Phase II Trial of Ibrutinib and PD-1 Blockade in High Risk Chronic Lymphocytic Leukemia to Improve Immune Function.

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Phase II Trial of Ibrutinib and PD-1 Blockade in High Risk Chronic Lymphocytic Leukemia to Improve Immune Function.

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LIST OF ABBREVIATIONS

AE	Adverse Event
BTK	Bruton's tyrosine kinase
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Science
CLL	Chronic Lymphocytic Leukemia
CMP	Clinical Monitoring Plan
CR	Complete response
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
ECI	Events of Clinical Interest
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICH E6	International Conference on Harmonisation Guidance for Industry, Good Clinical Practice: Consolidated Guidance
IGVH	Immunoglobulin Heavy Chain Variable Region Genes
IND	Investigational New Drug Application
IRB	Investigational Review Board
IRR	Infusion Related Reaction
ISO	International Organization for Standardization
IV	Intravenous
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
mAb	Monoclonal Antibody
MCC	Moffitt Cancer Center
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PD	Progressive Disease
PD-1	Programmed cell death protein 1
PDB	PD1:PDL1 blockade
PFS	Progression Free Survival
PI	Principal Investigator
PR	Partial Response
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
TH1	T Helper Cell 1
TLS	Tumor Lysis Syndrome
UP	Unanticipated Problem

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed of their obligation to meet the above commitments.

Principal Investigator: _____
Print/Type Name

Signed: _____ Date:_____

STUDY SUMMARY

Title: **Phase II Trial of Ibrutinib and PD-1 Blockade in High Risk Chronic Lymphocytic Leukemia to Improve Immune Function.**

Précis: Study intends to evaluate the impact of sequential overlapping treatment with PD-1 monoclonal antibody (mAb), pembrolizumab/MK-1375, followed by ibrutinib on endogenous immune function in previously untreated, high-risk CLL patients. Immune function will be evaluated through various laboratory correlative tests.

Objectives:

Primary

1. Assessment of the complete response of CLL to therapeutic intervention (defined per current iWCLL 2008 response criteria)

2. Time to response of CLL to therapeutic intervention (defined as time to achievement of response according to iWCLL 2008 criteria).

Secondary Objectives:

1. Assessment of the overall response rate (CR + PR) defined by the iWCLL 2008 criteria.

2. Restoration of immune response as measured by:

    a. Decreased markers of T-cell exhaustion

    b. Increased of quantitative immunoglobulin levels and subtype

2. Safety and toxicity of the combination

3. Progression free survival (PFS)

4. Incidence of Richter's transformation

Exploratory objectives

1. Alterations in T lymphocyte function, including changes in:

    a. TH1:TH2 polarization, and TReg:TH17 distributions

    b. Markers of T cell exhaustion and/or inhibition

    c. Alterations in distribution of naïve vs. memory

    d. Cellular activation and cell-mediated cytotoxic capacity

2. Alterations in B lymphocyte function, including changes in:

a. Serum anti-pneumococcal antibody titers in response to Prevnar vaccination

b. Quantitative serum immunoglobulin levels and subtyping

c. Fc-receptor (FcR) expression patterns

3. Alterations in global systemic cytokine patterns:

   Includes IFN-γ, TNF-α, IL-2, IL-4, IL-10, IL-6, IL-17A, allowing discrimination between TH1, TH2, and TH17 profiles (described in Section 4.2.2.2)

Endpoint:

Primary Endpoint:

1. Assessment of the complete response to the therapeutic intervention
2. Time to response to CLL to the therapeutic intervention

Secondary Endpoints:

1. Assessment of overall response rate (ORR) [CR + CR]
2. Restoration of immunosuppression:
   a. Decreased markers of T-cell exhaustion
   b. Improvement of the levels of quantitative immunoglobulins
3. Safety and Toxicity of the combination
4. Progression free survival (PFS)
5. Incidence of Richter's transformation

Exploratory Endpoints

1. Alterations of T-cell function: We postulate that there will be increased polarization towards TH1 compartment cells, which will be associated with increased cellular immunity. PD-1 blockage will increase TH1 mediated anti-tumor response. Alterations in B-cell function: Combination of BTK and PD-1 inhibition will restore B-cell function
2. Alterations in cytokine profile (as defined in Section 4.2.2.2)
3. Evaluation of toxicity and safety of the combined therapy: In order to minimize toxicity, pembrolizumab will started 6 weeks prior to ibrutinib

Population:	Sample size of 25 subjects, male and female, over 18 years of age, performance status ECOG 0 or 1 who are patients at Moffitt Cancer Center. Minority enrollment will be encouraged.
Phase:	Phase II
Number of Sites enrolling participants:	Moffitt Cancer Center
Description of Study Agents:	Pembrolizumab (anti-PD1, mAb) 200 mg IV every 3 weeks for a total of 51 weeks. Ibrutinib (BTK inhibitor) 420 mg by mouth starting at week 6 for a duration of up to 51 weeks..
Study Duration:	Three to four years.
Participant Duration:	Two years.

SCHEMATIC OF STUDY DESIGN

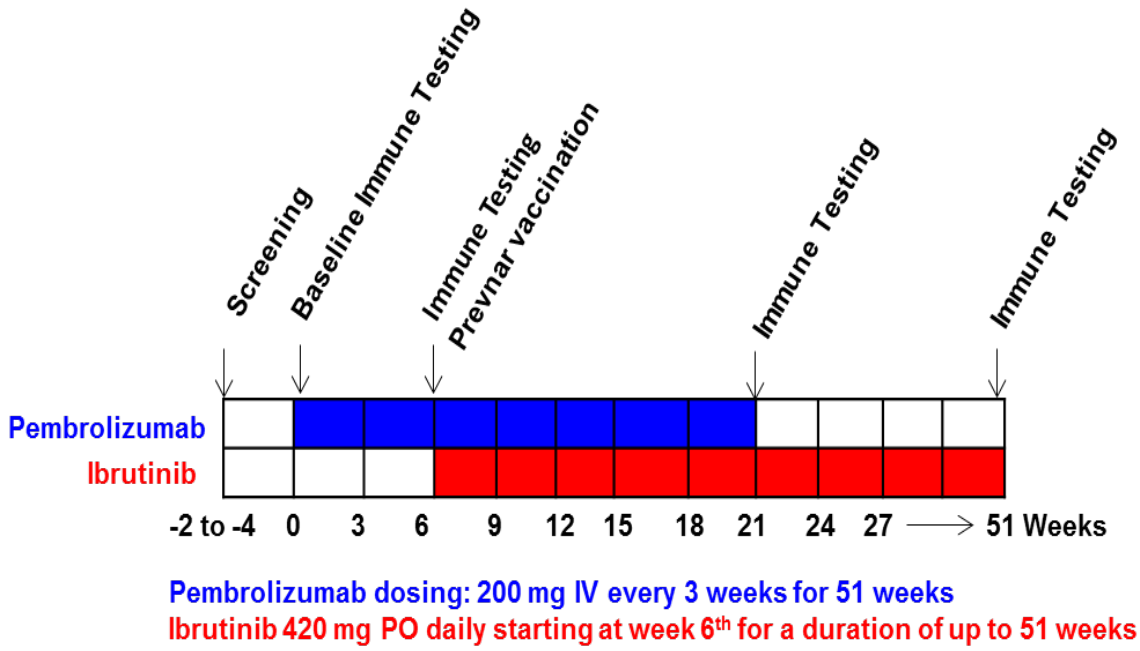

Figure 1. Treatment Schema Guideline

1 KEY ROLES

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

With an age-adjusted incidence of 4.1/100,000 inhabitants in the United States, chronic lymphocytic leukemia (CLL) is the most common type of leukemia in western countries. More than 15,000 newly diagnosed cases and 4,500 deaths are currently estimated annually[1].. The median age at diagnosis is between 67 and 72 years[2]. More male than female patients (1.7:1) are affected [2-4]. Because the incidence rate increases with age, the prevalence and mortality of CLL are likely to increase due to the demographic changes associated with an aging population over the next decades.

Moreover, the proportion of younger patients with early stage CLL and minimal symptoms seems to increase due to more frequent blood testing [5]. CLL is characterized by clonal proliferation and accumulation of mature, typically CD5-positive B cells within the blood, bone marrow, lymph nodes, and spleen[6]. It has recently been reported that in CLL the capacity to generate clonal B cells might be acquired at the hematopoietic stem cell (HSC) stage, suggesting that the primary leukemogenic event in CLL might involve multipotent, self-renewing HSCs[7]. The leukemic transformation is initiated by specific genetic alterations causing the deletion of specific micro-RNA genes and increasing the resistance of B cells towards apoptosis [8]. Deletions on the long arm of chromosome 13, specifically involving band 13q14 (del(13q14)), represent the single most frequently observed cytogenetic aberration in CLL, occurring in approximately 55% of all cases. An isolated del(13q14) is typically characterized by a benign course of the disease. Deletions of the long arm of chromosome 11 (del(11q)) can be found in ~25% of chemotherapy-naive patients with advanced disease stages and in 10% of patients with early stage disease[9, 10]. Deletions of the short arm of chromosome 17 (del(17p)) are found in 5%−8% of chemotherapy-naive patients. These deletions almost always include band 17p13 where the prominent tumor suppressor gene TP53 is located. Patients with CLL carrying a del(17p) clone show marked resistance against genotoxic chemotherapies that cannot be overcome by the addition of anti-CD20 antibodies in the context of state-of-the art chemoimmunotherapy [11]. Mutations of TP53 are found in 4%−37% of patients with CLL and have been associated with poor prognosis (ultra-high risk) in a number of studies [12]. The presence of an IgVH unmutated status is also associated to shorter time to therapy and worse progression free survival (PFS).

The recently reported whole genome sequencing projects in CLL have revealed a number of recurrent somatic gene mutations that occur in parallel to the above mentioned structural genomic aberrations. These include the genes NOTCH1, MYD88, TP53, ATM, SF3B1, FBXW7, POT1, CHD2, and others [10, 13].

More than 50% of CLL patients are asymptomatic at diagnosis and require no treatment. Symptoms appear as the disease progresses. Treatment is initiated when a patient's disease becomes symptomatic or progressive as defined by the international workshop on Chronic Lymphocytic Leukemia (iwCLL) updated guidelines for diagnosis and treatment of CLL[14].

Chronic lymphocytic leukemia (CLL) is associated with well-characterized profound immune dysregulation associated with an aberrantly dominant TH2 polarization [15, 16] often contributing significantly to morbidity and mortality in patients afflicted with this disease. Yet, humoral immunity is also impaired, as evidenced by compromised responses to vaccine challenge [17-19]. Vaccine efficacy against S. pneumoniae is dramatically diminished in CLL patients, demonstrating a more imposing refractoriness against polysaccharide antigens [17]. Although rarely curable, CLL typically follows an indolent course over many years. However, infection remains a prominent and frequent challenge in the management of CLL, and represents a leading cause of mortality in CLL. Immune dysfunction seen in CLL patients also likely contributes to the overall disease pathogenesis as progressive dysregulation

impairs the natural anti-tumor immune response that might otherwise contain if not eradicate the malignant clonal population [20].

Immune modulators have begun to change our approach to many malignancies. Monoclonal antibodies targeting the checkpoint inhibitor interaction, PD-1:PD-L1, are a new addition to our immunotherapeutic arsenal, demonstrating impressive clinical benefit in melanoma, lung cancer and promising early results in other solid tumor malignancies as well[21-26] PD-L1, expressed on a wide variety of cells including many tumor cells delivers an inhibitory signal to T cells through PD-1 which potently suppresses cellular immunity[27]. Thus, through blockade of the PD-1:PD-L1 axis, anti-tumor immune responses can be reconstituted. Importantly, PD-L1 has been implicated as one of several inhibitory signals incorporated into the dysfunctional T cell immune synapse leading to the defective immunity seen in CLL patients. [26, 27]

Ibrutinib is an irreversible inhibitor of Bruton's tyrosine kinase (BTK), an intrinsically important enzyme in the B cell activation signaling cascade [28, 29]. Ibrutinib has demonstrated therapeutic efficacy in several lymphoid malignancies with response rates as high as ~70% in relapsed or refractory CLL, and is currently indicated for the treatment of patients with CLL who have received at least one line of therapy, with del17p as initial therapy, Waldenstrom's macroglobulinemia and MCL who have received at least one prior therapy[30-32]. Accelerated approval in MCL was granted based on overall response rate [33]. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials. Interestingly, Ibrutinib also disrupts IL-2-inducible Kinase (ITK) signaling in T lymphocytes resulting in alteration of T cell receptor (TCR) signaling, particularly impeding maturation of TH2-type responses while leaving TH1-type responses relatively intact, and thus repolarizing responses toward more potent cellular immunity[34]. In the setting of CLL, in which immune dysfunction is widely felt to result from aberrantly dominant TH2 polarization, Ibrutinib potentially offers a second therapeutic benefit, not only directly targeting CLL B cells through inhibition of BTK, but also reengaging a potent anti-tumor response[34].

