgVH Mutation Analysis Report[1]	
Other Laboratory Results	
CLL FISH Report[1]	
Bone Marrow Biopsy Report[1]	
CT Scan Report[1]	
Research Tissue Submission - Baseline	
Psychology and QOL Assessments - Baseline	
End of Active Treatment/Cancel Notification	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy

1. Submit copy of the report, Attention: QAS for MC1481, Fax (507) 284-1902.
2. For patients who previously had full flow immunophenotyping performed and at pre-study workup had limited repeat flow immunophenotyping, submit a copy of both reports.

Test Schedule Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation
Evaluation/Treatment	X[2]	X	
Evaluation/Observation			X[1]
Nadir/Adverse Event	X	X	X
Measurement	X	X	X
Quantitative Flow Cytometry	X[4]	X	X
Research Blood Submission	X[4] (see Section 14.0)	X	
Research Bone Marrow Aspirate Submission	X[4] (see Section 14.0)	X	
Bone Marrow Biopsy	X[4]	X[4]	X[4]
Other Laboratory Results	X	X	X
Immunophenotyping/MRD Report[3]	X[4]	X[4]	
Bone Marrow Biopsy Report[3]	X[4]	X[4]	
CT Scan Report[3]	X[4]	X[4]	
Psychology and QOL Assessments	X[4]	X[4]	
End of Active Treatment/Cancel Notification		X	
ADR/AER	At each occurrence (see Section 10.0)		

1. Complete at each evaluation during Observation (see Section 4.0).
2. Complete at each evaluation during Active Treatment (see Section 4.0).
3. Submit copy of the report, Attention: QAS for MC1481, Fax (507) 284-1902.
4. Complete when required per the test schedule.

Follow-up Material(s)

	Event Monitoring Phase[1]				
CRF	q. 3 months until PD or subsequent treatment for CLL[2]	At PD or subsequent treatment for CLL[2]	q. 6 mos. after PD or subsequent treatment for CLL	Death	New Primary
Event Monitoring	X	X	X	X	At each occurrence

1. If a patient is still alive 5 years after registration, no further follow-up is required.
2. Submit copy of documentation of progression to the Operations Office, Attention: QAS for MC1481, Fax (507) 284-1902.

19.0 Budget

19.1 Costs charged to patient: All routine clinical care. Ibrutinib will be provided free of charge by Pharmacyclics.

19.2 Tests to be research funded: Correlative studies outlined in Sections 14.0.

19.3 Other budget concerns: Protocol administration, study coordinator time, data management, and statistical analysis efforts will be funded by Pharmacyclics.

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Appendix I Eastern Cooperative Oncology Group (ECOG) Performance Scale

ECOG Performance Status Scale	
Grade	***Descriptions***
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix II Rai Staging System for CLL

Modified 3-stage System	Rai Stage	Clinical Features
Low Risk	0	Lymphocytes (L) in blood > 5000/mm^3 and marrow > 30% only
Intermediate Risk	I II	L+ enlarged lymph nodes (LN) L + spleen and/or liver (LN + or -)
High Risk	III IV	L + anemia (Hb < 11 g/dl) L + Thrombocytopenia < 100,000/µl.

Subjects in the intermediate risk group must have evidence of active disease as demonstrated by at least one of the following criteria:

Massive or progressive splenomegaly and/or lymphadenopathy; (Massive splenomegaly is here defined by spleen tip > 6 cm below costal margin.)

Presence of weight loss > 10% over the preceding 6 month period;

Grade 2 or 3 fatigue;

Fevers > 100.5°F or night sweats for longer than 2 weeks without evidence of infection;

Progressive lymphocytosis with an increase of > 50% over a 2-month period or an anticipated doubling time of less than 6 months;

Worsening anemia or thrombocytopenia.

