Protocol with Statistical Analysis Plan Cover Page:

Official Title:	A Phase II Study of Ibrutinib, Fludarabine, and Pembrolizumab in High-Risk or Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)
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CLINICAL RESEARCH PROJECT

Protocol #: 17-H-0118
Drug Names: Ibrutinib, Fludarabine, Pembrolizumab
IND: Ibrutinib (113752)

Title: A Phase II Study of Ibrutinib, Fludarabine, and Pembrolizumab in High-Risk or Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

Short Title: Simultaneous targeting of B and T cells in CLL

Keywords: Ibrutinib, Fludarabine, Pembrolizumab, BTK Inhibitor, Checkpoint Inhibitor, CLL, SLL

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Company Providing Investigational Drug: Merck; Pharmacyclics, an Abbvie Company

Subjects of Study:

Number	Sex	Age-range
25 evaluable	M/F	> 18

(Accrual Ceiling 30, to account for ineligible subjects)

Ionizing Radiation for Research:	Yes
Off-Site Project:	No
Multi-center trial:	No
DSMB Involvement:	Yes

PRÉCIS

Background:

- Chronic lymphocytic leukemia and small lymphocytic lymphoma (hereby referred to as CLL) are tumors of B cells. A subset of patients categorized as high-risk CLL has unfavorable outcomes when treated with conventional chemotherapy. High-risk CLL is defined by relapsed/refractory disease status, or the presence of high-risk genetic changes, such as deletion 17p and aberrations affecting *TP53*, *NOTCH1, SF3B1* and *MYC* genes. Studies have indicated two critical factors are required for the proliferation of CLL cells. First, CLL cells grow and survive because they receive signals through the B-cell receptor (BCR). Second, CLL cells benefit from interactions with other immune cells, especially T cells.

- The stimulation through the BCR can be blocked by ibrutinib, which is an oral drug that selectively inhibits Bruton's tyrosine kinase. In clinical trials, ibrutinib demonstrated safety and high response rates in patients with high-risk disease. Ibrutinib has gained FDA approval as a treatment for CLL regardless of prior treatment or cytogenetic status. However, single-agent ibrutinib has limitations; the drug does not eliminate all tumor cells and, with time, the tumor cells may become resistant. Therefore, combination of ibrutinib with other drugs could be beneficial.

- This study investigates the combination of ibrutinib, fludarabine and pembrolizumab for treatment of CLL. Fludarabine is a well-tolerated drug that has been used widely to treat CLL. Also, fludarabine can kill both malignant B cells and T cells that support the growth of leukemia cells. Pembrolizumab targets immune checkpoint molecules and enhances the cell-killing activity of T cells. With this approach we aim to achieve a greater reduction in CLL cells than with single agent ibrutinib and restore healthier immune system that could contribute to durable responses.

Objectives:

- To investigate the rate of complete response to ibrutinib, short course fludarabine and pembrolizumab.

Key eligibility criteria:

- Patients with CLL meeting treatment indications per iwCLL guidelines.
- High-risk disease defined by one of the following:
    - Relapsed/refractory disease
      OR
    - High-risk genetic changes: deletion 17p, *TP53* or *NOTCH1* or *SF3B1* mutation, *MYC* aberration, or complex cytogenetics.

Design:

- This is a single-arm, open-label phase 2 study.
- Timeline: Treatment on this study is given in cycles from cycle -3 to 17, then in months beyond cycle 17. Cycles -3 to -1 are 28-day cycles. Cycles 1 to 17 are 21-day cycles. After completion of 1 year of pembrolizumab, the time on study is by chronological months on study from starting pembrolizumab.
- Treatment plan: Ibrutinib is given daily until disease progression or intolerable side effects occur. Fludarabine is given on cycle -2 only. Pembrolizumab is given every 3 weeks starting from cycle 1

for 1 year. Minimal residual disease will be measured at 2 years from cycle 1 to determine the need for long-term treatment with ibrutinib.

1.0 OBJECTIVES

1.1 Primary objective

- To test the rate of complete response of the combination of ibrutinib, fludarabine, and pembrolizumab in patients with high-risk and/or relapsed/refractory chronic lymphocytic leukemia (CLL) and small lymphocytic leukemia (SLL)

1.2 Secondary objectives

- Tolerability of the combination regimen
- Overall response rate (ORR)
- Duration of response (DOR)
- Best response
- Minimal residual disease (MRD) status
- Progression-free survival (PFS)
- Overall survival (OS)
- To explore the biologic effects on B- and T-cell subsets and function
- To identify predictors of clinical response

2.0 BACKGROUND & RATIONALE

2.1 Pathophysiology

CLL is characterized by clonal proliferation of auto-reactive B cells mediated by B cell receptor (BCR) signaling. The BCR is a multimeric complex formed by the assembly of surface immunoglobulin (Ig) homodimer and Igα/Igβ (CD79a/CD79b) heterodimer. Engagement of antigen at BCR phosphorylates immunoreceptor tyrosine-based activation motifs (ITAM) motif and links Ig chains to intracellular Src family tyrosine kinases. Activation of BCR signaling leads to downstream activation of Bruton tyrosine kinase (BTK).[1] Therefore, BTK is an important therapeutic target for BCR-addicted leukemic B cells.

The second key component of CLL pathogenesis is a bidirectional interaction between tumor and microenvironment. T cells in tumor microenvironment have a stimulatory role for the survival of CLL cells. *In vitro*, apoptosis of CLL cells can be rescued by stromal cell co-culture or by the addition of soluble factors.[2,3] In human, T and leukemic B cells aggregate to form 'proliferation centers' within bone marrow (BM) and lymphoid tissues, where these rallied cells form immune synapses.[4] CD40 ligand form a crosstalk between T and CLL cells which stimulates leukemic B cell survival and promotes resistance to apoptosis.[5,6] In addition, T cells in CLL are functionally[4] and phenotypically[7] defective, and allow malignant B cells to escape immune surveillance. "Pseudo-exhaustion" of effector T cells is explained by increased expression of immune checkpoints on CLL cells[4,8] and by increased number of regulatory T cells in CLL patients.[9]

2.2 Epidemiology

CLL is the most common leukemia of adults in Western countries with an annual incidence of 2-4.5 per 100,000 in general population. North American Association of Central Cancer Registries estimated that 14,620 men and women to be newly diagnosed with CLL in 2015.[10] CLL affects males more frequently than females. It is a disease of older individuals with the median age of 73 years for Caucasian.[11] Incidences vary by ethnicity. The highest incidence is seen in Caucasians, followed by African Americans, and it is much lower in Asians and Hispanics.

2.3 Diagnosis

2008 World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues defines CLL as an absolute count of >5.0x10^9 monoclonal B cells/L with a CLL immunophenotype in the peripheral blood (PB), if there is an absence of disease-related symptoms or cytopenia, or tissue involvement other than BM.[12] 2008 International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria uses two criteria to be met for the diagnosis of CLL:[13]

- The presence of at least 5x10^9/L morphologically mature-appearing small lymphocytes in the PB.
- Circulating monoclonal B lymphocytes defined by PB flow cytometry. The characteristic pattern of CLL immunophenotype is: expression of the T-cell surface antigen (CD5), expression of B-cell surface (CD19, CD20, and CD23), and low-level expression of surface Ig with either κ or λ (but not both) light chains.

Diagnosis of small lymphocytic lymphoma (SLL) requires the presence of lymphadenopathy and/or splenomegaly confirmed by histopathologic confirmation through lymph node (LN) biopsy when possible, while having < 5x10^9 circulating monoclonal B cells/L. For the purposes of this study, the term "CLL" will encompass both CLL and SLL.