Recognizing that CLL-associated immune dysfunction predisposes these patients to overwhelming infections that significantly impact survival, we hypothesize that ibrutinib, in addition to targeting the malignant clonal B cell population directly, will redirect the endogenous T cell responses and reverse the established immune dysregulation. Furthermore, we believe that a rational combination of ibrutinib with PD-1:PD-L1 blockade, targeting an inhibitory mechanism implicated in CLL-associated immune dysfunction, will elicit a more global impact on the systemic immunity, reengaging both anti-tumor immune responses as well as improve general immunologic health.

Pharmaceutical and Therapeutic Background

Pembrolizumab

Pembrolizumab (MK-3475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is currently FDA approved for the first-line treatment of metastatic wild type EGFR and ALK non-small lung cancer (NSCLC) that express high PD-L1 expression [Tumor Proportion Score (TPS) $\geq$ 50%], for metastatic NSCLC with progression on or after platinum containing chemotherapy with TPS $\geq$ 1% expression of PD-L1, for metastatic EGFR or ALK rearrangement NSCLC with progression after EGFR and/or ALK inhibitors, for unresectable or metastatic melanoma and for recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) after progression to platinum-containing chemotherapy.

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [15, 35]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [16-19, 21]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+

regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors[36].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control [37, 38]. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions[37, 39]. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2)[40]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules[40, 41]. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM)[40]. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade[40, 42]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins[40, 43]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells[44]. Expression has also been shown during thymic cells, T regs and Natural Killer cells [44]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [45, 46]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [38, 47]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments [43, 48]. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [17, 19, 38] . Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma [49]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention [38, 50, 51].

Ibrutinib

PCI-32765 (ibrutinib) is a first-in-class selective, irreversible small molecule inhibitor of Bruton's tyrosine kinase (BTK) currently indicated for the treatment of patients with CLL/Small Lymphocytic Lymphoma (SLL) who have received at least 1 prior line of therapy, CLL.SLL with 17p deletion, mantle cell lymphoma who have received at least one prior therapy, marginal zone lymphoma (MZL) who require therapy and have received at least one least one prior anti-CD20 based therapy, Waldestrom Macroglobulinemia, and chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy. Ibrutinib is being co-developed by Pharmacyclics, Inc. and Janssen Biotech, INC. "PCI-32765" and "ibrutinib" refer to the same molecule; hereafter, "ibrutinib" will be used.

The investigational drug product is an oral formulation in a hard gelatin capsule form containing micronized ibrutinib. For the most comprehensive nonclinical and clinical information regarding the efficacy and safety of ibrutinib, refer to the latest version of the US package insert.

B cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B cells express cell surface immunoglobulins comprising the BCR, which is activated by binding to antigen. Antigen binding induces receptor aggregation

and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways [29].

The process of B-cell maturation, including immunoglobulin chain rearrangement and somatic mutation, is tightly regulated. It is thought that B-cell lymphomas and CLL result from mutations acquired during normal B-cell development[28]. Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies [52-54].

The role of BTK in BCR signal transduction is demonstrated by the human genetic immunodeficiency disease X-linked agammaglobulinemia and the mouse genetic disease X-linked immunodeficiency, both caused by a mutation in the BTK gene. These genetic diseases are characterized by reduced BCR signaling and a failure to generate mature B cells. The BTK protein is expressed in most hematopoietic cells with the exception of T cells and natural killer cells, but the selective effect of BTK mutations suggests that its primary functional role is as an antigen receptor signaling in B cells[55]. In vitro, PCI-32765 inhibits purified BTK and selected members of the kinase family with 10-fold specificity compared with non-BTK kinases [56, 57].

In patients with recurrent B cell lymphoma >90% occupancy of the BTK active site in peripheral blood mononuclear cells was observed up to 24hrs after ibrutinib doses of >= 2.5mg/kg/day (>= 175mg/day for average weight of 70kg).

Ibrutinib is absorbed after oral administration with a median Tmax of 1-2 hours. Ibrutinib exposure increases with doses up to 840mg. The steady-state AUC (mean +/- standard deviation) observed in patients at 560mg is 953 +/- 705 ng.h/ml and in patients at 420mg is 680 +/- 517 ng.h/mL. Administration with food increased ibrutinib Cmax and AUC by approximately 2 to 4- and 2-fold, respectively, compared with administration of ibrutinib after overnight fast.

For the most comprehensive nonclinical and clinical information regarding in vitro and in vivo preclinical activity and toxicology of ibrutinib, refer to the latest version of the PCI-32765 Investigator's Brochure. Refer to the Investigator's Brochure for Preclinical and Clinical data for Pembrolizumab and the US Package Insert for IMBRUVICA (Ibrutinib).

2.2 RATIONALE

Rationale for the Trial and Selected Subject Population

Patients with untreated high-risk CLL (defined as presence of del17p or TP53, del11q or ATM mutation, unmutated IGVH or mutated IGVH with 3.21 phenotype)) have an unmet need as they tend to progress rapidly and develop resistance to standard therapies. There is growing evidence that disease progression is likely related to genetic evolution, manifested as disruption of the clonal architecture of CLL.

Although the current recommendation is to consider "watch" and "wait" approach as the best management for asymptomatic patients, it has been long debated whether that should be applied for high-risk CLL patients. This indication is based on experience with alkylator-only therapy, however novel therapies appear less toxic and more tolerable [58]. There is evidence that deferring treatment in high-risk patients may be detrimental due to a more aggressive course of disease and that patients with clonal evolution into high-risk features may fare even worse prognosis [59]. There have been prior attempts to treat early stage high-risk CLL patients with FCR with EFS benefit, although not OS improvement [60]. However, it should be noted that usually high-risk CLL (especially 17p deletion) are fludarabine-resistant and novel agents, such as ibrutinib, can overcome this situation. Per CLL-IPI score the HR(hazard ratio) of 17p deletion/TP53 mutated was 4.2 with a 5-year OS of 63% (score of 4). If a

patient has presence of 17p del/TP53 mutation, unmutated IGVH and age older >65 (CLL-IPI score of 7) the 5-year OS will be 23% thus, there is a potential role of early intervention for this high-risk features CLL population [61]. Given the great activity of ibrutinib in high-risk CLL, especially in 17p deletion, there is potential role of this drug in early stage high-risk CLL patients. This was already shown with great activity, good tolerance and improvement in quality of life [62]. Given the potential synergistic effect of ibrutinib in combination checkpoint blockade, its translation to clinical use under a controlled clinical trial is supported and potentially beneficial [63].

Since treatment naïve CLL patients may have a more preserved immune system, there should be a better efficacy of immune checkpoint inhibitors such as anti PD-1, to restore immune dysfunction and obtain a better anti-tumor response.

The therapeutic combination of PD1:PDL1 blockade (PDB) and ibrutinib can improve the severe immune function classically associated with CLL, thereby improving disease-related morbidity and mortality in high-risk, previously untreated patients.

The combination of ibrutinib and PD-1 inhibitor was already studied in 2 trials in B-cell malignancies, including CLL. In a phase I clinical trial of patients with refractory non-Hodgkin's lymphomas and CLL full doses of ibrutinib and nivolumab were given with acceptable toxicity. There were no DLTs with the doses administered [64]. A phase II clinical trial (there was no dose escalation) demonstrated the efficacy and safety of the combination ibrutinib at 420 mg and nivolumab at the standard doses of 3 mg/kg in refractory/relapsed CLL patients [65]. Even though these studies were conducted with a different PD-1 antibody, we do not expect a different toxicity profile with pembrolizumab. There is currently a phase II study of the combination of ibrutinib and pembrolizumab in advanced melanoma at the standard doses without going to dose-escalation (NTC03021460).

1. The combination of PDB and ibrutinib will reverse T cell dysfunction commonly seen in CLL patients, potentiating more robust anti-infective and anti-tumor immune responses.
2. The combination of PBD and ibrutinib will restore protective humoral responses in CLL patients. In particular, immunologic restoration will improve responses and protection against pneumococcal infection which represent a significant cause of morbidity and mortality.
3. The combination of PDB and ibrutinib can have a synergistic effect on the response rate.

Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) was conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. The dose 10.0 mg/kg Q2W, the highest dose tested in PN00. Data from other clinical studies within the pembrolizumab program has shown that a dose of 2mg/kg of pembrolizumab in a every three weeks schedule may be sufficient for target engagement and clinical activity. More recently a flat dose of 200mg every three weeks was shown to be equally effective. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication.

For the present trial, a 200mg flat dose every three weeks will be used.

Ibrutinib will be administered at the FDA-approved dose of 420 mg once daily orally for CLL.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

A. Ibrutinib

As previously described, ibrutinib is approved for the treatment of patients with relapsed/refractory CLL and patients with CLL with del 17p. The most common adverse events (≥ 20%) in patients with CLL treated with ibrutinib are neutropenia, thrombocytopenia, diarrhea, anemia, fatigue, upper respiratory infection, skin rashes, nausea and pyrexia (see IMBRUVICA package insert for most current and full listing of possible risks).

- Hemorrhage: Fatal bleeding events have occurred in patients treated with ibrutinib. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in 3% of patients, with fatalities occurring in 0.3% of patients in clinical trialsBleeding events of any grade, including bruising and petechiae, occurred in 44% of patients treated with ibrutinib. The mechanism for the bleeding events is not well understood.
  - For any planned 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 serosanguinous drainage or the need for drainage tubes.
  - For planned minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 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.
  - 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, or at the discretion of the investigator.
- Infections: Fatal and non-fatal infections have occurred with ibrutinib therapy. Grade 3 or greater infections occurred in 24% of patients in clinical trials. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP)have occurred in patients treated with ibrutinib. Evaluate patients for fever and infections and treat appropriately per current guidelines. Prophylaxis according to standard of care should be considered in patients who are at increased risk for opportunistic infections.
- Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (24%, thrombocytopenia (range, 8%), and anemia (3%) based on laboratory measurements occurred in patients treated with single agent ibrutinib. Monitor complete blood counts at least monthly.
- Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with ibrutinib therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of patients. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias. Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias appropriately, and if it persists, consider the risks and benefits of ibrutinib treatment and follow dose modification guidelines
- Hypertension: Hypertension (range, 12%) has occurred in patients treated with ibrutinib with a median time to onset of 5 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting ibrutinib. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.
- Second Primary Malignancies: Other malignancies (9%) including non-skin carcinomas (2%) have occurred in patients treated with ibrutinib. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

- Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with ibrutinib therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.
- Embryo-Fetal Toxicity: Based on findings in animals, ibrutinib can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with MCL, CLL/SLL or WM. Advise women to avoid becoming pregnant while taking ibrutinib and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

B. Pembrolizumab

Pembrolizumab does not have a current indication for CLL. It is currently approved for unresectable or metastatic melanoma, metastatic NSCLC, metastatic HNSCC and refractory Hodgkin lymphoma. Most adverse reactions ($\geq$ 20% of patients) were consistent with fatigue, pruritus, decreased appetite, skin rash, pyrexia, cough, dyspnea, musculoskeletal pain, constipation and nausea (KEYTRUDA package insert). Of clinical importance are the immune-related adverse events:

- Immune mediated pneumonitis: Pneumonitis occurred in 94 (3.4%) of 2799 patients receiving pembrolizumab, including grade 1 (0.8%), grade 2 (1.3%), grade 3 (0.9%), grade 4 (0.3%), and grade 5 (0.1%) pneumonitis. The median time to onset was 3.3 months (range: 2 days to 19.3 months), and the median duration was 1.5 months (range: 1 day to 17.2+ months). Sixty-three (67%) of the 94 patients received systemic corticosteroids, with 50 of the 63 receiving high-dose corticosteroids for a median duration of 8 days (range: 1 day to 10.1 months) followed by a corticosteroid taper. Pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (6.9%) than in patients who did not receive prior thoracic radiation (2.9%). Pneumonitis led to discontinuation of pembrolizumab in 36 (1.3%) patients. Pneumonitis resolved in 55 (59%) of the 94 patients.
- Immune-mediated colitis: Colitis occurred in 48 (1.7%) of 2799 patients receiving pembrolizumab, including grade 2 (0.4%), grade 3 (1.1%), and grade 4 (<0.1%) colitis. The median time to onset was 3.5 months (range: 10 days to 16.2 months), and the median duration was 1.3 months (range: 1 day to 8.7+ months). Thirty-three (69%) of the 48 patients received systemic corticosteroids, with 27 of the 33 requiring high-dose corticosteroids for a median duration of 7 days (range: 1 day to 5.3 months) followed by a corticosteroid taper. Colitis led to discontinuation of pemrbolizumab in 15 (0.5%) patients. Colitis resolved in 41 (85%) of the 48 patients.
- Immune-mediated hepatitis: Hepatitis occurred in 19 (0.7%) of 2799 patients receiving pembrolizumab, including grade 2 (0.1%), grade 3 (0.4%), and grade 4 (<0.1%) hepatitis. The median time to onset was 1.3 months (range: 8 days to 21.4 months), and the median duration was 1.8 months (range: 8 days to 20.9+ months). Thirteen (68%) of the 19 patients received systemic corticosteroids, with 12 of the 13 receiving high-dose corticosteroids for a median duration of 5 days (range: 1 to 26 days) followed by a corticosteroid taper. Hepatitis led to discontinuation of pembrolizumab in 6 (0.2%) patients. Hepatitis resolved in 15 (79%) of the 19 patients.
- Immune mediated endocrinopathies: Hypophysitis occurred in 17 (0.6%) of 2799 patients receiving pembrolizumab, including grade 2 (0.2%), grade 3 (0.3%), and grade 4 (<0.1%) hypophysitis. The median time to onset was 3.7 months (range: 1 day to 11.9 months), and the median duration was 4.7 months (range: 8+ days to 12.7+ months). Sixteen (94%) of the 17 patients received systemic corticosteroids, with 6 of the 16 receiving high-dose corticosteroids. Hypophysitis led to discontinuation of pembrolizumab in 4 (0.1%) patients. Hypophysitis resolved in 7 (41%) of the 17 patients.
- Thyroid disorders: Hyperthyroidism occurred in 96 (3.4%) of 2799 patients receiving pembrolizumab, including grade 2 (0.8%) and grade 3 (0.1%) hyperthyroidism. The median time to onset was 1.4 months (range: 1 day to 21.9 months), and the median duration was 2.1 months (range: 3 days to 15.0+ months). Hyperthyroidism led to discontinuation of pembrolizumab in 2 (<0.1%) patients. Hyperthyroidism resolved in 71 (74%) of the 96 patients. Hypothyroidism

occurred in 237 (8.5%) of 2799 patients receiving pembrolizumab, including grade 2 (6.2%) and grade 3 (0.1%) hypothyroidism. The median time to onset was 3.5 months (range: 1 day to 18.9 months), and the median duration was not reached (range: 2 days to 27.7+ months). Hypothyroidism led to discontinuation of pembrolizumab in 1 (<0.1%) patient. Hypothyroidism resolved in 48 (20%) of the 237 patients. The incidence of new or worsening hypothyroidism was higher in patients with HNSCC occurring in 28 (15%) of 192 patients receiving pembrolizumab, including grade 3 (0.5%) hypothyroidism. Of these 28 patients, 15 had no prior history of hypothyroidism. Thyroiditis occurred in 16 (0.6%) of 2799 patients receiving pembrolizumab, including Grade 2 (0.3%) thyroiditis. The median time of onset was 1.2 months (range: 0.5 to 3.5 months).

- Immune-mediated Nephritis and renal dysfunction: Nephritis occurred in 9 (0.3%) of 2799 patients receiving pembrolizumab, including grade 2 (0.1%), grade 3 (0.1%), and grade 4 (<0.1%) nephritis. The median time to onset was 5.1 months (range: 12 days to 12.8 months), and the median duration was 3.3 months (range: 12 days to 8.9+ months). Eight (89%) of the 9 patients received systemic corticosteroids, with 7 of the 8 receiving high-dose corticosteroids for a median duration of 15 days (range: 3 days to 4.0 months) followed by a corticosteroid taper. Nephritis led to discontinuation of pembrolizumab in 3 (0.1%) patients. Nephritis resolved in 5 (56%) of the 9 patients
- Infusion-related reactions: Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting. Pembrolizumab can cause severe or life-threatening infusion-related reactions and has been reported in 6 (0.2%) out of 2799 patients that received the drug.
- Embryo-fetal toxicity: Based on its mechanism of action, pembrolizumab can cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during treatment with pembrolizumab and for 4 months after the last dose of the drug.
- Immunogenicity: As with all therapeutic proteins, there is the potential for immunogenicity. Trough levels of pembrolizumab interfere with the electrochemiluminescent (ECL) assay results; therefore, a subset analysis was performed in the patients with a concentration of pembrolizumab below the drug tolerance level of the anti-product antibody assay. In clinical studies in patients treated with pembrolizumab at a dose of 2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every two or three weeks, 26 (2.0%) of 1289 evaluable patients tested positive for treatment-emergent anti-pembrolizumab antibodies. Among the 26 patients who tested positive for treatment emergent anti-pembrolizumab antibodies, only 4 patients were tested for neutralizing antibodies and one was positive. There was no evidence of an altered pharmacokinetic profile or increased infusion reactions with anti-pembrolizumab binding antibody development. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to pembrolizumab with the incidences of antibodies to other products may be misleading.

2.3.2 KNOWN POTENTIAL BENEFITS

In February 2014, ibrutinib was the first BTK inhibitor FDA approved for clinical use for the treatment of patients with CLL who had relapsed after at least one prior line of therapy or presence of 17p deletion. The indication was extended to patients with CLL 17p deletion as first line therapy and patients unfit for chemotherapy (older than 65 years old). Ibrutinib has received full approval for use in CLL/SLL.

Pembrolizumab is currently approved for metastatic/advanced melanoma, recurrent or metastatic NSCLC, recurrent or metastatic HNSCC and refractory classical Hodgkin Lymphoma. Pembrolizumab does not have current approval for CLL at this time. However activity of pembrolizumab has been documented in CLL and Richter's transformation with overall clinical responses and minimal toxicity.

As mentioned in the rationale, there is an opportunity of the drug combination to correct the immune dysfunction typical of patients with CLL. Restoration of immune function could lead to improvement of the antitumor response and immunity against infections. In addition, treating high risk CLL early may have beneficial effects on long term survival.

3 OBJECTIVES AND PURPOSE

Objective:
This is designed as a phase II study intended to evaluate the impact of sequential overlapping treatment with PD-1 monoclonal antibody (mAb), pembrolizumab/MK-1375, followed by ibrutinib on endogenous immune function in previously untreated, high-risk CLL patients (defined as presence of del17p or TP53, del11q or ATM mutation, unmutated IGVH or mutated IGVH with 3.21 phenotype) with absolute lymphocyte count >20,000 but without meeting iwCLL criteria to start therapy.

Primary Objectives:

1. Assessment of the complete response (CR) of CLL to therapeutic intervention (defined per current iWCLL 2008 response criteria)

2. Time to response of CLL to therapeutic intervention (defined as time to achievement of response according to iWCLL 2008 criteria).

Secondary Objectives

1. Assessment of the overall response rate (ORR) [CR + PR) per iWCLL 2008 response criteria

2. Restoration of immune response as measured by:

   a. Decreased markers of T-cell exhaustion

   b. Increased of quantitative immunoglobulin levels and subtype

2. Safety and toxicity of the combination

3. Progression free survival (PFS)

4. 3. Incidence of Richter's transformation (defined as transformation of CLL into an aggressive lymphoid/histiocytic histology including well defined World Health Organization 2008 subtypes). Richter's transformation should be biopsy proven

Exploratory Objectives:

1. Alterations in T lymphocyte function, including changes in:

   a. TH1:TH2 polarization, and TReg:TH17 distributions

   b. Markers of T cell exhaustion and/or inhibition

   c. Alterations in distribution of naïve vs. memory

   d. Cellular activation and cell-mediated cytotoxic capacity

2. Alterations in B lymphocyte function, including changes in:

   a. Serum anti-pneumococcal antibody titers in response to Prevnar vaccination

   b. Quantitative serum immunoglobulin levels and subtyping

   c. Fc-receptor (FcR) expression patterns

3. Alterations in global systemic cytokine patterns: Includes IFN-γ, TNF-α, IL-2, IL-4, IL-10, IL-6, IL-17A, allowing discrimination between TH1, TH2, and TH17 profiles (described in Section 4.2.2.2)

Hypothesis for Primary and Secondary Objectives:

The therapeutic combination of PD1:PDL1 blockade (PDB) and ibrutinib can improve the severe immune dysfunction classically associated with CLL, thereby improving disease-related morbidity and mortality in high-risk, previously untreated patients.

A. The combination of PDB and ibrutinib will reverse T cell dysfunction commonly seen in CLL patients, potentiating more robust anti-infective and anti-tumor immune responses.

B. The combination of PBD and ibrutinib will restore protective humoral responses in CLL patients. In particular, immunologic restoration will improve responses and protection against pneumococcal infection which represent a significant cause of morbidity and mortality.

C. The combination of PDB and ibrutinib can have a synergistic effect on the response rate.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

Trial Design

The trial is an open-label, single arm phase II study to be conducted only at the Moffitt Cancer Center. Anticipated accrual will be 25 subjects. One of the secondary endpoint of this study is reconstitution of immune function, using response to pneumococcal vaccination as a clinical surrogate representation of global immune function. The study is designed to test the null hypothesis that, in high risk CLL (defined as presence of del17p or TP53, del11q or ATM mutation, unmutated IGVH or mutated IGVH with 3.21 phenotype) patients who do not require treatment of CLL and receive PD-1:PD-L1 blockade along with ibrutinib, challenge with the 7-valent pneumococcal vaccine will elicit an immunologic response <40%, defined as the generation of detectable antibody responses to >6 antigens. Our specified alternative hypothesis is that vaccination in the context of PD-1 blockade and ibrutinib will elicit on immunologic response >60% with 90% power.

Overall treatment Schema: All intravenous treatments will be administered at the outpatient Moffitt Cancer Center Infusion Center. The patients will receive a combination of IV pembrolizumab (anti-PD1) and oral ibrutinib according to the scheduled depicted in Figure 1. Briefly, patients will receive pembrolizumab on a 3-week interval schedule for a total of at least 51 weeks (it could be extended for up to 2 years if clinical benefit per investigator); starting with week 6, patients will additionally start daily oral ibrutinib which will be continued through 54 weeks of ibrutinib therapy. The rationale of starting pembrolizumab first is to avoid overlapping toxicity of ibrutinib and the anti-PD1 antibody.

Biomarker Research
Immune Monitoring Laboratory Correlates:

1. Global Immune function will be assessed in terms of serum cytokine patterns. Patient sera will be evaluated by flow cytometric means using cytokine bead arrays to measure serum cytokine levels quantitatively. The cytokine panel will include IFN-γ, TNF-α, IL-2, IL-4, IL-10, IL-6, IL-17A, allowing discrimination between TH1, TH2, and TH17 profiles.
2. T cell function will be assessed for changes in multiple characteristics including memory formation, TH-polarity, markers of exhaustion, and activation via flow cytometric analysis. Naïve and memory sub-populations will be defined according to expression of CD45RA, CD62L, CCR5 and CCR7. TH-polarization, including TH1, TH2, TH17 and TReg subsets, will be determined by intracellular cytokine and FoxP3 profiles. Changes in T cell exhaustion phenotype will be tracked in terms of surface expression of several well-defined markers, including CD160, CD200R, CD244, CD272, CD274, CD279, as well as the intracellular markers Lag3 and Tim3. Alterations in cellular activation will be measured in terms of phosphorylation of critical T cell signaling pathways, STAT 1, 3 and 5, as well as by surface expression of CD107a, correlating to secretory/cytotoxic activity.
3. Humoral immunity will be monitored in terms of quantitative serum immunoglobulin levels as well as IgG subtyping by ELISA assay. FcR subtype utilization patterns will also be evaluated by flow cytometric means to identify potential alterations in cellular interpretation of antibody-mediated signaling.
4. Evaluation of MRD by 4-color flow cytometry. It will be performed in patients who achieved CR and PR per iwCLL criteria. If CBC with differential demonstrates the normalization of WBC to normal limits with no evidence of lymphocytosis, a peripheral blood sample will be obtained (within 14 days) to determine the MRD status of the CLL in peripheral blood by multiparameter flow cytometry. If MRD is negative, a confirmation of MRD status in the bone marrow will be performed at the discretion of the investigator.
5. Peripheral blood to collect DNA and RNA will be stored for future assessments.