Appendix III Criteria for Diagnosis of Disease

Specific diagnosis of B-Cell CLL meeting the following criteria at any time during the course of disease (e.g., at initial diagnosis, at relapse, etc.):

- An absolute lymphocytosis of > 5,000/mm^3.
- Morphologically, the lymphocytes must appear mature with < 55% prolymphocytes by manual differential.
- The aspirate smear must show > 30% of nucleated cells to be lymphoid or the bone marrow core biopsy must show lymphoid infiltrates compatible with marrow involvement by CLL. The overall cellularity must be normocellular or hypercellular.
- Local institution lymphocyte immunophenotype must reveal a predominant B-cell monoclonal population sharing a B-cell marker (CD19, CD20, CD23, CD24) with the CD5 antigen in the absence of other pan-T-cell markers. While the absence of CD23 expression will not exclude subjects, it should prompt close re-examination of the lymphocyte morphology to exclude the diagnosis of mantle cell lymphoma in the leukemic phase.

Appendix IV Definition of Symptomatic B-Cell

Active disease should be clearly documented for protocol therapy. At least one of the following criteria should be met:

Evidence of progressive marrow failure as manifested by the development of or worsening of anemia (Hb < 11.0 g/dL) and/or thrombocytopenia (Platelets < 100 x 10^9)

Massive (e.g., at least 6 cm below the left costal margin) or progressive or symptomatic splenomegaly

Massive nodes (e.g., at least 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy

Progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time (LDT) of less than 6 months. LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In patients with initial blood lymphocyte counts of less than 30 x 10^9/L (30 000/μL), LDT should not be used as a single parameter to define a treatment indication. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (e.g., infections) should be excluded.

Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy.

Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs:

Unintentional weight loss of 10% or more within the previous 6 months;

significant fatigue (e.g., inability to work or perform usual activities);

fevers higher than 100.5°F or 38.0°C for 2 or more weeks without other evidence of infection; or

night sweats for more than 1 month without evidence of infection.

Appendix V Grading Scale for Hematologic Toxicity in CLL Studies

Non Hematologic Toxicity will be scored using NCI CTCAE (version 4.0) for toxicity and adverse event reporting.

Hematologic toxicity will be assessed using IWCLL/Hallek December 2008[6]

Grading scale for hematologic toxicity in CLL studies

Grade*	Decrease in platelets† or Hb‡ (nadir) from pretreatment value, %	Absolute neutrophil count/µL§ (nadir)
0	No change to 10%	≥ 2000
1	11%-24%	≥ 1500 and < 2000
2	25%-49%	≥ 1000 and < 1500
3	50%-74%	≥ 500 and < 1000
4	≥ 75%	< 500

* Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be recorded as grade 5.

†Platelet counts must be below normal levels for grades 1 to 4. If, the platelet count is < 20 x 10^9/L (20 000/µL) at any level of decrease, this will be considered grade 4 toxicity unless a severe or life-threatening decrease in the initial platelet count (eg, 20 x 10^9/L [20 000/µL]) was present pretreatment. In this case, the patient will not be evaluable for toxicity referable to platelet counts.

‡Hb levels must be below normal levels for grades 1 to 4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity but should be documented.

§If the absolute neutrophil count (ANC) reaches < 1 x 10^9/L (1000/µL), it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count or in circulating neutrophils are not to be considered because a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was < 1 x 10^9/L (1000/µL) before therapy, then the patient will not be evaluable for toxicity referable to the ANC. The use of growth factors such as G-CSF is not relevant to the grading of toxicity but should be documented.

Appendix VI – Medication Diary

Patient Instructions

- Please indicate on the calendar below *every* day that you take your study medication by placing the dose taken on the line under the date.
- If you miss a dose, place a check "**0**" under the date, but remember to take your prescribed dose at the next regularly scheduled time.
- Bring ***all*** bottles and any unused study medication along with this diary when you return for your next appointment.