2.4 Staging and other prognostic categories

There are two prognostic staging systems in CLL called Rai and Binet. Rai staging allows stratification of patients into five distinct prognostic groups (Table 1).[14]

Table 1. Rai staging system

Stage	Risk	Manifestation	Median survival (months)
0	Low	Lymphocytosis	120
I	Intermediate	Lymphocytosis with adenopathy	108
II		Lymphocytosis with hepatomegaly or splenomegaly	94
III	High	Lymphocytosis with anemia (Hemoglobin < 11g/dL)	60
IV		Lymphocytosis with thrombocytopenia (Platelet < 100K/μL)	60

The limitation of Rai staging is underestimation of the risk of progression in early stages of disease. For this reason, various prognostic markers have been developed to identify patients with aggressive clinical phenotype. Prognostic markers predictive of poor clinical outcome include the presence of unmutated immunoglobulin variable heavy chain gene (IGHV-U),[15] ξ (zeta)-chain associated protein-70 (ZAP-70),[16] CD38, lymphocyte doubling time (LDT),[17] BM histologic pattern,[18] β-2 microglobulin,[19] and complex cytogenetics.[20]

Among many markers, detection of cytogenetic abnormalities with fluorescence in situ hybridization (FISH) is widely used for risk stratification (Table 2).[21] Deletion 17p, found in 7-10% of newly diagnosed CLL, predicts the worst prognosis. The poor prognosis of deletion 17p is attributable to the functional loss of *TP53* tumor suppressor gene mapped at the deleted loci.

Table 2. Cytogenetic Abnormalities in CLL

Chromosome	Median survival (months)	Median time to first treatment (months)

Deletion 17p13	32	9
Deletion 11q22-23	79	13
Trisomy 12	114	49
Normal	111	33
Deletion 13q14	133	92

More recently, whole genome and exome sequencing have revealed complex mutational landscapes of CLL and the prognostic impact of several driver mutations.[22,23] *NOTCH1* mutation, for instance, is found in 10% of newly diagnosed CLL and is predictive of shorter survival compared to the wild-type (OS: 79.2 months with *NOTCH1* mutation *vs.* not-reached with *NOTCH1* wild-type).[24] Similarly, *SF3B1* mutation is associated with poorer clinical outcome compared to the wild-type.[24] *TP53* mutation is an independent factor predictive of unfavorable outcome in CLL.[25] *MYC* aberration is characterized by an aggressive clinical phenotype with median survival from genetic detection of 19 months.[26]

2.5 Indications of treatment

Newly diagnosed patients with asymptomatic early stage disease (Rai 0, Binet A) should be monitored without intervention unless there is an evidence of rapid disease progression.[27] Symptomatic patients with advanced stage (Rai 3 or 4, Binet B or C) stages usually benefit from treatment. 2008 IWCLL defines active disease by following criteria:[13]

- Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia
- Massive (i.e., at least 6 cm below the left costal margin) or progressive or symptomatic splenomegaly
- Massive (i.e., at least 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy
- Progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time (LDT) of less than 6 months. LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months. In patients with initial blood lymphocyte counts of less than $30x10^9$/L (30,000/μL), LDT should not be used as a single parameter to define a treatment indication. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (i.e., infections) should be excluded.
- Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy
- Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs:
  - Unintentional weight loss of 10% or more within the previous 6 months;
  - Significant fatigue (i.e., ECOG performance status 2 or worse; inability to work or perform usual activities);
  - Fevers higher than 100.5°F or 38.0°C for 2 or more weeks without other evidence of infection; or
  - Night sweats for more than 1 month without evidence of infection.

2.6 Treatment options

2.6.1 Watchful waiting

Asymptomatic early stage disease should be monitored without intervention until disease progression.[13] During the observation period, patients are periodically assessed for the evidence of progressive disease based on symptoms, physical exam and laboratory evaluations.

2.6.2 Frontline chemoimmunotherapy

Treatment for CLL should be individualized based on host and biological factors, including fitness of a patient, comorbidities, disease burden, and cytogenetic features.

Alkylating agents, purine analogues and monoclonal antibodies have different mechanisms of action and toxicity profiles. Combinations of different classes of drugs have improved treatment efficacy in CLL. In previously untreated and medically fit CLL population, ORR was 90% with the combination of fludarabine, cyclophosphamide, and rituximab (FCR),[28] and 88% with bendamustine and rituximab (BR).[29] Efficacy and safety of frontline BR and FCR are being directly compared in an ongoing randomized phase III trial by the German CLL Study Group.[30] Interim report showed identical ORR and similar survival between FCR and BR, while PFS and the depth of response were better in the FCR arm.

Other regimens investigated in CLL are; cladribine plus rituximab, methylprednisolone plus rituximab, fludarabine plus alemtuzumab, and fludarabine, cyclophosphamide plus alemtuzumab. None of these regimens resulted in efficacy comparable to FCR.[31] There are second generation of anti-CD20 monoclonal antibodies including obinutuzumab and ofatumumab. Obinutuzumab plus chlorambucil showed survival benefit compared to chlorambucil alone, and resulted in superior ORR and PFS compared to rituximab plus chlorambucil in previously untreated elderly CLL patients.[32]

The major limitation of conventional chemoimmunotherapy is toxicity. High efficacies of FCR or BR regimens occur at the expense of short- and long-term adverse events and, at times, mortality. Rates of treatment-related mortality are 3.9% with FCR and 2.1% with BR.[30] More than 90% of patients treated with FCR and 78.5% treated with BR experience moderate to severe adverse events equivalent to CTCAE Grade 3 to 5.[30] Hematologic toxicities such as severe neutropenia can occur while on treatment (81.7%) or after treatment completion.[33] Infusional reactions related to monoclonal antibodies also limit the successful delivery of treatment. As a part of long-term toxicities, secondary malignancy can occur after being exposed to alkylating agents. Intergroup E2997 trial reported 8.2% cumulative incidence of myeloid neoplasia at 7 years after treatment with fludarabine plus cyclophosphamide (FC).[34]

The other critical limitation of conventional chemoimmunotherapy is the lack of efficacy with the presence of high-risk mutations. Patients with deletion 17p have inferior overall and depth of responses compared to the overall CLL population after FCR.[28] In addition to FISH-defined high-risk disease, the presence of *TP53* or *NOTCH1* mutation detected by targeted sequencing predicts inferior survival after FCR.[24] Response to the BR regimen is by far inferior in a cohort with 17p deletion (37.5%) than in the overall population (88%).[29] While alemtuzumab-based chemoimmunotherapy increased ORR in 17p deletion to 75-88%, the benefit of high efficacy was offset by toxicity.[35,36] The rate of opportunistic infection increases by 2.5-fold after the addition of alemtuzumab to FC, and is poorly tolerated among elderly patients.[35]

2.6.3 Salvage chemoimmunotherapy

In spite of intensive chemoimmunotherapy, approximately half of the patients treated with frontline FCR return with relapsed and/or refractory diseases.[37] Relapsed/refractory CLL is incurable in most cases and requires multiple lines of salvage treatment.

Conventional chemotherapy options for relapsed/refractory CLL encompass aforementioned regimens. An early study using salvage FCR reported high ORR of 73%.[38] However, the majority of the study population was fludarabine-sensitive (61%) and rituximab-naïve (81%), which are no longer the features of the

relapsed/refractory population due to the frequent frontline use of a purine analog and rituximab. The presence of fludarabine-refractory disease, deletion 17p, or more than 3 prior treatments predict shorter survival.[39] BR is an alternative treatment option, which resulted in ORR of 59% in a multicenter phase II trial of 78 relapsed/refractory CLL.[40] However, the duration of response with BR was short-lived (median event-free survival (EFS): 14.7 months). Ofatumumab was approved by the U.S. FDA in 2009 for CLL refractory to both fludarabine and alemtuzumab, based on the ORR of 47-58% in the heavily pre-treated CLL population.[38] While various chemotherapy regimens are available for relapsed/refractory CLL patients, many have accompanying toxicities, and durable remissions are rare. Prior to the advent of BCR targeted agents, the goal of salvage chemotherapy in CLL was to bridge patients into next treatment or to reduce tumor burden before hematopoietic stem cell transplant.