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINT

1. Complete response (CR) to the therapeutic intervention
2. Time to response to CLL to the therapeutic intervention

4.2.2 SECONDARY ENDPOINTS

1. Overall response rate (ORR) [CR + PR]
2. Restoration of immune response as measured by:

a. Decreased markers of T-cell exhaustion

b. Increased of quantitative immunoglobulin levels and subtype

2. Safety and toxicity of the combination

3. Progression free survival (PFS)

4. Incidence of Richter's transformation

4.2.3 EXPLORATORY ENDPOINTS

1. Alterations of T-cell function: We postulate that there will be increased polarization towards TH1 compartment cells, which will be associated with increased cellular immunity. PD-1 blockage will increase TH1 mediated anti-tumor response.

2. Alterations in B-cell function: Combination of BTK and PD-1 inhibition will restore B-cell function

3. Alterations in cytokine profile (as defined in Section 4.2.2.2)

4. Evaluation of toxicity and safety of the combined therapy: In order to minimize toxicity, pembrolizumab will started 6 weeks prior to ibrutinib

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

Patients must meet all of the following criteria to be eligible for study entry:

1. Have high risk CLL which includes one or more of the following characteristics:

   a. 17p deletion by FISH or TP53 by NGS.

   b. 11q deletion or ATM mutation by NGS.

   c. IgVH unmutated or IgVH mutated 3.21 phenotype by NGS assay

2. Have documented previously untreated CLL according to IWCLL criteria.

   a. Monoclonal B cells that are clonally co-expressing at least 1 B-cell marker on flow cytometry:

      1) CD19
      2) CD20
      3) CD5

   b. Prolymphocytes may comprise no more than 55% of blood lymphocytes

3. Be willing and able to provide written informed consent/assent for the trial.

4. Be greater than 18 years of age on day of signing informed consent.

5. Have a performance status of 0 or 1 on the ECOG Performance Scale.

6. Demonstrate adequate organ function as defined in Table 1.

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥11 g/dL
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥ 25 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

7. Negative serum pregnancy test within 3 days prior to receiving the first dose of study medication for a female subject of childbearing potential. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year. Women who are pregnant or breastfeeding are ineligible for this study.

8. Female subjects of childbearing potential must be willing to use 2 methods of highly effective contraception, be surgically sterile, or abstain from heterosexual activity for the course of the study through 30 days and 90 days after the last dose of study medication for ibrutinib and pembrolizumab, respectively (Reference Section 5.7.2). Male subjects must agree to use an adequate method of contraception starting with the first dose of study therapy through 90 days after the last dose of study therapy. Men must agree to not donate sperm during and after the study.

9. Is able to take oral medication and is willing to adhere to the medication regimen.

5.2 PARTICIPANT EXCLUSION CRITERIA

Any of the following is a criterion for exclusion from the study:

1. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.

2. Has had any treatment for CLL including any investigational agent, chemotherapy, mAb, anti-PD-1, anti-PDL-1, or anti-CTLA-4.

3. Meets iwCLL criteria to start therapy (Appendix A).

4. Transformation of CLL to aggressive NHL (Richter's transformation or pro-lymphocytic leukemia)

5. Known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

6. Has an active autoimmmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents including subjects with uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.

7. Has history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

8. Has an active infection requiring systemic therapy.

9. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

10. Subjects with a history of a different malignancy are ineligible unless they have been disease free for 1 year and considered low risk for relapse, except for: cervical cancer in situ, ductal carcinoma in situ, localized prostate cancer with no detectable disease by imaging studies, and non-melanoma skin cancers which are eligible at any time.

11. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

12. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 90 days after the last dose of trial treatment.

13. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

14. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

15. Has received a live vaccine within 30 days prior to the first dose of trial treatment. Patients who had pneumococcal vaccination within 6 months from starting trial will not be eligible for the study.

16. Major surgery or a wound that has not fully healed within 4 weeks of first dose.
17. History of stroke or intracranial hemorrhage within 6 months prior to first dose.
18. Requires anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon).
19. Requires chronic treatment with strong CYP3A inhibitors.
20. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment of the 25 participants for this trial will occur from new or established patients treated at the Hematology Clinic at Moffitt Cancer Center. Screen failure is anticipated to be less than 10%. The target accrual is expected to be reached in 18-24 months. All faculty members in the Lymphoma Section will be sub-investigators on the trial. They will be trained on the trial design, study agents, and eligibility criteria. This will equip each investigator to discuss the trial with potential participants as appropriate. The trial will be listed on the Moffitt Cancer Center website (www.moffitt.org) for the availability of local physicians to refer patients who could be eligible for the trial.

All investigators will be made aware of the emphasis to enroll women and minorities. The design of the trial and eligibility criteria are not restrictive relative to women and minorities. As stated in the background section of the protocol, CLL affects more males than females (1.7:1) [2-4]. The clinical research team for this trial has experience with recruiting in another frontline investigator-initiated trial (MCC16622). Of the 45 participants accrued, 15 were women. The sex, ethnicity, and race of each participant on this trial will be captured in the Oncore electronic data base for reporting purposes.

Median age at diagnosis of CLL patients is between 67 and 72 years [2]. Therefore, strategies for retention of elderly participants must be considered. Older adults may have medical conditions that cause them to drop out if side effects are severe or interact with medical treatment for comorbidities [58]. They are often concerned with cost of travel or distance to the study site. Moffitt Cancer Center has the unique barrier to enrollment of patients who may decline participation or want to discontinue as they live in Florida only during the winter months. Researchers have examined patient satisfaction in older adults and determined having continuity in staff and frequent visits increases the sense of being treated in a thorough manner [58]. This relationship building promotes retention. Potential participants will be assessed prior to screening for any perceived barriers related to the clinical trial process. Referrals will be made to a social worker, supportive care services, financial services, or the research nurse to address barriers prior to consent. Once consented, the participant will have contact with the research nurse at a minimum of every three to four weeks during treatment for the duration of the 12 month treatment process.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur that may jeopardize participant safety. In addition, a subject may be withdrawn by the investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Unacceptable adverse events
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 7.3.7 (schedule of events) and Section 7.3 (Visit Requirements). After the end of treatment, each subject will be followed until 90 days after the end of pembrolizumab infusions and 30 days after the last dose of ibrutinib.(serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). The last dispensing of ibrutinib will occur at week 51 and dosing will continue for an additional 3 weeks. Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status and toxicity up to 30 days after stopping ibrutinib and 90 days after stopping pembrolizumab. Follow-up rules will apply unless participant initiates a non-study cancer treatment, withdraws consent, or becomes lost to follow-up (unsuccessful attempts to contact for 3 months). After documented disease progression each subject will be followed by telephone every 12 weeks for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Every effort will be made to maintain contact with a subject who withdraws early. If the subject remains at MCC for further care, clinic visits may be tracked and the condition of the subject followed. If the subject is not continuing care at MCC, contact information will be updated at the end of treatment visit, including accurate phone numbers, and email address. The importance of the follow-up period for AEs and SAEs will be stressed to the subject.

Replacement of participants who screen fail or drop out prior to completing 9 weeks of treatment are permitted to be replaced in order to meet the accrual goal of this study.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, funding agency, the IND/IDE sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug
5. Determination of futility

In the event Merck or Janssen decide to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

Investigational products for this trial will be supplied by Merck & Co, Inc. (pembrolizumab) and Janssen Pharmaceuticals, Inc. (ibrutinib).

Pembrolizumab
An order form supplied by Merck will be utilized. The form will have instructions on how to order. Pharmacy will complete the quantity needed and the shipment address. Orders will require 7 business days to arrive on site.

Ibrutinib
Ibrutinib will be shipped from Janssen as bottles of capsules. For the initial supply, the Janssen trial manager will make arrangements for shipment of bottles expected to be used in the first one to two months, dependent on planned enrollment. Future re-orders will be submitted using a drug request form supplied by Janssen. Order forms will be submitted by email to the team email address (IIS-BIO-VIRO-GCO@its.jnj.com) printed on the order form. Allow 7 business days for drug to arrive on site.

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

IBRUTINIB

Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK). Ibrutinib is a small-molecule inhibitor of BTK. Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro. It is a white to off-white solid with the empirical formula C25H24N6O2 and a molecular weight 440.50. Ibrutinib is freely soluble in dimethyl sulfoxide, soluble in methanol and practically insoluble in water. Ibrutinib capsules for oral administration are supplied as white opaque capsules that contain 140 mg ibrutinib as the active ingredient. Each capsule also contains the following inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate. The capsule shell contains gelatin, titanium dioxide and black ink. Each white opaque capsule is marked with "ibr 140 mg" in black ink. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.
The white opaque 140 mg capsules marked with "ibr 140 mg" in black ink are available in white HDPE bottles with a child-resistant closure:

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

PEMBROLIZUMAB

Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occur in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.
Based on dose/exposure efficacy and safety relationships, there are no clinically significant differences in efficacy and safety between pembrolizumab doses of 200 mg or 2 mg/kg every 3 weeks in patients with

NSCLC
Pembrolizumab injection will be provided as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

6.1.3 PRODUCT STORAGE AND STABILITY

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

PEMBROLIZUMAB
Pembrolizumab for injection (lyophilized powder): carton containing one 50 mg single-dose vial (NDC 0006- 3029-02). Store vials under refrigeration at 2°C to 8°C (36°F to 46°F).
Pembrolizumab injection (solution): carton containing one 100 mg/4 mL (25 mg/mL), single-dose vial (NDC 0006-3026-02). Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

6.1.4 PREPARATION

IBRUTINIB
N/A

PEMBROLIZUMAB
The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.
Clinical Supplies will be provided by Merck as summarized in the table below:

Table Product descriptions

Product Name & Potency	**Dosage Form**
Pembrolizumab 100 mg/ 4mL	Solution for Injection

Pembrolizumab is provided as a liquid solution (100 mg/vial) in Type I glass vials intended for single use only.
The liquid drug product are a clear to opalescent solutions, essentially free of visible particles. The liquid product is intended for IV administration. The liquid drug product can be further diluted with normal saline or 5% dextrose in the concentration range of 1 to 10 mg/mL in intravenous (IV) containers made of polyvinyl chloride (PVC) or non-PVC material. Reconstituted vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered. Diluted pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. In addition, IV bags can be stored at 2 to 8°C for up to a cumulative time of 20 hours. This recommendation is based on up to 24 hours of room temperature and up to 24 hours of refrigerated stability data of diluted pembrolizumab solutions in the IV bags.

6.1.5 DOSING AND ADMINISTRATION

IBRUTINIB
Ibrutinib will be administered orally once daily at approximately the same time each day at the dose of 420

mg daily (3 capsules of 140 mg daily). Capsules will be swallowed whole with water. Capsules shall not be opened, broken or chew.

PEMBROLIZUMAB
Pembrolizumab will be administered intravenously at 200 mg every 3 weeks

6.1.6 ROUTE OF ADMINISTRATION

IBRUTINIB
Ibrutinib is only indicated for oral administration

PEMBROLIZUMAB
Pembrolizumab will be administered as is approved route of administration (IV)

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

IBRUTINIB
The starting dose will be the recommended for chronic lymphocytic leukemia at 420 mg daily (three capsules daily orally). There will be no escalation schedule of ibrutinib in this study.

PEMBROLIZUMAB
The starting dose of pembrolizumab will be at the recommended of 200 mg IV every 3 weeks. There will be no dose escalation of pembrolizumab in this study.

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

GENERAL MANAGEMENT OF DOSE ADJUSTMENT S/MODIFICATIONS WITH IBRUTINIB AND/OR PEMBROLIZUMAB

Below is the table for general management/adjustments of ibrutinib and pembrolizumab for hematologic and non-hematologic adverse events.

If study treatment is held for an adverse event and the subject is approved to resume treatment, the subject will resume with the timepoint at which the treatment was held.