Medication(s)	Dose
Ibrutinib	420 mg

Study Drug	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Date							
Ibrutinib							

Study Drug	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**
Date							
Ibrutinib							

Study Drug	**Day 15**	**Day 16**	**Day 17**	**Day 18**	**Day 19**	**Day 20**	**Day 21**
Date							
Ibrutinib							

Study Drug	**Day 22**	**Day 23**	**Day 24**	**Day 25**	**Day 26**	**Day 27**	**Day 28**
Date							
Ibrutinib							

Date:_____ Participants Signature_____

Area Below Only To Be Completed only by Coordinator

Number of pills returned_____ Study Coordinator Initials_____

Date_____ Discrepancy Yes____ No_____

Appendix VII – Child-Pugh Score

Measure	1 point	2 points	3 points
Total bilirubin, µmol/L (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/L (g/dL)	>35 (>3.5)	28-35 (2.8-3.5)	<28 (<2.8)
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	Class
5-6	A
7-9	B
10-15	C

Source:

1. Child CG, Turcotte JG. “Surgery and portal hypertension”. In Child CG. *The liver and portal hypertension.* Philadelphia:Saunders. 1964. pp. 50-64.
2. Pugh RN, Murray-Lyon IM, Dawson L, Pietroni MC, Williams R . “Transection of te oesophagus for bleeding oesophageal varices”. *The British journal of surgery*, 1973;60: 646-9.

Appendix VIII – Patient Health Questionaire 8

MAYO CLINIC

TO BE SCANNED

Patient Health Questionnaire

This form collects information that is part of the medical record. **Route to Scanning.**

Number (above) and Name

Instructions: Over the last 2 weeks, how often have you been bothered by any of the following problems? (use "√" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
add columns:		+	+	

(HBBithcare professional: For Interpretation of TOTAL, please refer to accompanying scoring card.

TOTAL:

9. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?	☐ **Not difficult at all** ☐ **Somewhat difficult** ☐ **Very difficult** ☐ **Extremely difficult**

This form is adapted from PHQ-9, developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an education grant from Pfizer Inc.

Patient Signature	Date *(Month DD, YYYY)*	Time

Official Use Only	
Unique	PPQ

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MCJ7227-01

Appendix IX – Generalized Anxiety Disorder 7-item (GAD-7) scale

Generalized Anxiety Disorder 7-item (GAD-7) scale

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Add the score for each column	+	+	+	
Total Score *(add your column scores)* =				

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all _____
Somewhat difficult _____
Very difficult _____
Extremely difficult _____

Source: Spitzer RL, Kroenke K, Williams JBW, Lowe B. A brief measure for assessing generalized anxiety disorder. *Arch Inern Med.* 2006;166:1092-1097.

Appendix X – Medical Outcomes Study: Social Support Survey (MOS-SSS)

The following 4 questions are from the Medical Outcomes Study: Social Support Survey (MOS-SSS). (Questions correspond to variable IDs [MOSSSS_Q01] through [MOSSSS_Q04])

These questions are modified from the MOS-SSS. Any and all copyrights in these questions vest in RAND. RAND reserves all rights. © 1994-2014 RAND Corporation.

People sometimes look to others for companionship, assistance, or other types of support. How often is each of the following kinds of support available to you if you need it? Select one answer on each line

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
Someone to share your most private worries and fears with	○	○	○	○	○
Someone to turn to for suggestions about how to deal with a personal problem	○	○	○	○	○
Someone to do something enjoyable with	○	○	○	○	○
Someone to love and make you feel wanted	○	○	○	○	○

Appendix XI – Linear Analogue Self-Assessment

LINEAR ANALOGUE SELF ASSESSMENT

Patient Name: _____ Date: _____
Patient Number: _____

Directions: Please circle the number (0-10) best reflecting your response to the following that describes your feelings **during the past week, including today**.
How would you describe:

1. your overall Quality of Life?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

2. your overall mental (intellectual) well being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

3. your overall physical well being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

4. your overall emotional well being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

5. your level of social activity?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

6. your overall spiritual well being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

Appendix XII – Clinical Response Criteria

Clinical Response Definitions:
The International Working Group criteria (IWCLL)[6] will be used to assess response to therapy.