2.6.4 Stem cell transplant

Allogeneic hematopoietic stem cell transplant remains as the sole curative option for CLL to date. However, only a selected subset of patients can be transplant candidates due to the advanced age of the population (median age at diagnosis: 72),[41] comorbidities, and limitations inherent to the search for optimal stem cell donors. Despite transplant platforms using reduced-intensity conditioning and improved supportive care, non-relapse mortalities in CLL still ranges from 16 to 27% in 3-5 years after transplant.[42] Transplant is currently reserved for a small subset of patients with an available donor, good performance status, minimal comorbidities, and high-risk features.

2.6.5 Targeted agents

BCR signaling is a critical survival signal for malignant B cells. Orally bioavailable kinase inhibitors, such as ibrutinib and idelalisib, can effectively target downstream kinases involved in BCR signaling.

Ibrutinib

Once daily administration of ibrutinib causes sustained inactivation of BTK in malignant B cells.[43,44] The phase 1b/2 trial in 85 relapsed CLL treated with either 420 mg or 840 mg of ibrutinib demonstrated ORR of 71% in both dosing groups with an additional 15-20% with a partial response with lymphocytosis (PR-L).[45] Ibrutinib was compared to ofatumumab in a phase III randomized trial, which showed superior ORR (42.6% vs. 4.1%, $p<.001$) and survival (12-month OS: 90% vs. 79%, hazard ratio 0.43, $p=.005$) of the ibrutinib arm.[46] Responses to ibrutinib appear to be independent of clinical and genomic risk factors. In the elderly CLL population of age 65 years or older, ibrutinib was an effective and well-tolerated initial therapy.[47] In the high-risk CLL population with *TP53* mutation, treatment with a single-agent ibrutinib led to an unprecedented response rate of 97%.[48] Ibrutinib is approved by the U.S. FDA for the treatment of CLL patients regardless of prior therapy or cytogenic status.

Ibrutinib has been investigated in combinations with chemoimmunotherapy. Ibrutinib was combined with rituximab,[49] ofatumumab,[50] FCR or BR[51] in early studies, which appeared to be tolerable and have an improved depth of response. However, an ongoing randomized phase III study comparing BR with or without ibrutinib did not fully translate the promising results of early phase studies. Combination of ibrutinib and 6 cycles of BR led to ORR of 83% and CR of 10%,[52] which were comparable to the efficacy of a single-agent ibrutinib (ORR of 90%, CR of 7%).[46] There is an ongoing randomized study comparing ibrutinib-based combination to ibrutinib alone, which will define the role of chemotherapy in the era of targeted agents.[53]

Idelalisib

Idelalisib selectively inhibits p110δ isoform of PI3K. A phase I study enrolled 54 heavily pretreated relapsed/refractory CLL patients, and demonstrated ORR of 73% with 6 different dose levels of oral idelalisib (range: 50-350mg once or twice daily).[54] The highest median PFS was seen in patients receiving 150mg twice daily or greater (median PFS: 29 months), and no dose-limiting toxicities was observed. Using the 150mg twice daily dosing, the combination of idelalisib and rituximab was compared to placebo and rituximab in a randomized phase III trial.[55] The idelalisib arm had a higher ORR (81% *vs.* 13%, p<0.001) and 12-month OS (92% *vs.* 80%, p=0.02) compared to the placebo arm. Idelalisib was FDA approved in 2014 for the treatment of patients with relapsed CLL, in combination with rituximab, for whom rituximab alone would be considered appropriate therapy due to other co-morbidities, and for patients with SLL who have received at least two prior systemic therapies.

Venetoclax

CLL has dysfunctional intrinsic apoptotic pathways due to the mutation of genes encoding pro-apoptotic proteins, such as p53, or due to overexpression of anti-apoptotic proteins, such as Bcl-2. Venetoclax (ABT-199) is a potent, orally bioavailable, small molecule inhibitor of Bcl-2 that induces apoptosis.[56] A phase I study with venetoclax led to deep and durable remissions in 84 patients with relapsed/refractory CLL (CR or CRi in 22%).[57] The most common adverse events were diarrhea (46%), neutropenia (43%), fatigue (34%), upper respiratory tract infection (29%), and cough (25%). Notably, early studies reported an 11% incidence of grade 3-4 tumor lysis syndrome, which decreased to <5% after dose modification with a ramp-up schedule adopted for later studies. Venetoclax is approved for treatment of CLL patients, with or without deletion 17p, who have received at least one line of therapy.

2.7 Clinical and scientific justification for protocol design

2.7.1 Limitations of currently available treatment options

A subset of CLL patients is at an increased risk of poor clinical outcome when treated with chemoimmunotherapy. High-risk CLL is defined by the relapsed/refractory disease status, or by presence of high-risk cytogenetic mutations, such as deletion 17p, *TP53*, and *NOTCH1*. ORR and PFS in the subgroup with deletion 17p are inferior compared to those in overall CLL population (Table 3). Poor prognosis of deletion 17p persists in spite of the addition of anti-CD20 monoclonal antibodies.

Table 3. Comparison of response: all studied CLL *vs*. subgroup with deletion 17p

Regimen	Ref	N, all studied	N, 17p-	ORR, all studied (%)	ORR, 17p- (%)	PFS, all studied	PFS, 17p-
Treatment-naïve							
FC	[28]	409	29	88	34	45% at 3 years	0% at 3 years
FCR	[28]	408	22	95	68	65% at 3 years	18% at 3 years
BR	[29]	117	8	88	37.5	33.9 months*	NA
Relapsed/refractory							
FCR	[39]	284	20	74	35	20.9 months**	5 months**
Ibrutinib	[58]	132	36	89	79	76% at 30 months	48% at 30 months

BR Bendamustine, rituximab
FC Fludarabine, cyclophosphamide

FCR	Fludarabine, cyclophosphamide, rituximab
NA	Not assessed
PFS	Progression-free survival
Ref	References
17p-	Deletion 17p
*	Median event-free survival
**	Median progression-free survival

BCR inhibitors improved the treatment outcome of high-risk CLL to an unprecedented level. Treatment with a single-agent ibrutinib led to ORR of 82.6% and 12-month PFS of 79.3% in 144 relapsed/refractory CLL with deletion 17p.[59] At the NHLBI, Farooqui *et al.* reported 51 patients with either deletion 17p or *TP53* mutation treated with ibrutinib.[48] ORR (94% at 24 weeks) and PFS (82% at 24 months) were higher in this trial, which was attributable to the study population mix of previously untreated and relapsed/refractory diseases. Ibrutinib is approved by the U.S. FDA for the treatment of CLL patients regardless of prior treatment or the status of deletion 17p.