Toxicity	Grade	Dose Modification	Toxicity Management	Agent to be considered for dose modification
Thrombocytopenia (Unless it is related to CLL bone marrow involvement)	1,2	N/A	N/A	Ibrutinib Pembrolizumab
	3 (Platelets < 50 000 cells/mm3 [$50x10^9$])	**Ibrutinib:** No dose modification required **Pembrolizumab:** No dose modification required	Monitor CBC/differential at least weekly Platelet transfusions are permitted per AABB guidelines	

	4 (Platelets < 25 000 cells/mm3 [$50x10^9$])	**Ibrutinib:** If thrombocytopenia resolves to ≤ Grade 1 (platelets ≥75,000 cells /mm3 [75 × 109/L] or baseline, restart the dose. If toxicity recurs, reduce dose by 140 mg. If toxicity persists following two dose reductions, discontinue ibrutinib **Pembrolizumab:** Decision to discontinue will depend upon clinical situation and per clinical investigator's judgment and in consultation with Supporting company	Monitor CBC/differential at least weekly Platelet transfusions are permitted per AABB guidelines	
Neutropenia (Unless it is related to CLL bone marrow involvement)	1,2	N/A	N/A	Ibrutinib Pembrolizumab
	3 ANC < 1000 cells/m^3 [$1x10^9$])	**Ibrutinib** Hold ibrutinib if Grade 3 associated with infection or fever (temperature ≥ 38.5°C) If neutropenia resolves to ≤ Grade 1 (ANC ≥1500 /mm3 [≥1.5 × 10^9 /L]) or baseline, restart the dose. If toxicity recurs, reduce dose by 140 mg. If toxicity persists following 2 dose reductions, discontinue the drug **Pembrolizumab** Hold pembrolizumab until resolution to ≤ Grade 1 or baseline For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume IP/study regimen administration at next scheduled dose. Otherwise, discontinue pembrolizumab	Monitor CBC/differential at least weekly Use of myeloid growth factors (MGF) are permitted per ASCO or NCCN guidelines	
	4 ANC < 500 cells/m^3 [$1x10^9$])	**Ibrutinib** Hold ibrutinib for Grade 4 If neutropenia resolves to ≤ Grade 1 (ANC ≥1500 /mm3 [≥1.5 × 10^9 /L]) or baseline, restart the dose. If toxicity recurs, reduce dose by 140 mg. If toxicity persists following 2 dose reductions, discontinue the drug **Pembrolizumab** Decision to discontinue will depend upon clinical situation and per clinical investigator's judgment and in consultation with supporting company	Monitor CBC/differential at least weekly Use of myeloid growth factors (MGF) are permitted per ASCO or NCCN guidelines	
Non-Hematological	**1**	**N/A**		Pembrolizumab

toxicity (non-immune related toxicity)	**2**	**Pembrolizumab** Hold drug until resolution to Grade ≤ 1 toxicity or baseline **Ibrutinib** No dose interruption is needed		Ibrutinib
	3 or 4	**Pembrolizumab** Hold drug until resolution to Grade ≤ 1 toxicity or baseline For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume IP/study regimen administration at next scheduled dose. Otherwise, discontinue pemrbolizumab For Grade 4 AEs the decision to discontinue will depend upon clinical situation and per clinical investigator's judgment and in consultation with supporting company **Ibrutinib** Hold Ibrutinib If toxicity resolves to ≤ Grade 1 or baseline, restart the dose. If toxicity recurs, reduce dose by 140 mg. If toxicity persists following two dose reductions, discontinue ibrutinib		

IBRUTINIB DOSE MODIFICATIONS

Interrupt ibrutinib therapy for any Grade 3 or greater non-hematological toxicities, Grade 3 or greater neutropenia with infection or fever, or Grade 4 hematological toxicities. Once the symptoms of the toxicity have resolved to Grade 1 or baseline (recovery), ibrutinib therapy may be reinitiated at the starting dose. If the toxicity reoccurs, reduce dose by one capsule (140 mg per day). A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue ibrutinib.

Recommended dose modifications are described below:

Toxicity occurrence	**Withhold/Discontinue ibrutinib?**
First	Restart at 420 mg daily
Second	Restart at 280 mg daily
Third	Restart at 140 mg daily
Forth	Discontinue ibrutinib

MANAGEMENT/SUPPORTIVE CARE OF IMMUNE RELATED ADVERSE EVENTS RELATED TO PEMBROLIZUMAB

Events of clinical interest of a potential immunologic etiology (irECIs) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. irAEs may be predicted based on the nature of the pembrolizumab compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Information on how to identify and evaluate irAEs has been developed and is included in the Event of Clinical Interest and Immune-Related Adverse Event Guidance Document located in the Administrative Binder. Subjects who develop a Grade 2 or higher irAE should be discussed immediately with the Sponsor.

It is not expected that ibrutinib will cause immune related AEs.

Recommendations to managing irAEs not detailed elsewhere in the protocol are detailed in the table below

irAE	Withhold/Discontinue pembrolizumab?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold pembrolizumab	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3 and Grade 4	Withhold pembrolizumab Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

Management of specific irAEs

Pneumonitis:

For Grade 2 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

For Grade 3-4 events, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.

Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

Diarrhea/Colitis:

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.

For Grade 2 diarrhea/colitis, administer oral corticosteroids.

For Grade 3 or 4 diarrhea/colitis, treat with intravenous steroids followed by high dose oral steroids.

When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks

Type 1 diabetes mellitus

If new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)

For T1DM or Grade 3-4 Hyperglycemia

Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.

Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

Hypophysitis:
For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
For Grade 3-4 events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Hyperthyroidism or Hypothyroidism:
Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
Grade 2 hyperthyroidism events (and Grade 2-4 hypothyroidism):
In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
Grade 3-4 hyperthyroidism
Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Hepatic:
For Grade 2 events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
Treat with IV or oral corticosteroids
For Grade 3-4 events, treat with intravenous corticosteroids for 24 to 48 hours.
When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks

Renal Failure or Nephritis:
For Grade 2 events, treat with corticosteroids.
For Grade 3-4 events, treat with systemic corticosteroids.
When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Management of Pembrolizumab Infusion Related Reactions (IRR):
Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Management of IRR are recommended based on Moffitt institutional policies. Below is a table of general recommendations.

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS,	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with:

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

6.1.9 DURATION OF THERAPY

The duration of ibrutinib therapy will be up to 51 weeks.
The duration of therapy of pembrolizumab will be up to 51 weeks. Pemrbolizumab dosing could be extended for up to 2 years if clinical benefit per investigator.
Patients will be considered evaluable if they complete at least 9 weeks or three infusions of pembrolizumab.

6.1.10 TRACKING OF DOSE

For ibrutinib there will be a Patient Compliance Pill Diary for oral medications provided to the subject when

each new supply of ibrutinib is dispensed.
For pembrolizumab there will be documentation in the patient's electronic medical record of dosing and a pharmacy dispensing/accountability log to determine the adherence.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

The study drugs will be stored in the Moffitt Investigational Pharmacy Department. There will be an accountability log for each drug. Any unused study drug will be destroyed on site per Investigational Pharmacy standard procedures.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES

7.1.1 Overview

The Schedule of Events - Section 7.3.7 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the PI and/or Merck or Janssen for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.2 Informed Consent

Prior to any study procedure, informed consent must be obtained and documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form. The dated signature of the person conducting the consent discussion must also appear on the consent form.

7.1.3 Inclusion/Exclusion Criteria

Prior to any trial treatment, all inclusion and exclusion criteria will be reviewed and signed by the PI or Sub-Investigator to ensure the subject qualifies for the trial.

7.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed that is considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.4 Concomitant Medications Review

The investigator or qualified designee will record medication, if any, taken by the subject starting at screening until end of trial treatment. All medications related to reportable SAEs and ECIs should be recorded as defined in the SAE section of the protocol.

7.1.5 Post-Study Anticancer Therapy Status

The investigator or qualified designee will review all new CLL anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.6 Adverse Event Review

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse events will be collected from the time of consent , and will continue every 3 weeks during treatment. For adverse event collection after treatment discontinuation, see Section 8.3.

7.1.7 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

7.1.8 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.9 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Schedule of Events (Section 7.3.7). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.10 Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or qualified designee will assess ECOG status (see Appendix B) as specified in the Schedule of Events.

7.1.11 Assessment of Disease

Assessment of response (ORR) is a primary end point and will be reported using the latest Response Criteria Guidelines per the International Working Group of CLL. (Appendix C)

7.1.12 Laboratory Procedures/Assessment

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided in the Schedule of Events. Tests specific to screening include hepatitis B and C panel, HIV evaluation at screening, serum *B*-HCG as defined, PT/INR and aPTT, urinalysis, CLL specific testing (ZAP-70, B-2 microglobulin, IgVH mutation, FISH), T3, free T4, and TSH.

7.1.13 Correlative Studies Blood Sampling

Blood samples will be collected pre-dose on Day 1, Week 6, Week 21, and end of ibrutinib therapy for immune testing per Schedule of Events. They will be performed at investigator's discretion if early study termination. For sampling requirements, see Section 7.2.

7.1.14 Laboratory Safety Evaluations

Laboratory testing for safety will be performed at time points per Schedule of Events. These tests include CBC/differential and CMP (albumin, BUN, creatinine, alkaline phosphatase, ALT, AST, CO2, calcium, chloride, glucose, potassium, sodium, total bilirubin, total protein, LDH). Additional safety evaluations for tumor lysis syndrome (LDH, uric acid, phosphorus, Creatinine and BUN) will occur as defined in the Schedule of Events.

7.1.15 Tumor Imaging

Tumor imaging will consist of CT scan of the neck, chest, abdomen and pelvis. CT scan will be done at screening (if not done within 3 months prior to consent). Response assessments will be done at week 12 (+/-3 days), week 24 (+/-3 days), and after 51 weeks of ibrutinib. If the subject discontinues treatment early or progression of disease is suspected, CT will be done at the discretion of the investigator. Imaging during follow-up will be performed per investigator discretion.

7.1.16 Bone Marrow Biopsy

A bone marrow biopsy will be performed at screening (if not performed within 30 days), after the end of pembrolizumab and ibrutinib therapy (28-35 days after week 51). If subject discontinues treatment early or progression of disease is suspected, a bone marrow biopsy will be done at the discretion of the investigator. During follow-up, bone marrow biopsies will be performed per investigator discretion.

7.2 RESEARCH BLOOD SPECIMEN PREPARATION, HANDLING, AND STORAGE

Blood samples for correlative studies will be collected at baseline (prior to first dose of study drug), at week 9, week 12, and end of ibrutinib treatment. Peripheral blood will be utilized with an estimated volume of 50 cc collected in five green top tubes.

1. Preparation of Samples
   Whole blood samples in 5 green top tubes (10ml/tube) will be received in the laboratory of Eva Sahakian, PhD. Plasma will be isolated by centrifugation of the green top tubes for 5min at 1500rpm and lymphocyte isolation will be performed using Ficol gradient isolation for the purpose of immune testing.

2. Sample Storage
   For storage, plasma will be held in 1.5 ml aliquots and placed in a -20C freezer. Lymphocytes will be frozen using 90% FBS and 10% DMSO and placed in a -80C freezer for short term storage. Long term storage of lymphocytes will be conducted utilizing liquid nitrogen.

3. Long-Term Use of Samples

Any isolated plasma and lymphocytes will be stored for the duration of the trial utilizing the short term method above and will be tested per protocol parameters outlined in Section 4.1. With the subject's permission, any samples remaining at the end of the trial will be placed in long term storage for use in future research. If any subject does not agree, that subject's remaining samples will be destroyed at the final closure of the trial.

4. Procedure for Clinical Trial Staff
   The following procedure is recommended to be used for collaboration with the Research Science Lab:
   a. Notify the Research lab at least 2 days prior to the collection, using the template below. Email to alex.achille@moffitt.org and cc eva.sahakian@moffitt.org
      Follow up with a phone message to x6335.
   b. Prepare a plastic bag with 5 green top tubes (tubes obtained from Dr. Sahakian's lab). Attach label to tubes with MCC #, subject MRN, and date of collection. Each bag will have a label attached with the MCC #, subject MRN, DOB, initials, date/time of collection. Label should have research lab contact information. ("Contact extension 6335 or pager 256-4415 for pick-up").
   c. Deliver bag of tubes to the Blood Draw area the day prior to collection.

7.3 STUDY SCHEDULE

7.3.1 SCREENING

Screening Visit (Day -28 to -1)

- Obtain and review medical history to determine eligibility based on inclusion/exclusion criteria.
- Written informed consent to be obtained prior to any screening procedures
- Review medications history (including over-the-counter drugs, vitamins, herbs, alcohol) to determine eligibility based on inclusion/exclusion criteria.
- Perform physical examination needed to determine eligibility based on inclusion/exclusion criteria
- Vital signs measurements Evaluation of ECOG performance status
- Twelve-lead ECG
- Serum beta-human chorionic gonadotropin (β-hCG) pregnancy test for women of childbearing potential
- Clinical laboratory testing including urinalysis, serum chemistry, hematology, viral serology (Hepatitus B, Hepatitis C, and HIV serology), β-2microglobulin, baseline thyroid function tests (T3, T4, and TSH) and coagulation parameters. Clinical assessments performed as part of the subject's routine clinical evaluation and not specifically for this study need not be repeated after signed informed consent has been obtained provided the assessments fulfill the study requirements and are performed within 28 days of starting study treatment.
- Peripheral blood samples for ZAP-70, IgVH mutational status, and FISH only required if they have not ever been performed.
- Evaluation of disease status through disease-related symptoms and radiological examinations by CT scans. Results of radiologic assessments obtained prior to signing the informed consent as part of the subject's standard of care may be used for this study if performed within 3 months before date of consent. Subsequent assessments performed throughout the study must use the same method of assessment per subject.