A. COMPLETE RESPONSE (CR) requires all of the following for a period of at least 2 months.

1. Absence of lymphadenopathy (e.g. lymph nodes >1.5 cm) by physical examination.

2. No hepatomegaly or splenomegaly by physical examination.

3. Absence of constitutional symptoms.

4. CBC demonstrating:
   - Neutrophils >1500/ul.
   - Platelets >100,000/ul (without transfusion).
   - Hemoglobin >11.0 gm/dl (without transfusion).
   - Peripheral blood lymphocytes <4000/uL.

   Note: Patients who fulfill all criteria for a CR but who have a persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity rather than residual CLL will be classified as **CR with incomplete marrow recovery (CRi)** according to the international criteria.[6]

5. Bone marrow aspirate and biopsy should be performed **within two months** after documentation of clinical and laboratory evidence of a complete response to document that a **complete response (CR)** has been achieved as per standard practice based upon IWCLL. The marrow sample should ideally be at least normocellular with <30% of nucleated cells being lymphocytes. Samples are to be analyzed by a pathologist and the presence or absence of nodules noted. Repeat bone marrow aspirate and biopsy are not necessary to document sustained CR.

   NOTE: Patients who fulfill all criteria for a CR but who have hypocellular marrow will be classified as a CR with incomplete marrow recovery (CRi).

   In a subset of patients who are otherwise in a complete response, bone marrow nodules can be identified histologically. In such cases, special stains will be performed to determine whether such nodules represent "regenerative nodules" or residual "clonal nodules". The presence of regenerative nodules is consistent with CR while the presence of residual clonal nodules will be classified as an **nPR (nodular PR)** which is a sub-classification of PR. Per the PR criteria, patients must fulfill one or more of the blood count

parameters (Section 11.224, 11.225, 11.226) but are not required to meet all 3 of these conditions.

Note: In a patient who achieves clinical and laboratory evidence of a complete response, the objective status should be recorded as a CCR on the cycle where the formal response evaluation occurred until a bone marrow biopsy and aspirate have been performed. At that time, the objective status should be amended to classify the patient as a CR, CRi, or nPR **on the cycle where the formal response evaluation occurred**.

6. Patients who have clinical and laboratory evidence of CR but who have not yet had a bone marrow biopsy to distinguish between CR and nPR will be classified as having a **Complete Clinical Response (CCR)** until the marrow biopsy is obtained. Patients must meet all of the blood count parameters listed in section 11.214.

7. In some settings MRD assays may be considered as a surrogate of response as discussed in section 11.3. No other laboratory assays (e.g., quantitative immunoglobulins) will be used currently as an index for response but will be recorded for clinical correlations.

8. For patients whose only measurable disease at the time of enrollment is on CT scan, a CT scan showing absence of lymphadenopathy (e.g. lymph nodes >1.5 cm) is required before classifying patients a CR.

B. PARTIAL RESPONSE (PR) requires the patient exhibits at least two of the features in Sections 11.221, 11.222, and 11.223 below (if abnormal prior to therapy) as well as one or more of the remaining features (Sections 11.224, 11.225, 11.226) for at least 2 months. In addition to the parameters listed below, the presence or absence of constitutional symptoms will be recorded.

1. ≥ 50% decrease in peripheral blood lymphocyte count from the pretreatment baseline value. Note: This criteria will not be applicable if patients are experiencing ibrutinib associated lymphocytosis as noted above in section 11.0. (LRF workshop)[52]

2. ≥ 50% reduction in the sum of the products of the maximal perpendicular diameters of the largest measured node or nodal masses in the right and left cervical, axillary, and inguinal lymph node regions on physical examination.