Nevertheless, accumulating clinical experiences revealed several limitations of targeted agents. *First,* poor prognosis of the high-risk subgroup is not fully overcome by targeted agents. Long-term follow up data of single-agent ibrutinib clearly shows the inferior rate and shorter duration of response with the presence of deletion 17p (Table 3). *Second,* deep responses are infrequent. CR was reported in 2% of relapsed/refractory CLL[45] and 4-13% of previously untreated CLL.[47,60] When ibrutinib was combined with other agents, the CR rate minimally increases to 8% (ibrutinib/rituximab)[49] and 10% (ibrutinib/bendamustine/rituximab).[52] The lack of deep response mandates the continued use of targeted agents, which increases the risk of long-term toxicities and poses a significant financial burden on health care. *Third,* drug resistance can develop during treatment with a single-agent ibrutinib. Acquired mutations at the drug binding site of BTK or its downstream target called phospholipase C-gamma 2 (PLCγ2) were identified in patients who developed secondary resistance to ibrutinib.[61,62] Clinical outcome of patients who present with disease progression or transformation while on ibrutinib is extremely poor, and their median survival was reported to be only 3 months.[63] These limitations call for a novel treatment approach that is both efficacious and safe for high-risk CLL population.

2.7.2 Rationale for simultaneous B- and T-cell targeting

CLL is a clonal proliferation of auto-reactive B cells that escape immune surveillance. BCR activation generates a critical survival signal for malignant B cells, and is pharmacologically targetable with ibrutinib.[43] However, single-agent ibrutinib has limitations; the drug does not eliminate all the tumor cells and, with time, resistance can emerge - more commonly in high-risk CLL.

T cells interact with and support the survival of malignant B cells. Apoptosis of CLL cells can be rescued by stromal cell co-culture or by the addition of soluble factors.[3] Elimination of T cells *in vivo* was shown to be sufficient to abrogate CLL cell growth.[64] CD40 ligand forms a crosstalk between T and CLL cells, which stimulates CLL survival and promotes resistance to apoptosis.[5,6] Fludarabine is a biologically plausible addition to ibrutinib for it can effectively reduce T cell help in CLL pathogenesis, and has been widely used as a conditioning agent in immunotherapies.

CLL cells escape endogenous immune surveillance due to functionally and phenotypically defective effector T cells and due to immune regulatory signals from Treg.[9] Among many signals suppressing cytotoxic anti-tumor activity, PD-L1 is a key immune checkpoint molecule overexpressed by CLL cells and myeloid dendritic cells within the microenvironment.[4,65,66] Preclinical studies have shown an animal model can recapitulate human CLL with an increased PD-1/PD-L1 expression in T cells and decreased effector function of CD8+ T cells.[67]

Blockade of PD-1/PD-L1 axis led to reduction of CLL from lymphoid tissues, decreased inflammatory cytokines, and restored effector T cell phenotype *in vivo* and *ex vivo*.[68] PD-1 can be effectively blocked by pembrolizumab, an anti-PD-1 monoclonal antibody. Pharmacologic properties of pembrolizumab are further discussed under section *2.8 Pembrolizumab.*

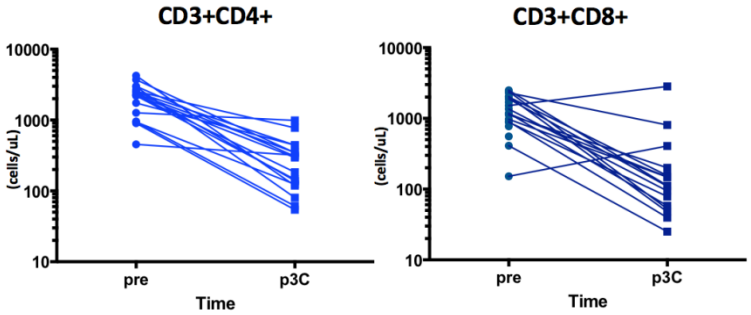
We hypothesize simultaneous targeting of B and T cells can augment the depth and the duration of responses, and the addition of pembrolizumab to ibrutinib and fludarabine can help restore immune surveillance against the tumor. To achieve this aim, three agents are needed to modulate B and T cells. First, ibrutinib is given daily for continued BCR inhibition. Second, a short-course fludarabine is added prior to the introduction of pembrolizumab with aims to reconstitute a favorable microenvironment for effector T cells and minimize immune-related toxicities of pembrolizumab. Third, pembrolizumab is added later to restore cytotoxic function of effector T cells.

2.7.3 Preliminary data on lymphocyte dynamics

Both published data from outside and preliminary data from our institutional experience with fludarabine-based regimen supports lymphocyte modulatory role of fludarabine. *First,* fludarabine effectively reduces regulatory T cells in CLL.[9] Accumulating preclinical data support the key role of regulatory T cells in T cell exhaustion. In a mouse model infected with lymphocytic choriomeningitis virus (LCMV), ablation of regulatory T cells was able to rescue exhausted T cells, expanded virus-specific CD8+ T cells, and up-regulated expression of PD-L1.[69] Simultaneous treatment with PD-L1 blockade and CD4+ T cell depletion led to superior viral control in the LCMV mouse model.[70] *Second,* fludarabine removes inhibitory signals on effector T cells. Given that untreated CLL has dramatically increased CD8+ T cells, reduction of abnormal T cell population may be important to prior to the addition of pembrolizumab. After fludarabine-based chemoimmunotherapy, CD4+ and 8+ T cells initially decrease (Figure 1) then gradually return to the lower normal range within 6 months to 1 year (Figure 2). Incremental recovery of the number of effector T cells may be critical to reduce potential toxicities related to autoimmune flare. Another benefit obtained by a lead-in phase with ibrutinib and fludarabine is a proportional recovery of effector T cells (Figure 2). Treatment with conventional chemoimmunotherapy reduces the tumor burden, which in turn elevates the proportion of CD8+ cells per absolute lymphocytes.

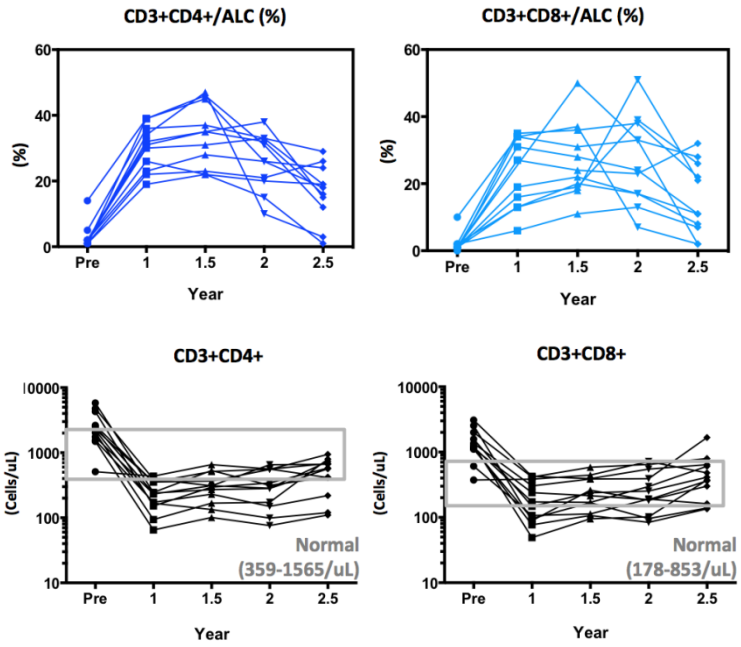
In summary, fludarabine, a purine analog cytotoxic to both B and T cells,[71-73] can help reduce regulatory T cells while increasing the ratio of effector T cells. Safety of fludarabine is justified by a large body of experience in CLL.

Figure 1. Absolute numbers of CD4+ and CD8+ T cells after 3 cycles of fludarabine-based chemoimmunotherapy*



* Preliminary data from an ongoing phase II trial, 10-H-0141. 12 CLL patients were treated with fludarabine and ofatumumab with or without cyclophosphamide for up to 4-6 cycles (unpublished).
Pre Before treatment
p3C After 3 cycles of fludarabine-based chemoimmunotherapy.