- Bone marrow biopsy including flow cytometry and FISH testing for CLL (if not performed within 30 days of consent).

7.3.2 ENROLLMENT/BASELINE

7.3.2.1 Baseline Visit (Week 0)

- Verify subject still meets inclusion/exclusion criteria.
- Review results of serum pregnancy test, if applicable.
- History and assessment to include directed physical examination, vital signs, and concomitant medication review. Assess and record baseline symptoms prior to study drug administration.
- ECOG performance status assessment
- CBC with differential
- Chemistry profile (ALT, AST, alkaline phosphatase, total bilirubin, calcium, bicarbonate, sodium, potassium, chloride, creatinine, BUN, total protein and albumin)
- Tumor lysis syndrome evaluation (TLS) using BUN, creatinine, phosphorus, potassium, LDH, uric acid results.
- Blood for correlatives studies
- Study drug administration (initiation of pembrolizumab IV).

7.3.2.2 Week 1 and 2

- Serum chemistry profile and TLS evaluation by laboratory tests. TLS evaluation will occur on days 1-3 from initiation of therapy.
- Review of tests and assessment for TLS by the investigator or qualified designee.

7.3.2.3 Week 3

- Directed physical examination, vital signs and brief review of systems.
- Medication reconciliation.
- Toxicity/ AE assessment
- ECOG performance status assessment.
- Hematology (hemoglobin, HCT, RBC, WBC with differential [neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils)
- Chemistry (ALT, AST, alkaline phosphatase, total bilirubin, LDH, calcium, bicarbonate, sodium, potassium, chloride, creatinine, BUN, total protein and albumin)

- TLS evaluation
- Study drug administration (pembrolizumab).

7.3.2.4 Week 6

- Directed physical examination, vital signs and brief review of systems.
- Medication reconciliation.
- Toxicity/ AE assessment
- ECOG performance status assessment.
- Hematology (hemoglobin, HCT, RBC, WBC with differential [neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils)
- Chemistry (ALT, AST, alkaline phosphatase, total bilirubin, LDH, calcium, bicarbonate, sodium, potassium, chloride, creatinine, BUN, total protein and albumin)
- TLS evaluation
- Blood for correlative studies
- Prevnar 13 vaccination
- Study drug administration (pembrolizumab and start of ibrutinib by mouth daily for up to 12 months). Medications may be administered in any order on days of infusions.
- Provide pill diary and instruct subject on the recording of data on diary.

7.3.2.5 Week 7 and 8

- Serum chemistry profile and TLS evaluation by laboratory tests.
- Review of tests and assessment for TLS by the investigator or qualified designee.

7.3.2.6 Week 9

- Directed physical examination, vital signs and brief review of systems.
- Medication reconciliation.
- Toxicity/ AE assessment
- ECOG performance status assessment.
- Hematology (hemoglobin, HCT, RBC, WBC with differential [neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils)
- Chemistry (ALT, AST, alkaline phosphatase, total bilirubin, LDH, calcium, bicarbonate, sodium, potassium, chloride, creatinine, BUN, total protein and albumin)
- Study drug administration (pembrolizumab and ibrutinib).

- Provide pill diary
- Serum chemistry profile and TLS evaluation by laboratory tests.
- Review of tests and assessment for TLS by the investigator or qualified designee.

7.3.2.7 Week 10

- Serum chemistry profile and TLS evaluation by laboratory tests.
- Review of tests and assessment for TLS by the investigator or qualified designee.

7.3.2.8 Weeks 12, 15, 18, 21

- Directed physical examination, vital signs and brief review of systems.
- Medication reconciliation.
- Toxicity/ AE assessment
- ECOG performance status assessment.
- Hematology (hemoglobin, HCT, RBC, WBC with differential [neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils)
- Chemistry (ALT, AST, alkaline phosphatase, total bilirubin, LDH, calcium, bicarbonate, sodium, potassium, chloride, creatinine, BUN, total protein and albumin)
- Study drug administration (ibrutinib and pembrolizumab).
- CT scan week 12.
- Blood for correlatives studies week 21
- Provide pill diary.

7.3.2.9 Week 24

- Directed physical examination, vital signs and brief review of systems.
- Medication reconciliation.
- Toxicity/ AE assessment
- ECOG performance status assessment.
- Hematology (hemoglobin, HCT, RBC, WBC with differential [neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils)
- Chemistry (ALT, AST, alkaline phosphatase, total bilirubin, LDH, calcium, bicarbonate, sodium, potassium, chloride, creatinine, BUN, total protein and albumin)
- Tumor imaging (CT scans).

- Study drug administration (ibrutinib and pembrolizumab).
- Provide pill diary

7.3.2.10 Every 3 Weeks from Week 24 (up to 51 weeks of treatment)

- Directed physical examination, vital signs and brief review of systems.
- Medication reconciliation.
- Toxicity/ AE assessment
- ECOG performance status assessment.
- Hematology (hemoglobin, HCT, RBC, WBC with differential [neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils)
- Chemistry (ALT, AST, alkaline phosphatase, total bilirubin, LDH, calcium, bicarbonate, sodium, potassium, chloride, creatinine, BUN, total protein and albumin)
- Tumor imaging as clinically indicated per investigator
- Study drug administration (ibrutinib).
- Provide pill diary

7.3.2.11 End of Treatment Visit (0-7 days after last dose, includes early termination)

- Directed physical examination, vital signs and brief review of systems.
- Medication reconciliation.
- Toxicity/ AE assessment
- ECOG performance status assessment.
- Hematology (hemoglobin, HCT, RBC, WBC with differential [neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils)
- Chemistry (ALT, AST, alkaline phosphatase, total bilirubin, LDH, calcium, bicarbonate, sodium, potassium, chloride, creatinine, BUN, total protein and albumin)
- Blood for correlative studies (at investigator's discretion if early termination)
- Bone marrow biopsy (if early termination, at the discretion of the investigator)
- Tumor Imaging (at the investigator discretion)
- Collect remaining bottles of ibrutinib and final pill diary.

7.3.2.12 Safety Follow-Up Visit (30-35 days after last dose of study treatment)

- Directed physical examination, vital signs and brief review of systems.

- Medication reconciliation.
- Toxicity/ AE assessment
- ECOG performance status assessment.
- Hematology (hemoglobin, HCT, RBC, WBC with differential [neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils)
- Chemistry (ALT, AST, alkaline phosphatase, total bilirubin, LDH, calcium, bicarbonate, sodium, potassium, chloride, creatinine, BUN, total protein and albumin)

7.3.3 FOLLOW-UP

Follow-Up Visits (every 12 weeks +/- 7 days after Safety Visit up to 12 months)

- Directed physical examination, vital signs and brief review of systems.
- Survival status and anti-cancer therapy status
- Medication reconciliation.
- Toxicity/ AE assessment
- ECOG performance status assessment.
- Hematology (hemoglobin, HCT, RBC, WBC with differential [neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils)
- Chemistry (ALT, AST, alkaline phosphatase, total bilirubin, LDH, calcium, bicarbonate, sodium, potassium, chloride, creatinine, BUN, total protein and albumin)

7.3.4 FINAL STUDY VISIT

When it is determined the patient will end treatment under this study, an End of Treatment (EOT) Visit will be carried out. A Final Study Visit will occur at the next regularly scheduled 12 week Follow-Up Visit after trial closure is confirmed. This visit is to discuss study closure with the subject. Any AE that is ongoing will be considered ongoing at the Final Study Visit.

- Directed physical examination, vital signs and brief review of systems.
- Medication reconciliation.
- Toxicity/ AE assessment
- ECOG performance status assessment.
- Hematology (hemoglobin, HCT, RBC, WBC with differential [neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils)

- Chemistry (ALT, AST, alkaline phosphatase, total bilirubin, LDH, calcium, bicarbonate, sodium, potassium, chloride, creatinine, BUN, total protein and albumin)

- Provide final instructions to the subject and inform subject if results will be available or any planned presentation or publication of study data.

7.3.6 UNSCHEDULED VISIT

Any visit not included on the Schedule of Events Table that includes examination in the Moffitt hematology clinic, inpatient hospitalization, laboratory evaluations or management of adverse events, will be considered an Unscheduled Visit. It will be documented in the subject's medical record and included on the adverse event log. Adverse event or serious adverse event data will be collected in Oncore. No separate Oncore form for an unscheduled visit will used to collect additional data.

7.3.7 SCHEDULE OF EVENTS TABLE

All visits beginning at week 0 may be performed within +/- 3 days	Screening (day -28 to -1)	Week 0	Week 1	2	3	6	7	8	9	10	12	15	18	21	24-51 (every 3 weeks)	EOT Visit	30 days post EOT [13]	Follow-up[14]
Informed Consent	X																	
Inclusion/Exclusion Criteria	X																	
Demographics and Medical History	X																	
Concomitant Medication Review	X	X			X	X			X		X	X	X	X	X	X	X	X
Prevnar 13 vaccination						X												
Pembrolizumab administration [2]		X			X	X			X #4		X	X	X	X	X			
Ibrunitib dosing [2]						X	X	X	X	X	X	X	X	X	X			
Post-study anticancer therapy status																		X
Survival Status																		X
Review Adverse Events[1]		X			X	X			X		X	X	X	X	X	X	X	X
Full Physical Examination	X																	
Directed Physical Examination		X			X	X			X		X	X	X	X	X	X	X	X
Vital Signs (temp, pulse, resp, BP)/ Weight	X	X			X	X			X		X	X	X	X	X	X	X	X
ECOG Performance Status	X	X			X	X			X		X	X	X	X	X	X	X	X
Hepatitis B and C Panel, HIV AB/AG combo	X																	
Pregnancy Test – Serum Beta-HCG[3]	X																	
PT/INR and aPTT	X																	
Hematology[4]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive metabolic panel (CMP)[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TLS evaluation[6]		X	X	X	X	X	X	X	X	X								
Urinalysis	X																	
Peripheral blood for:	X																	

All visits beginning at week 0 may be performed within +/- 3 days	Screening (day -28 to -1)	Week 0	Week 1	2	3	6	7	8	9	10	12	15	18	21	24-51 (every 3 weeks)	EOT Visit	30 days post EOT [13]	Follow-up[14]
ZAP-70, IgHV mutational status, FISH for CLL[7]																		
Peripheral blood for: *B*-2 microglobulin	X																	
T3, T4 and TSH	X																	
EKG	X																	
Tumor Imaging[10]	X										X				X week 24 only	X		
Bone marrow biopsy[11]	X															X		
Correlative Studies Blood Collection[12]		X				X								X		X		

[1] Baseline symptoms will be assessed and recorded on day 1. Adverse event data will be captured from the time of consent. Events will be reviewed and assessed on days of the clinic visits for physical examinations. Additional safety evaluation will be performed 30 days from last dose of ibrutinib and 90 days from pembrolizumab.

[2] Pembrolizumab infusions will be every 3 weeks (+/- 3 days) for 51 weeks. Ibrutinib will be dispensed every 3 weeks on the day of the pembrolizumab infusion. The last dispensing of ibrutinib will occur at week 51 and dosing will continue for an additional 3 weeks. A pill diary will be provided to participants with every dispensing of ibrutinib supply. Pill diary from previous dispensing will be reviewed for accountability.

[3] Serum pregnancy test will be performed on females of childbearing potential (FCBP). A FCBP is considered when a sexually mature female: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months.

[4] Hematology will consist of CBC and differential with platelet counts. CBC/differential will be performed at day 1, week 0,1,2 after starting pembrolizumab and then weekly for the first month on ibrutinib (weeks 6, 7, 8, 9, 10). Starting at week 12, CBC/diff will be performed on days of the clinic visits for physical examinations/drug administration. Further CBCs with differential will be performed per physician discretion.

[5] CMP includes: sodium, potassium, chloride, CO2, calcium, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, AST/SGOT, ALT/SGPT, LDH. Subjects will have CMP , week 0, 1, 2 after starting pembrolizumab and then weekly for the first month on ibrutinib (weeks 6, 7, 8, 9, 10). Starting at week 12, CMP will be performed on days of the clinic visits for physical examinations/drug administration. Further CMPs will be performed per investigator discretion.