3. ≥ 50% reduction in size of liver and/or spleen as measured by physical exam noting the maximal distance below the respective costal margins of palpable hepatosplenomegaly during rest.

4. Neutrophils >1500/ul or 50% improvement over baseline.

5. Platelets >100,000/ul or 50% increase over baseline.

6. Hemoglobin >11.0 gm/dl or 50% increase over baseline without transfusions.

7. For patients whose only measurable disease at the time of enrollment is on CT scan, a CT scan demonstrating > 50% reduction of target nodes enlarged at baseline is required before classifying patients a PR.

C. PROGRESSION (PD): Patients will continue to receive protocol therapy unless they have evidence of disease progression according to the IWCLL criteria[6] as evidenced by:

1. ≥ 50% increase in the sum of the products of at least 2 lymph nodes on 2 consecutive determinations 2 weeks apart (at least one node must be ≥2 cm) that persist for > 3 months or the appearance of new palpable lymph nodes >1.5 cm not due to a tumor flare. Enlargements or the appearance of new nodes due to a tumor flare do NOT qualify as progression.

2. ≥ 50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin on 2 consecutive determinations 2 weeks apart and with a minimum of a ≥ 2 cm increase in size from baseline; or appearance of hepatomegaly or splenomegaly which was not previously present at baseline and not due to a tumor flare.

3. Transformation to a more aggressive histology (e.g. Richter's transformation).

   Note: If a patient develops DLBCL at any time, it will be considered disease progression. If the patient develops any other hematologic malignancy while on study, it will not be considered progressive disease.

4. ≥ 50% increase in the absolute number of circulating lymphocytes NOT due to infection, tumor flare or drug-associated lymphocytosis (taking as reference for progressive disease the smallest absolute lymphocyte count recorded since the treatment started). The absolute lymphocyte count must be at least 5000/mm^3 to qualify as disease progression.

5. In the absence of progression as defined by 1, 2, 3, or 4 above, the presence of a ≥ 2 g/dl decrease in HGB, or ≥ 50% decrease in platelet count or absolute neutrophil count will NOT exclude a patient from continuing the study. Work-up of such decreases to exclude auto-immune hemolytic anemia, pure red cell aplasia, or idiopathic thrombocytopenic purpura (ITP) should be considered.

6. For patients who achieve a CR or nodular PR, progression will be defined as recurrence of circulating leukemia cell clone and an ALC >5000 or recurrence of adenopathy >1.5 cm not due to a tumor flare.

D. Not PD: The patient was evaluated for progression only in this cycle and a formal response evaluation did not occur. The patient did not meet the criteria for progression per section 11.23.

Note: Formal response evaluation should occur every 2 cycles during treatment, with the first response evaluation occurring at the end of cycle 2. Formal response evaluation should occur every cycle during observation. Objective status should be classified as PD vs. Not PD on cycles when a formal response evaluation does not occur.

E. Summary Definition of objective response for patients with B-CLL

	CCR[1]	CR[2]	CRi[3]	nPR[4]	PR5	PD6
PHYSICAL EXAMINATION						
Nodes[7]	None	None	None	None	≥50% ↓	≥50% ↑, new nodes
Liver/spleen[8]	Not palpable	Not palpable	Not palpable	Not palpable	≥50% ↓	≥50% ↑, newly palpable
Symptoms	None	None	None	None	N/A	N/A
PERIPHERAL BLOOD						
ANC	>1500/µL	>1500/µL	See footnote 3	>1500/µL or >50% improvement from baseline	>1500/µL or >50% improvement from baseline	See footnote 6
Platelets	>100,000/µL	>100,000/µL	See footnote 3	>100,000/µL or >50% improvement from baseline	>100,00/µL or >50% improvement from baseline	See footnote 6
Hemoglobin	>11.0 g/dL without transfusion	>11.0 g/dL without transfusion	See footnote 3	>11.0 g/dL or >50% improvement from baseline without transfusion	>11.0 g/dL or >50% improvement from baseline without transfusion	See footnote 6
Lymphocytes	<4000/µL	<4000/µL	<4000/µL	<4000/µL	≥50% ↓	≥50% ↑ to at least 5,000/µL
BONE MARROW	N/A	Normocellular[3]; <30% lymphocytes; no nodules	<30% lymphocytes; no nodules	<30% lymphocytes; bone marrow nodules[4]	N/A	N/A