Figure 2. Absolute numbers and proportions of CD4+ and CD8+ T cells on a long-term follow up after fludarabine-based chemoimmunotherapy



* Preliminary data from an ongoing phase II trial, 10-H-0141. 11 CLL patients were treated with fludarabine and ofatumumab with or without cyclophosphamide for up to 4-6 cycles (unpublished).

In this study, we will investigate the effect of the combination therapy on the depth of response and on the composition of the T-cell compartment. The depth of response is quantified by PB flow cytometry, which defines minimal residual disease (MRD) negativity as clonal B cells below detection frequency of 10^{-4} cells/uL. MRD negativity will be used as a marker to guide treatment decisions on the long-term use of ibrutinib. T cell subsets are quantified and compared to the ongoing study using ibrutinib and short-course fludarabine (15-H-0172).

2.8 Pembrolizumab

2.8.1 Mechanism of Action

The programmed cell death 1 (PD-1) pathway represents a major immune control switch, which may be engaged by tumor cells to overcome active T cell immune surveillance. 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. PD-1 (encoded by the gene Pdcd1) is a type I transmembrane glycoproteins. Upon engagement of its ligands, PD-L1 and PD-L2, the cytoplasmic tail of PD-1 recruits tyrosine phosphatases SHP-1 and SHP-2 to the immunoreceptor tyrosine-based switch motif (ITSM) motif, and dephosphorylates effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The ligands for PD-1 are constitutively expressed or can be induced in a variety of cell types. 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. 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. 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/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab (KEYTRUDA®, MK-3475; previously known as SCH 900475 and ORG 307488-0 [herein referred to as pembrolizumab unless otherwise noted]) is a potent and highly selective humanized monoclonal antibody of the immunoglobulin G4 (IgG4)/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection.

Pembrolizumab potentiates existing immune responses only in the presence of antigen-receptor stimulation and does not nonspecifically activate all T cells. Pembrolizumab was tested for its capacity to enhance T cell activity in vitro using blood cells from healthy volunteers stimulated with staphylococcus enterotoxin B (SEB). Pembrolizumab enhanced IL-2 production over control on average 2- to 4-fold at the highest antibody concentration tested (25 μg/mL). In addition to IL-2, levels of tumor necrosis factor alpha (TNFα), IL-17, IL-6, and interferon gamma (IFNγ) increased by 1.2 to 1.7 folds after the addition of pembrolizumab to SEB-stimulated whole blood cells.

2.8.2 Pharmacokinetics

Pembrolizumab potently blocks binding of PD-1 to both PD-L1 and PD-L2 with half maximal inhibitory concentration (IC50) values below 1 nM. Pembrolizumab enhances T-cell responses in human donor blood cell cultures, with a half-maximal effective concentration (EC50) of approximately 0.1 to 0.3 nM.

The pharmacokinetics (PK) of pembrolizumab was studied in 479 patients who received doses of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. Based on a population PK analysis, the mean [% coefficient of variation (CV%)] clearance (CL) is 0.22 L/day (28%) and the mean (CV%) elimination half-life (t1/2) is 26 days (24%). Steady-state concentrations of pembrolizumab were reached by 18 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.1-fold. The peak concentration (Cmax), trough concentration (Cmin), and area under the plasma concentration versus time curve at steady state (AUCs) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

PK data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to Investigator Brochure). Pharmacodynamics data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamics data provides scientific rationale for monthly dosing schedule.

An open-label phase I trial (Protocol 001) is being 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 MK-3475 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. Recent data from other clinical studies within the pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure).

2.8.3 Metabolism and Clearance

No traditional metabolism studies were conducted with pembrolizumab per current ICH S (R1) guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals. However, in vivo studies were conducted in C.B17 SCID mice to demonstrate the lack of Fab-arm or half molecule exchange for pembrolizumab. IgG4 wild type molecules can undergo in vitro and in vivo molecular rearrangement called Fab -arm (or half molecule) exchange by swapping their half molecule with other IgG4 half molecules, thereby generating bispecific or hybrid antibodies. A point mutation (S228P) in the core hinge region in IgG4 has been shown to be sufficient to prevent the Fab-arm exchange. The results supported that pembrolizumab, which has a hinge mutation from S to P at position 228, did not form detectable hybrid antibodies with co-administered wild type IgG4 molecules in vivo in SCID mice. This observation is consistent with the results of extensive *in vitro* characterization of pembrolizumab and indicates that pembrolizumab is not likely to engage in Fab-arm exchange in humans

Renal Impairment

The effect of renal impairment on the clearance (CL) of pembrolizumab was evaluated by population PK analyses in patients with mild (eGFR 60 to 89 mL/min/1.73 m^2; n=210), moderate (eGFR 30 to 59mL/min/1.73m^2; n=43), or severe (eGFR 15 to 29mL/min/1.73 m^2; n=2) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73m^2; n=221) renal function. No clinically important differences in the CL of pembrolizumab were found between patients with renal impairment and patients with normal renal function.

Hepatic Impairment

The effect of hepatic impairment on the CL of pembrolizumab was evaluated by population PK analyses in patients with mild hepatic impairment (total bilirubin (TB) less than or equal to upper limit of normal (ULN) and AST greater than ULN or TB between 1 and 1.5 times ULN and any AST; n=59) compared to patients with normal hepatic function (TB and AST less than or equal to ULN; n=410). No clinically important differences in the CL of pembrolizumab were found between patients with mild hepatic impairment and normal hepatic function. Pembrolizumab has not been studied in patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment.

2.8.4 Summary of clinical efficacy and safety

Clinical efficacy

Pembrolizumab demonstrated clinically meaningful benefit in the treatment of melanoma, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), head and neck squamous cell carcinoma (HNSCC), classic Hodgkin lymphoma (cHL), primary mediastinal B cell lymphoma (PMBCL), urothelial cancer (UC), microsatellite instability-high (MSI-H) cancer, gastric or gastroesophageal junction (GEJ) adenocarcinoma, esophageal cancer, cervical cancer, hepatocellular carcinoma (HCC), Merkel cell carcinoma (MCC), renal cell carcinoma (RCC), endometrial carcinoma, tumor mutational burden-high (TMB-H) cancer, cutaneous squamous cell carcinoma (cSCC), and MSI-H colorectal carcinoma (CRC). A dosing regimen of 400 mg pembrolizumab Q6W also demonstrated clinically meaningful benefit for all of the approved adult indications. Clinical trials using pembrolizumab in other solid and hematologic malignancies are ongoing, including a phase 1b/2 trial combining a BTK inhibitor and pembrolizumab in B cell malignancies (NCT02362035).

Monotherapy Safety Data

Pembrolizumab monotherapy has a positive benefit-risk profile and is well tolerated in the approved indications, as evidenced by a low rate of toxicity Grade 3 to 5 drug-related AEs (13.8%), discontinuations due to AEs (11.9%), and deaths due to drug-related AEs (0.4%) in the reference safety dataset (RSD). Furthermore, the frequency of immune-mediated AEs of special interest is low, and these events are readily managed in the clinical setting for guidance on management of immune and non-immune-mediated events of interest. Overall, the safety profile of pembrolizumab as defined by the RSD has remained generally consistent with accrual of additional data and participant exposure as represented by the cumulative running safety dataset (CRSD).