[6] TLS (tumor lysis syndrome) laboratory assessment will include: BUN, creatinine, phosphorus, potassium, LDH, uric acid. TLS laboratory evaluation will occur at days 1-3 of week 0 weeks 1 and 2 after starting pembrolizumab and then weekly for the first month on ibrutinib (weeks 6, 7, 8, 9, 10). Further TLS assessments will depend on clinical condition and/or at investigator discretion.

[7]Peripheral blood samples for ZAP-70, IgVH mutational status, and FISH testing will be done ONLY if not ever performed. Previous results must be available in the medical record for determination of eligibility.

[10] Tumor imaging will consist of CT of the neck, chest, abdomen and pelvis that will be performed at screening, if not done within 3 months prior to study entry. Response assessment will be done at week 12, week 24, and end of 51 weeks of treatment. CT scans may be performed at different intervals at investigator discretion (i,e. suspicion of progressive disease). Imaging studies post treatment discontinuation will be performed per investigator discretion (including end of treatment imaging assessment).

[11] Bone marrow biopsy will be performed at screening (if not performed within 30 days) and after the end of pembrolizumab and ibrutinib therapy (28-35 days after week 51). If subject discontinues treatment early or progression of disease is suspected, a bone marrow biopsy will be per investigator discretion. During follow-up, bone marrow biopsies will be performed per investigator discretion.

[12] Correlative studies. Please refer to Section 4.1 for biomarkers to be studied. They will be performed at baseline (prior to first dose of study drug), at week 6, week 21, and end of ibrutinib treatment. See Section 7.2 for correlative sample collection procedure. They will be performed at investigator's discretion if early study termination

[13] Safety follow-up will be 90 days after the end of pembrolizumab treatment (may be at the regularly scheduled monthly visit that is nearest to 90 days if continuing on ibrutinib treatment) and 30 days post discontinuation of ibrutinib treatment. If the subject discontinues early, safety follow up must occur before first dose of the next therapy.

[14] Follow-up after a subject has discontinued trial treatment will be every 12 weeks for 12 months.

7.4 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

All patients should be maintained on the same medications throughout the study period, as medically feasible. The investigator should instruct the patient to notify the study staff about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be recorded:

- Administration of pegfilgrastim or filgrastim following initiation of protocol therapy is at investigator's discretion for all patients;
- Administration of erythropoietin or darbopoietin is allowed;
- Patients must be instructed not to take any additional medications (including herbal supplements and over-the-counter products) during the trial without prior consultation with the investigator. All medications taken within 30 days of screening should be recorded. If concomitant therapy must be added or changed, the reason and name of the drug/therapy should be recorded;
- In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient are allowed, including drugs given prophylactically (e.g. antiemetics or steroids), with the following exceptions:
- CYP3A Inhibitors/Inducers o Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.
  - Strong inhibitors of CYP3A (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone, or cobicistat) should be avoided
  - If a strong CYP3A inhibitor must be used in the short term, ibrutinib will be held for the duration of inhibitor use. Subjects will be monitored more closely for signs of ibrutinib toxicity (at the investigator's discretion). No dose adjustment is required in combination with mild inhibitors.
  - Grapefruit and Seville oranges should be avoided during ibrutinib treatment, as these contain moderate inhibitors of CYP3A
  - Avoid use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.
  - Dose modifications of ibrutinib are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors.
  - Refer to package insert for a complete chart of recommended dose modifications for use with CYP3A inhibitors.
  - 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.

Anti-platelet 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 with congenital bleeding diathesis have not been studied. For guidance on ibrutinib and the use of anticoagulants during procedures/surgeries see Section 5.3.
- Patients who need to be on anticoagulant therapy during treatment with ibrutinib should be treated with

low molecular weight heparin as the preferred therapy.

- Subjects requiring the initiation of therapeutic anticoagulation therapy (e.g., 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.

7.5 JUSTIFICATION FOR SENSITIVE PROCEDURES

Not Applicable

7.5.1 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

See Section 7.4

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial: (except for ibrutinib at 420mg and pembrolizumab as they are part of the trial)

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab or ibrutinib
- Radiation therapy. Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed..
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Principal Investigator.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.
The Exclusion Criteria describes other medications, which are prohibited in this trial.
There are no prohibited therapies during the Post-Treatment Follow-up Phase.

7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Tumor lysis syndrome
It will follow our Moffitt Cancer Center institutional standards for TLS prophylaxis. All patients with high tumor burden (WBC > 25 000 and/or bulky disease [masses or lymphadenopathy greater than 7.5cm) must be treated with allopurinol (or alternative) starting 12 to 24 prior to the first infusion of pembrolizumab. TLS prophylaxis medications may be discontinued at the investigator discretion.

Anti-infectives prophylaxis
If clinically indicated, antiviral, antifungal, antiparasitic (such as Pneumocystis Jiroveci pneumonia) and/or antibacterial may be considered but it Is not mandated in this study.

Prevnar 13 vaccination

For standard evaluation of immunogenicity the Pneumococcal 13-valent Conjugate Vaccine (Prevnar 13) will be utilized. Patients will receive Prevnar 13 n week 6 day 1 (if not given in the prior 8 weeks). The dose will be the standard 0.5 mg single dose prefilled syringe administered by intramuscular (IM) route

7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

If it is determined that the patient continuing to receive clinical benefit from the trial at the end of the study. The treating physician will work with the patient's insurance in order to obtain ibrutinib

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Schedule of Events and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version v5.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Merck and Janssen products include any pharmaceutical product, biological product, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck or Janssen for human use.

8.1.1.1 Merck Definition of an Overdose and Reporting of Overdose

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20% over the prescribed dose. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.
If an adverse event(s) is associated with ("results from") the overdose of a product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.
If a dose of a product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical

Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect." All reports of overdose with and without an adverse event must be reported within 24 hours Merck Global Safety (See SAE Section 8.1.2).

8.1.1.2 Reporting of Pregnancy and Lactation to Merck and Janssen.

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 90 days of completing the trial or 30 days following cessation of treatment. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Any subject who becomes pregnant during the study, must be promptly withdrawn from the study and discontinue further study treatment. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, congenital anomaly, ectopic pregnancy, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours of their knowledge of the event to Janssen using the Serious Adverse Event Form and to Merck Global Safety (See Section 8.1.2). Because the effect of the Janssen medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen medicinal product will be reported by the Investigator within 24 hours of their knowledge of the event using the Serious Adverse Event Form. Depending on local legislation, this may require prior consent of the partner. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.1.1.3 Event of Clinical Interest for Pembrolizumab

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report form and reported within 24 hours to Merck Global Safety (See Section 8.1.2).

Events of clinical interest for this trial include:

1. An overdose of Merck product, (as defined in Section 8.1.1.1 - Definition of an Overdose) that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.
3. In the event a subject develops any of the following AEs, a detailed narrative of the event should be reported as an ECI within 24 hours to Merck Global Safety (See Section 8.1.2)
    a. Grade $\geq$ 3 diarrhea
    b. Grade $\geq$ 3 colitis
    c. Grade $\geq$ 2 pneumonitis
    d. Grade $\geq$ 3 hypo- or hyperthyroidism

A separate guidance document has been provided entitled "event of Clinical Interest and Immune-Related Adverse Event Guidance Document." This document provides guidance regarding identification, evaluation and management of ECIs and irAEs. Additional ECIs are identified in this guidance document and also need to be reported within 24 hours to Merck Global Safety.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing

should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

ECIs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the Merck's product, must be reported within 24 hours to Merck Global Safety (See Section 8.1.2).

8.1.1.4 Event of Clinical Interest for Ibrutinib

Adverse events of special interest are events that Janssen Scientific Affairs, LLC. is actively monitoring as a result of a previously identified signal (even if non-serious). These adverse events are:

- Major Hemorrhage

Major hemorrhage is defined as any hemorrhagic event that is Grade 3 or greater in severity or that results in 1 of the following: intraocular bleeding causing loss of vision, the need for a transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization, or prolongation of hospitalization.

- Intracranial Hemorrhage

Any intracranial hemorrhage adverse event, including subdural hematoma/hemorrhage, epidural hematoma/hemorrhage and intracerebral hemorrhage, of any grade severity, will be captured as an event of special interest.

- Other Malignancies

In addition to all routine AE reporting, all new malignant tumors, including solid tumors, skin malignancies and hematologic malignancies, are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

Any Adverse Event of Special Interest that is to be reported to Janssen Scientific Affairs should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs (see Section 8.4.2) within 24 hours of knowledge of the event.

8.1.1.5 Janssen Individual Case Safety Report (ICSR)

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a Janssen medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected Janssen medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

8.1.1.6 Janssen Product Quality Complaints (PQC)

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available. Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Suspected Contamination
- Suspected Counterfeit

8.1.1.7 Janssen Special Reporting Situations

Safety events of interest for a Janssen medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

These safety events may not meet the definition of an adverse event; however, from Janssen Scientific Affairs, LLC perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

AEs and suspected adverse reactions are considered "serious" if, in the view of either the investigator or sponsor, they result in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS

Unanticipated problems (UPs) involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- 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 participant

population being studied;

- Related or possibly related to participation in the research ("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
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

All AEs of unknown etiology associated with pembrolizumab or ibrutinib exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) or UP.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

All AEs will be graded using the CTCAE 5.0 criteria.

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 RELATIONSHIP TO STUDY AGENT

For all collected AEs, the investigator will evaluate the participant and will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other

concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3 EXPECTEDNESS

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews with study participants presenting for medical care, or upon review by a study monitor. All AEs, including local and systemic reactions not meeting the criteria for SAEs, will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of event. All AEs occurring during the study must be documented appropriately, regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of AEs will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as "intermittent" require documentation of onset and duration of each episode in the medical record.

Adverse events for the purpose of this study will be reported from the time period beginning when the consent form is signed until 90 days after the end of pembrolizumab infusions and 30 days after the last dose of ibrutinib. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization are achieved. Any AE present at the time of final study closure will be considered ongoing.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

Adverse event documentation will be performed by entry into the Moffitt OnCore electronic database. Reporting of adverse events to the FDA for IND renewal will occur annually by a report obtained from the AEs collected in OnCore. Reporting to Merck and Janssen will be as noted in the section on AEs of special interest.

All AEs will be documented on a paper log with columns for the replication of the fields in the OnCore AE data form. The treating physician/investigator will review the log for accuracy and assign CTCAE grade and the attribution of a study agent to the AE.

Adverse events for the purpose of this study will be reported from the time period beginning when the consent form is signed until study drug discontinuation per the following guidelines:

1. Pembrolizumab- 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier.

2. Ibrutinib- 30 days following cessation of treatment

8.4.2 SERIOUS ADVERSE EVENT REPORTING

Merck: For the time period beginning when the consent form is signed until treatment allocation, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study, whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Janssen: For the time period beginning when the consent form is signed until 30 days after cessation of ibrutinib, all serious adverse events will be reported within 24 hours to Janssen Scientific Affairs.

Any adverse event classified as an SAE, will be reported by the appropriate research staff to the following within 24 hours of knowledge of the event.

1. To the Protocol Monitoring Committee via entry into the OnCore data base
2. To the IRB as required by the Chesapeake IRB reporting criteria
3. Janssen Scientific Affairs
   Preferred- electronically via Janssen SECURE email IIS-BIO-VIRO-GCO@its.jnj.com
   For business continuity purposes, if SECURE email if non-functional:
   a. Fax- 1-866-451-0371 (retain confirmation receipt)
   b. Telephone- if neither email nor fax are functional- 902-405-2671

4. Merck Global Safety
   Attn: Worldwide Product Safety
   Fax: 215-993-1220

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by Merck Safety or Janssen Scientific Affairs and should be provided as soon as possible. The study sponsor will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of

the information.

8.4.3 UNANTICIPATED PROBLEM REPORTING

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the study sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the study sponsor within 2 business days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures) and the supporting agency head (or designee), within 7 days of the IRB's receipt of the report of the problem from the investigator.

8.4.4 EVENTS OF SPECIAL INTEREST

8.4.4.1 Event of Clinical Interest for Pembrolizumab

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report form and reported within 24 hours to Merck Global Safety (See Section 8.1.2).