1. Clinical complete response (CCR) requires fulfillment of all physical exam and peripheral blood criteria as noted in the table above. No bone marrow biopsy is required to call a patient a CCR; however, patients should have a bone marrow analysis performed within two month of the formal response evaluation where clinical and laboratory evidence of complete response was first seen as instructed in the test schedule to confirm CR as per standard guidelines by the IWCLL.
2. Complete response (CR) requires fulfillment of all physical exam and peripheral blood criteria for a duration of ≥2 months. A bone marrow aspirate and biopsy are required to document the response as a complete within two month of the formal response evaluation where clinical and laboratory evidence of complete response was first seen (see Section 11.21).

3. Patients who fulfill all criteria for a CR but who have a persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity rather than residual CLL or have hypocellular marrow will be classified as CR with incomplete marrow recovery (CRi).
4. Nodular partial response (nPR) is essentially a patient who appeared to have a CR but nodules were present in the bone marrow. It requires fulfillment of all physical exam and lymphocyte criteria for CR; however, when the bone marrow is done to confirm CR, nodules of malignant lymphocytes are found. Patients must fulfill one or more of the blood count parameters (ANC, Platelets, Hemoglobin) but are not required to meet all 3 of these conditions. See Section 11.215 regarding the distinction between clonal and regenerative nodules.
5. Partial response (PR) requires fulfillment of at least two of the above-noted decrease in circulating lymphocytes, regression in adenopathy and regression in hepatosplenomegaly, and at least one other parameter listed above for a duration of ≥ 2 months. See Section 11.22.
6. Progression: Fulfilling the criteria as noted in section 11.23. Prior to the formal response evaluation, baseline on study measurements will be used to determine disease progression (e.g. not cycle by cycle comparisons). Once patients undergo formal response evaluation, the nadir value at either baseline or time of response will be used for evaluating future disease progression. In the absence of other indices of clinical progression, the presence of a ≥ 2 g/dL decrease in hemoglobin or a ≥ 50% decrease in platelet count and/or absolute neutrophil count will not exclude a patient from continuing on the study. Although not mandatory, bone marrow aspirate and biopsy are strongly encouraged to better define the cause of the suppressed counts (e.g., treatment versus disease-related).
7. Measurement of lymphadenopathy will be determined on physical exam by adding the sum of the products of the maximal perpendicular diameters of measured lesion(s). No simultaneous increase in the size of any lesions or the appearance of any new lesions may occur for 2 consecutive evaluations at least 1 month apart Minor fluctuations are acceptable as long as they don't exceed 50% of previous measurement. However, if they do exceed 50% of the previous measurement, treatment should be held for 2 consecutive cycles to rule out the possibility of nodes that wax and wane. For purposes of determining CCR and nPR, all nodes on physical exam need to be ≤ 1.5 cm in maximal dimension or documented to be free of CLL by biopsy. NOTE: Information from CT scans regarding lymphadenopathy is not considered in the standard classification of response with the exception of the patients fitting criteria of section 11.218 and 11.227.
8. Measurement of hepatosplenomegaly will be determined by noting the maximal distance below the respective costal margins of palpable hepatosplenomegaly during rest (e.g., not during deep inspiration). NOTE: Information from CT scans regarding hepatosplenomegaly is not considered in the standard classification of response with the exception of the patients fitting criteria of section 11.218 and 11.227.