Combination Therapy Safety Data

Safety data for pembrolizumab combination therapies were investigated in KN021, KN189, KN407, KN048, KN426, and KN146. In NSCLC and HNSCC, the safety profiles for pembrolizumab combination therapies were generally consistent with the known safety profiles of pembrolizumab monotherapy and the respective chemotherapy regimens administered (KN021, KN189, KN407, and KN048). In RCC, the safety profile of pembrolizumab in combination with axitinib was generally consistent with the established safety profile of pembrolizumab monotherapy in solid tumors and the observed safety profile for axitinib monotherapy, with the exception of increased incidences of Grades 3 and 4 elevated ALT and AST. ALT and AST elevations were generally manageable with interruption or discontinuation of pembrolizumab and axitinib, with or without concomitant steroid therapy (KN426). In endometrial carcinoma, the safety profile of pembrolizumab, when used in combination with lenvatinib, was generally consistent with the known safety profiles of each drug when used as monotherapy, with the exception of an increase in immune-related AEs largely comprised of low-grade hypothyroidism, with smaller increases in other immune-related AEs (KN146).

For more detailed information refer to the current version of the Investigator Brochure.

2.9 Ibrutinib

2.9.1 Pharmacokinetics and product metabolism

Following oral administration of ibrutinib at doses ranging of 420, 560, and 840 mg/day, exposure to ibrutinib increased as doses increased with substantial intersubject variability. The mean half-life ($t_{1/2}$) of ibrutinib across 3 clinical studies ranged from 4 to 6 hours, with a median time to maximum plasma concentration (T_{max}) of 1 to 2 hours. Taking into account the approximate doubling in mean systemic exposure when dosed with food and the favorable safety profile, ibrutinib can be dosed with or without food. Ibrutinib is extensively metabolized primarily by cytochrome P450 (CYP) 3A4. The on-target effects of metabolite PCI-45227 are not considered clinically relevant. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure. About 8% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with creatinine clearance (CrCl) >30 mL/min. Patients with severe renal impairment or patients on dialysis have not been studied. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. A higher proportion of Grade 3 or higher adverse reactions were reported in patients with B-cell malignancies (CLL, MCL and WM) with mild hepatic impairment based on NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction compared to patients with normal hepatic function.

For the most up to date and comprehensive pharmacokinetics (PK) and product metabolism information regarding ibrutinib, please refer to the current IB.

2.9.2 Summary of clinical safety

A brief summary of safety data from the monotherapy and combination therapy studies is provided below. For more comprehensive safety information please refer to the current version of the IB. Additional safety information is available for approved indications in prescribing labels in the United States.

For monotherapy studies:

Integrated safety data for a total of 1,600 patients with hematologic malignancies treated with ibrutinib monotherapy in 21 studies that have completed primary analysis or final analysis as of the 12 November 2020 for the current IB. Results are summarized below. The median duration of ibrutinib exposure for patients with hematologic malignancies receiving ibrutinib monotherapy was 15.3 months and the mean was 18.4 months.

Treatment-emergent AEs (TEAEs) were reported in 98.8% of subjects. The most frequently reported TEAEs (> 20%) were diarrhea, fatigue, cough, nausea, upper respiratory tract infection, anemia, and pyrexia. Grade 3 or 4 TEAEs were reported in 70.9% of subjects. The most commonly reported Grade 3 or 4 TEAEs (> 5%) were neutropenia, pneumonia, thrombocytopenia, anemia, and hypertension.

Serious TEAEs were reported in 53.33% of subjects. The most frequently reported (> 2%) serious TEAEs were pneumonia, atrial fibrillation, pyrexia, febrile neutropenia, sepsis, and cellulitis. Fatal TEAEs (Grade 5) were reported in 9.9% of subjects during study treatment or within 30 days of discontinuation of treatment. The most frequently reported (>0.3%) fatal TEAEs (other than disease progression) were MCL, Richter's syndrome, pneumonia, sepsis, respiratory failure, cardiac arrest, CLL, and death.

For combination therapy studies:

Integrated safety data for a total of 1,971 subjects with hematologic malignancies treated with ibrutinib as combination therapy in 17 studies that have completed primary or final analysis on 12 November 2020 are summarized below. Various therapies were used in combination with ibrutinib in these studies: BR (bendamustine and rituximab), FCR (fludarabine, cyclophosphamide, and rituximab), ofatumumab, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), cytarabine, azacitidine, dexamethasone, durvalumab, ofatumumab, lenalidomide with cyclophosphamide, EPOCH-R (doxorubicin, etoposide, vincristine, prednisone, rituximab), nivolumab, obinutuzumab, rituximab, carfilzomib with or without dexamethasone, pomalidomide plus dexamethasone, and bortezomib plus dexamethasone. The median duration of ibrutinib exposure for patients receiving ibrutinib as combination therapy was 9.2 months and the mean was 19.6 months.

Treatment-emergent AEs were reported in 99.5% of subjects receiving ibrutinib as combination therapy. The most frequently reported hematologic TEAEs (>20%) were anemia, neutropenia, and thrombocytopenia. The most frequently reported nonhematologic TEAEs (>20%) were diarrhea, fatigue, nausea, pyrexia, cough, upper respiratory tract infection, and constipation. Treatment-emergent AEs that were considered by the investigator to be related to ibrutinib were reported in 89.1% of subjects. The most frequently reported (>10%) hematologic TEAEs related to ibrutinib were neutropenia, anemia, thrombocytopenia, platelet count decreased, and neutrophil count decreased. The most frequently reported (>10%) nonhematologic TEAEs related to ibrutinib were diarrhea, fatigue, and nausea. Grade 3 or 4 TEAEs were reported in 82.9% of subjects. The most frequently reported (>5%) grade 3 or 4 hematologic TEAEs were neutropenia, anemia, neutrophil count decreased, thrombocytopenia, lymphocyte count increased, febrile neutropenia, and white blood cell count decreased. Pneumonia and hypertension were the most frequently reported non-hematologic Grade 3 or 4 TEAEs (>5%).

Serious TEAEs were reported in 55.7% of subjects; the most frequently reported (> 2%) were pneumonia, febrile neutropenia, atrial fibrillation, pyrexia, and anemia. Fatal TEAEs were reported in 7.5% of subjects. The most frequently reported (>0.3%) fatal TEAEs (other than disease progression) were pneumonia, septic shock, death, and sepsis.

Pneumonia was rarely, in less than 1% of cases, attributed to the infection of *Pneumocystis jirovecii.* Most cases of Pneumocystis pneumonia (PCP) were reported from different monotherapy studies or combination studies. In Pharmacyclics's analysis of cases of PCP in the Ibrutinib Clinical Trial Database and noted in the Ibrutinib Investigational Brochure, which utilized a broad search strategy, the rate of PCP (regardless of seriousness or relatedness) was <1%.

3.0 STUDY DESIGN

This is a phase II, single-center, open-label study. The study has a single treatment arm using ibrutinib, short-course fludarabine, and pembrolizumab in CLL or SLL patients with high-risk features defined by the protocol. Treatment plan is discussed in detail under section *5.0 Treatment Plan.*

4.0 ELIGIBILITY ASSESSMENT AND ENROLLMENT

4.1 Inclusion Criteria

1. Men and women with histologically confirmed CLL or SLL as defined by the following:
   - CLL: clonal B lymphocytosis ≥ 5,000 cells/μL.
   - SLL: lymphadenopathy with the tissue morphology of CLL but are not leukemic (< 5,000 circulating clonal B lymphocytes/μL).
   - Immunophenotypic profile or immunohistochemistry read by an expert pathologist as consistent with CLL. This will include CD5, CD19, and CD20 expression by the CLL cells typically also with CD23 expression, but CD23 negative cases may be included if there is an absence of t(11;14).
2. Active disease as defined by at least one of the following (IWCLL consensus criteria):
   - Weight loss ≥10% within the previous 6 months.
   - Extreme fatigue.
   - Fevers of greater than 100.5ºF for ≥2 weeks without evidence of infection.
   - Night sweats for more than one month without evidence of infection.
   - Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia.
   - Massive or progressive splenomegaly.
   - Massive nodes or clusters or progressive lymphadenopathy.
   - Progressive lymphocytosis with an increase of >50% over a 2-month period, or an anticipated doubling time of less than 6 months.
3. High-risk disease defined by meeting at least one of the following criteria:
   - Relapsed and/or refractory CLL/SLL.
   - Presence of high-risk genetic changes detected by FISH, karyotype, sequencing or tissue expression, regardless of prior treatments status.
     - Deletion 17p
     - Complex cytogenetics (3 or more abnormalities)

- *TP53* or *NOTCH1* or *SF3B1* mutation. Pathologic mutations occurring at the coding regions are accepted as relevant mutations.
- *MYC* aberration. Aberration includes rearrangement, amplification, and tissue expression by immunohistochemistry.