Events of clinical interest for this trial include:

1. An overdose of Merck product, (as defined in Section 8.1.1.1 - Definition of an Overdose) that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.
3. In the event a subject develops any of the following AEs, a detailed narrative of the event should be reported as an ECI within 24 hours to Merck Global Safety (See Section 8.1.2)
    a. Grade ≥ 3 diarrhea
    b. Grade ≥ 3 colitis
    c. Grade ≥ 2 pneumonitis
    d. Grade ≥ 3 hypo- or hyperthyroidism

A separate guidance document has been provided entitled "event of Clinical Interest and Immune-Related Adverse Event Guidance Document." This document provides guidance regarding identification, evaluation and management of ECIs and irAEs. Additional ECIs are identified in this guidance document and also need to be reported within 24 hours to Merck Global Safety.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

ECIs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the Merck's product, must be reported within 24 hours to Merck Global Safety (See Section 8.1.2).

8.4.4.2 Janssen Special Reporting Situations

Safety events of interest for a Janssen medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

These safety events may not meet the definition of an adverse event; however, from Janssen Scientific Affairs, LLC perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

8.5 STUDY HALTING RULES

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology and blood chemistry parameters and regular physical examinations. Adverse events will be evaluated continuously throughout the study. Safety and tolerability will be assessed according to the NIH/NCI Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) that is available at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

The Protocol Monitoring Committee (PMC) at Moffitt monitors its assigned ongoing research protocols for: adverse event reporting, data and safety monitoring, and internal audit findings. The PMC, upon review of any agenda item, may approve the study for continuation, require revisions, suspend or close a protocol.

Investigators of studies which are designated to be reviewed by the PMC for data and safety monitoring, shall provide a statistical report of the study's progress and summary of adverse events and deviations based on the phase of the study and the associated risk of the study or more often if applicable. The PI will be notified for recommendations or notifications after the PMC review in regards of continuation or stopping the clinical trial

8.6 SAFETY OVERSIGHT

Serious Adverse Events: Serious Adverse Events (SAEs) from this protocol will be reported concurrently to the IRB and the study sponsor within 24 hours of staff awareness of the event. The Protocol Monitoring Committee (PMC) will review these SAEs in accordance with their policy. The data and safety plan will define dose limiting toxicities, rules for escalation of dose, and criteria for stopping the trial according to rules set forth by this protocol. This trial will be continuously monitored by the PI and the research team. A final safety and monitoring report will be submitted to the PMC. This protocol will be subject to periodic internal audits based on risk or as recommended by the PMC.

9 CLINICAL MONITORING

Data will be captured in OnCore, Moffitt's electronic Clinical Trials Database. For each participant enrolled, the electronic CRF must be completed by the assigned data manager or other authorized study staff. Any paper forms should be typed or filled out indelible ink and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his/her authorized delegate. This also applies to records for those patients who fail to complete the study. If a patient stops dosing or terminates from the study, the dates and reasons must be noted on the CRF. If a patient terminates from the study because of a DLT, thorough efforts should be made to clearly document the outcome. Regulatory documents and case reports forms will be monitored internally according to the Moffitt Cancer Center monitoring policies. Monitoring will be performed regularly by the MCC Clinical Monitoring Core for accuracy, completeness, and source verification on data entry, validation of appropriate consent process, reporting on SAEs, and adherence of the protocol, GCP guidelines and applicable regulatory requirements.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

Enrolled patients will be evaluable for response assessment if receiving at least 4 weeks into ibrutinib therapy and at least 2 cycles of pembrolizumab. It will be used for efficacy and safety analysis. The primary endpoint of this trial is the complete response (CR) with the hypothesis of obtaining CR in 30% of patients and the secondary end point is the overall response rate (ORR, the immune response to the vaccine measured as T cell subset alterations, B-cell immune response potency to the vaccine and the cytokine patterns in treated patients. Exact binomial 95% confidence intervals for the true ORR will be calculated.

10.2 DESCRIPTION OF STATISTICAL METHODS

10.2.1 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The Simon's minmax two-stage design will be used to test the null hypothesis that complete response (CR) $\leq$ 10% versus the alternative that CR $\geq$ 30% with 90% power and a type I error rate of 10%. This will result in an expected sample size of 20.37 and a probability of early termination of 0.52. After testing the drug combination on 16 patients in the first stage, the trial will be terminated if 1 or fewer respond. If the trial goes on to the second stage, a total of 25 patients will be studied. If the total number responding is less than or equal to 4, the drug combination will be rejected. Statistical analyses will be descriptive in nature. Patients' demographics, AEs and serious AEs, disease status, and CR will summarized by descriptive statistics.

Clinical response rates will be calculated with 95% CIs.

10.2.2 ANALYSIS OF THE SECONDARY ENDPOINT(S)

1. Change in T cell exhaustion and/or inhibition following treatment
2. Change in serum immunoglobulin levels following treatment
3. Progression free survival (PFS) and association with immune biomarkers

To determine if T cell exhaustion or inhibition have change due to treatment with the combination therapy at baseline immune testing to immune testing following completion of pembrolizumab and ibruntinib treatments (week 52) using paired t-tests with the null hypothesis being that there is no change in immune measurements following treatment (i.e., $Ho: \mu_d = 0$). If the assumptions of normality do not hold upon assessment, we will instead use nonparametric t-tests (i.e., Wilcoxon Sign Rank Test). Similar tests will be used to determine if changes in serum immunoglobulin levels also resulted following treatment. Tests will be one-sided as based on biology expect the change in immune response to be in one direction following treatment. Tests will be considered statistically significant if the p-value is less than 0.05. Assuming the study go on to stage II and enroll 25 patients, we will be able to detect a modest effect size of 0.60. To determine the association of progression free survival (PFS) with immune biomarkers (T cell exhaustion and/or inhibition, serum immunoglobulin levels), Cox proportional hazards models will be fit with assumption of proportional hazards (PH) assumption check via Schoenfeld residuals. If the PH assumption does not hold, we will rely on use of non-parametric methods (Kaplan-Meier curve with log-rank tests) where the biomarkers will be dichotomized for analysis based on an optimal cut-point determination based on an outcome-oriented approach outlined by Contral and O'Quigley (Contal C, O'Quigley J. An application of changepoint methods in studying the effect of age on survival in breast cancer. Computational Statistics & Data Analysis. 1999;30:253-70.). A Cox regression of the log hazard ratio on the continuous biomarker (assuming a standard deviation of 1 and an anticipated event rate of 0.50) will have 80% power at a 0.05 significance level to detect a regression coefficient equal to 0.79 (i.e., hazard ratio of 2.20).

10.2.3SAFETY REVIEW

Evaluation is based on strict stopping criteria for unacceptable toxicities. Specifically, in the 1st stage, we continuously evaluate toxicity for the 1st 16 patients (e.g., patients in first stage of Phase II study). Toxicity will be also evaluated at end of the 2nd stage for the total 25 patients. We consider 20% as the maximum allowable unacceptable toxicity rate (failure to engraft included) with a 0.05 probability of stopping early. Sequential boundaries will be used to monitor dose-limiting toxicity rate as outlined by Ivanova et al. [59]. The accrual will be halted if excessive numbers of dose-limiting toxicities are seen, that is, if the number of dose-limiting toxicities is equal to or exceeds b_n out of n patients (see table below).

Number of Patients, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Boundary, b_n	-	-	3	4	4	4	5	5	5	6	6	6	7	7	7	7

10.2.4 EXPLORATORY ANALYSES

Biological samples for each of the 25 patients enrolled in the trial will be collected at 4 time-points. As the correlative experiments are not the primary focus of the study and are more exploratory in nature, no sample size / power calculations were completed. Summary statistics will be used to summarize the quantitative measures (e.g., cytokine levels, expression levels) for the patients at the 4 time-points with two-sample t-test use to determine if quantitative measurements differ between patients that response and patients that do not response at each time point. When assessing changes in quantitative measurements between time-points (e.g., pre and post treatment measurements) paired t-tests will be used. Longitudinal analysis with linear mixed models will also be used to look for statistical differences between the responders and non-responders using quantitative measurements at all 4 time-points. Correlation between quantitative measurements will be assessed with Spearman correlation.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The PI and other appropriate study staff are responsible for maintaining appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. Representatives of Merck, Janssen, and federal regulatory agencies may examine records for the purpose of quality assurance reviews, evaluation of the study safety, progress of the trial, and data validity.

Source documentation in both electronic and paper form shall be retained for at least two years after the final closure of the trial. These include hospital records, clinical research subject charts (with paper AE logs), research laboratory notes, electronic CRFs, and pharmacy dispensing records.

12 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control procedures will be implemented beginning with the OnCore data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the staff for clarification/resolution.

Following written SOPs, the Moffitt internal monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., good laboratory practices (GLP), good manufacturing practices (GMP)).

The investigational site will provide direct access to source data/documents, and reports for the purpose of monitoring and auditing, and inspection by local and regulatory authorities.

All staff will be trained by the PI through a site initiation presentation, power point training for training on the initial protocol for those staff unable to attend the initiation presentation, and ongoing self-study as protocol amendments are approved. Training will be documented on a signature log that will be filed in the electronic regulatory binder.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study agent, study procedures, and risks will be given to the participant and written documentation of informed consent will be required prior to starting intervention/administering study product.
Other documents to be submitted for review:

- Oral study drug Patient Compliance Diary

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the

sponsor and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The Moffitt study monitor, other authorized representatives of Moffitt, representatives of the IRB or pharmaceutical companies supplying study products may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Moffitt. This will not include the participants' contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Moffitt research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Moffitt.

13.5 FUTURE USE OF STORED SPECIMENS

Data collected for this study will be analyzed and stored at Moffitt Cancer Center. After the study is completed, the de-identified, archived data will be stored at Moffitt Cancer Center, under the supervision of Eva Sahakian, PhD, for use by other researchers including those outside of the study. Software tracking programs include FileMaker Pro and Excel.

With the participant's approval and as approved by local IRBs, de-identified biological samples will be stored at Dr. Sahakian's lab at Moffitt Cancer Center. These samples could be used for research into the causes of CLL, its complications, and other conditions for which individuals with CLL are at increased risk, and to improve treatment. After completion of the study, samples to be stored will be identified by using only the subject initials and date of collection.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage will not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through Eva Sahakian, PhD or her successor.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. All paper source documents will be scanned into the electronic medical record of each subject for storage. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into OnCore, a 21 CFR Part 11-compliant data capture system provided by Moffitt. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the drug combination studied in this protocol. No records will be destroyed without the written consent of the sponsor, if applicable.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations as defined by the Moffitt Clinical Trials Office standard. All deviations must be addressed in study source documents. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

14.4 PUBLICATION AND DATA SHARING POLICY

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in

patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine.

The PI will provide to the Protocol Information Specialist at Moffitt Cancer Center, details as requested for registering and reporting results for this clinical trial on ClinicalTrials.gov. At the conclusion of the trial, the PI will make study results available to the research community and the public-at-large.
Authorship in publications will be determined by the PI depending on participation, enrollment, and significant contribution during trial process and manuscript elaboration.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

Not Applicable

16 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership and the Moffitt Cancer Center have established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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APPENDIX

Appendix A

iwCLL Criteria to Initiate Treatment of CLL (Reference #14)

c. Evidence of progressive marrow failure manifested as worsening anemia and/or thrombocytopenia (Rai stages III or IV)

d. Massive or progressive or symptomatic splenomegaly.

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

f. 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 also be obtained as liner regression at 2 weeks intervals over an observation period of 2 to 3 months.

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

h. Constitutional symptoms defines as: unintentional weight loss of 10% or more within the previous 6 months, significant fatigue (i.e, ECOG PS 2 or worse, inability to work or perform usual activities), fever higher than 100.5 ^{o}F (38.0 ^{o}C for 2 or more weeks without evidence of infection, night sweats.

Appendix B

ECOG Performance Status

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

Appendix C

Response Criteria per International CLL Working Group

The International Workshop on Chronic Lymphocytic Leukemia (IWCLL) included updated response criteria in their 2008 publication [14].

The response categories are:

- **Complete remission (CR)**, requiring absence of peripheral blood clonal lymphocytes by immunophenotyping, absence of lymphadenopathy, absence of hepatomegaly or splenomegaly, absence of constitutional symptoms and satisfactory blood counts
- **Complete remission with incomplete marrow recovery (CRi)**, defined as CR above, but without normal blood counts
- **Partial remission (PR)**, defined as ≥ 50% fall in lymphocyte count, ≥ 50% reduction in lymphadenopathy or ≥ 50% reduction in liver or spleen, together with improvement in peripheral blood counts
- **Progressive disease (PD)**, defined as ≥ 50% rise in lymphocyte count to > 5 x10^9/L, ≥ 50% increase in lymphadenopathy, ≥ 50% increase in liver or spleen size, Richter's transformation, or new cytopenias due to CLL
- **Stable disease**, defined as not meeting criteria for CR, CRi, PR or PD