- CLL or SLL with disease transformation with Hodgkin-like cells regardless of prior treatment status.

4. Eastern Cooperative Oncology Group (ECOG) performance status of ≤1.
5. Adequate organ function as defined in Table 4.

Table 4. Summary of adequate organ function for eligibility

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 750/μL
Platelets	≥ 50,000/μL
Hemoglobin	≥ 9 g/dL or ≥ 5.6 mmol/L without EPO dependency (within 7 days of assessment). Post-transfusion hemoglobin is accepted.
Renal	
Measured or calculated GFR	GFR ≥ 30ml/min/1.73m^2 based on CKD-EPI
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels ≥ 1.5 ULN due to Gilbert's disease **OR** Direct bilirubin may be > 1.5 x ULN if due to hemolytic anemia AND other labs relevant to hepatic function (i.e. AST/ALT, Alk Phos) are within normal ranges
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤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
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

6. Agreement to use acceptable methods of contraception during the study and for 90 days after the last dose of study drug if sexually active and able to bear or beget children.
   - Female subjects who are of non-reproductive potential (i.e., post-menopausal by history - no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy).
   - Female subjects of childbearing potential must have a negative serum pregnancy test upon study entry.
   - Male and female subjects who agree to use both a highly effective methods of birth control (i.e., implants, injectables, combined oral contraceptives, some intrauterine devices, complete abstinence, or sterilized partner) and a barrier method (i.e., condoms, vaginal ring, sponge, etc) during the period of therapy and for 90 days after the last dose of study drug
7. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.

8. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations).
9. Individuals ≥ 18 years old

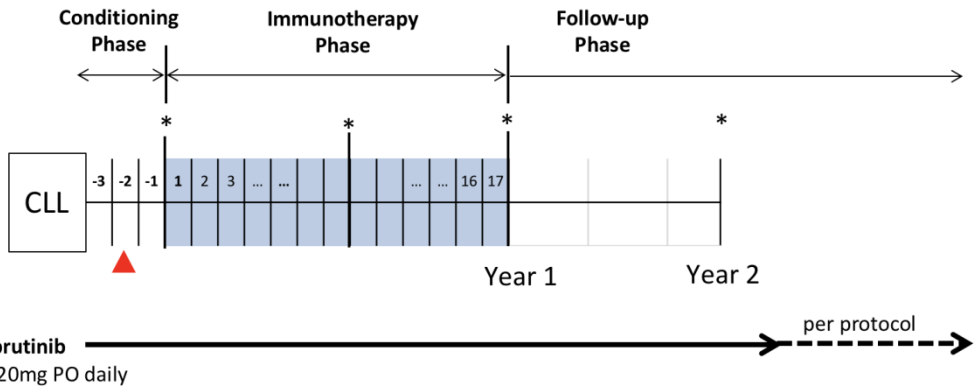
4.2 Exclusion Criteria

- Transformation of CLL into lymphomas other than those with Hodgkin-like cells.
- Currently receiving or previously participated to receive an investigational agent within 4 weeks prior to study treatment.
- Currently receiving or previously received monoclonal antibodies, immunomodulatory therapy, chemotherapy, radiation, or radioimmunotherapy within 4 weeks prior to study treatment, or has not recovered (i.e., ≤ Grade 1 or at baseline) from non-hematologic adverse events due to a previously administered agent.
    - Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to CTCAE, v4.03, grade 0 or 1, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia.
- Major surgery within 4 weeks of first dose of study drug
    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
- Currently receiving systemic steroid therapy (i.e. prednisone) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
- Prior therapy with BTK inhibitor, anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
    - Note: Prior therapy with fludarabine is not excluded.
- Active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g.., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
- Known additional malignancy that is progressing or requires active treatment.
    - Note: Exceptions include basal cell carcinoma of skin, squamous cell carcinoma of skin, and in situ cervical cancer that has undergone potentially curative therapy. Exceptions include other cancers from which the subject has been disease-free for ≥ 2 years or which will not limit survival to < 2 years
- Known history of, or any evidence of active, non-infectious pneumonitis that required steroids.
- Known bleeding disorders (i.e., von Willebrand's disease or hemophilia).
- Known HIV infection (i.e., HIV 1 and 2 antibodies).
- Active hepatitis B (i.e., HBsAg reactive) or hepatitis C (i.e., HCV RNA is detected by a qualitative test) infection.
- Recent known active infection requiring systemic therapy that was completed ≤ 14 days before the first dose of study drug.
- Known history of active tuberculosis.
- Any uncontrolled active systemic infection.
- Known hypersensitivity to ibrutinib, fludarabine, or pembrolizumab.
- Requires concomitant anticoagulation with Coumadin (warfarin) or other vitamin K antagonists.

- Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction
- History of stroke or intracranial hemorrhage within 6 months before the first dose of study drug
- Subjects who received a strong cytochrome P450 (CYP) 3A inhibitor within 7 days prior to the first dose of ibrutinib or subjects who require continuous treatment with a strong CYP3A inhibitor (Appendix B).
- Currently active, clinically significant cardiovascular disease including uncontrolled or symptomatic arrhythmias, Class 3 or 4 congestive heart failure as defined by New York Heart Association Functional Classification, or a history of myocardial infarction, unstable angina or acute coronary syndrome within 6 months of screening.
- Life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ibrutinib and fludarabine, or put the study outcomes at undue risk
- Female patients who are currently in pregnancy or unwilling to use acceptable methods of contraception or refrain from pregnancy if of childbearing potential or currently breastfeeding. Male patients who are unwilling to follow the contraception requirements described in this protocol.
- Psychiatric illness/social situations that would limit the patient's ability to tolerate and/or comply with study requirements.
- Unable to understand the investigational nature of the study or give informed consent.
- Currently active, clinically significant hepatic impairment Child-Pugh class B or C according to the Child Pugh classification (Appendix C).
- Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.

5.0 TREATMENT PLAN

5.1 Drug administration and treatment schedule



1) Conditioning phase (12 weeks):

• Cycle -3 and -1 (28-day cycle ±5 days): ibrutinib 420mg PO daily

Ibrutinib is given 420mg (3 x 140mg) PO daily starting from cycle -3. Administration of ibrutinib will take place at the outpatient facility of the NIH clinical center or at the patient's home. Each dose of ibrutinib is taken around the same time each day with a glass of water. The capsules should be swallowed intact and subjects should not attempt to open the capsule or dissolve them in water. There is one specific dietary restriction to avoid grapefruit juice and Seville oranges due to CYP450 3A4 inhibition. No dose adjustments are required for creatinine clearance.

• Cycle -2 (28-day cycle ±5 days): ibrutinib 420mg PO daily, fludarabine 25mg/m2/day IV on day 1-5

Ibrutinib is continued 420mg PO daily during cycle -2. Fludarabine is given 25 mg/m2/day IV on days 1-5 of cycles -2. Fludarabine administration will take place in the Clinical Center Day Hospital. At the PI's discretion, select subjects may be admitted to the inpatient unit for the first few days of fludarabine infusion. Subjects will have a peripheral line placed. At the PI discretion, a central line may be placed in select patients. Dosing will be based on actual weight for all patients. No dose adjustment is required based on age. In the event of renal impairment, dose reduction will be as follows;

- Creatinine clearance of 30-70 mL/min/1.73m2 using the CKD-EPI equation with actual body weight: Fludarabine will be dose reduced by 20%.
- Creatinine clearance of ≤ 30 mL/min/1.73m2 using the CKD-EPI equation with actual body weight: Fludarabine will be held at the discretion of the PI.

2) Immunotherapy phase (1 year):

• Cycle 1 to 17 (21-day cycle ±5 days): ibrutinib 420mg PO daily, pembrolizumab 200mg IV on D1 of each cycle

Ibrutinib is continued 420mg PO daily during the immunotherapy phase. Pembrolizumab is given as 200mg IV every 3 weeks from cycle 1 to 17 (or 1 year of immunotherapy phase, whichever is earlier). Pembrolizumab will be administered in the Clinical Center Day Hospital. At the PI's discretion, select subjects may be admitted to the inpatient unit for the first pembrolizumab infusion. Subjects will have a peripheral line placed. At the PI discretion, a central line may be placed in select patients. No dose adjustments are required for age or creatinine clearance.

3) Follow-up phase (indefinite):

After 1 year of pembrolizumab, time on study equals chronological months from cycle 1 (when pembrolizumab is first given). At 2 years, all patients are evaluated for response and MRD status.

- All patients are followed up in 4-month intervals (±14 days) after 1 year of pembrolizumab.
- Ibrutinib will be discontinued at the first follow up visit after 2 years in patients who achieve both CR and MRD negativity at 2 years. This is to allow sufficient turn-around time for flow cytometry results.
- For previously untreated patients who do not achieve both CR and MRD negativity at 2 years, ibrutinib will be continued as 420mg PO daily until progression or intolerable side effects occur.
- Relapsed/refractory patients will continue ibrutinib 420mg PO daily until progression or intolerable side effects occur regardless of response or MRD status at 2 years.

5.2 Prophylactic medications

- Allopurinol (or alternative agent if the subject cannot tolerate allopurinol) during cycle -2 days 1-7 for all subjects, and beyond at the discretion of the PI.
- Sulfamethoxazole/trimethoprim (or alternative agent in case of sulfa allergy) from cycle -3 to 4 (for approximately 6 months), and beyond at the discretion of the PI.
- Acyclovir or valacyclovir at the discretion of the PI (not mandatory).

5.3 Dose modification guidelines for drug-related adverse events

An interruption of study drug administration is permissible. Dose changes must be recorded in the Dose Administration eCRF.

5.3.1 Hematologic Toxicities

Dose modifications for hematologic toxicities have been updated to reflect recommended dose modifications from the May 2022 FDA label for ibrutinib.

Drug	Cycle	Condition at the start of cycle	Action*
Ibrutinib	3 and onwards	Grade >= 3 neutropenia with infection or fever **OR** Grade >=3 thrombocytopenia with bleeding **OR** Grade 4 hematologic toxicities	Check CBC with differential weekly. Hold ibrutinib until recovery to Grade ≤ 1 or baseline. • First occurrence: Resume ibrutinib at 280 mg once daily. • Second occurrence: Resume ibrutinib at 140 mg once daily. Third occurrence: discontinue ibrutinib.
Fludarabine	-2	HGB <11 g/dL with indications of autoimmune hemolysis	Omit fludarabine.
		ANC <1,000/µL **OR** PLT <75,000/µL	Hold fludarabine for 4 weeks and check CBC with differential weekly. Give fludarabine if ANC ≥1,000/µL **AND** PLT ≥75,000/µL. Cycle -2 can be extended in 4-week increments. Up to two dose delays are allowed (total 8 weeks). If count recovery does not occur in 8 weeks, omit fludarabine.
Pembrolizumab	1 through 17	ANC <750/µL, **OR** HGB <9g/dL **OR** PLT <50,000/µL	Hold pembrolizumab for 3 weeks and check CBC with differential weekly. Reevaluate at the next cycle. Give pembrolizumab if ANC ≥750/µL **AND** Hgb ≥9 g/dL **AND** PLT ≥50,000/µL. Up to three dose delays are allowed (total 9 weeks). If count recovery does not occur in 9 weeks, omit pembrolizumab.

ANC - absolute neutrophil count; HGB - hemoglobin; PLT - platelet.

* Dose delay or reduction is not required if cytopenia is considered related to CLL.

5.3.2 Cardiac Toxicities

Atrial fibrillation

- For new-onset atrial fibrillation, ibrutinib will be held until cardiac evaluation has been completed. The decision to restart ibrutinib will be made after the PI and a consulting physician determine the subject is sufficiently stable following diagnostic testing and institution of treatment if required.
- Anticoagulation with atrial fibrillation: If anticoagulation is deemed necessary by consulting physician and/or PI, patients will be allowed to start treatment with anti-platelet or anti-coagulant therapies except warfarin. Co-administration with warfarin has been associated with grade 3 or higher bleeding events such as (subdural hematoma, gastrointestinal bleeding, hematuria, and post procedural hemorrhage). Other forms of anti-platelet, anti-coagulant, direct thrombin inhibitors, or factor Xa inhibitors may be used concomitantly with ibrutinib, however the risk of increased bruising or bleeding is unknown. Patients will be counseled and monitored closely for signs of bleeding and/or bruising and will be instructed to contact the research team and primary care physician in the case of any complications.

Heart Failure
Dose modifications for heart failure have been updated to reflect recommended dose modifications from the May 2022 FDA label for ibrutinib.

Adverse Reaction	Occurrence	Action
Grade 2 Heart failure	1st	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (280 mg daily).
	2nd	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (140 mg daily).
	3rd	Discontinue ibrutinib
Grade 3 or 4 Heart failure	1st	Discontinue ibrutinib

Cardiac arrhythmias
Dose modifications for cardiac arrhythmias have been updated to reflect recommended dose modifications from the May 2022 FDA label for ibrutinib.

Adverse Reaction	Occurrence	Action
Grade 3 Cardiac arrhythmias	1st	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (280 mg daily).
	2nd	Discontinue ibrutinib
Grade 4 Cardiac arrrhythmias	1st	Discontinue ibrutinib

5.3.3 Hepatic impairment

- Refer to Appendix C for Child-Pugh classification.
- Ibrutinib is metabolized in the liver. In the population PK analysis (1,202 subjects), 179 subjects (14.9%) had mild hepatic impairment according to National Cancer Institute criteria and 12 subjects (1.0%) had moderate hepatic impairment. These subjects did not show a significantly higher ibrutinib exposure compared with subjects with normal hepatic function. Therefore, subjects with clinically

significant hepatic impairment at the time of screening (Child- Pugh class B or C) are excluded from study participation.

- Concomitant use of strong CYP inhibitors is not permitted in subjects with chronic hepatic impairment. In a hepatic impairment study, data showed an increase in ibrutinib exposure. For subjects with mild liver impairment (Child-Pugh class A), the recommended dose is 280mg daily. For subjects with moderate liver impairment (Child-Pugh class B), the recommended dose is 140mg daily. Monitor subjects for signs of ibrutinib toxicity and follow dose modification guidance as needed. It is not recommended to administer ibrutinib to subjects with severe hepatic impairment. Dose modification of ibrutinib for subjects who develop hepatic impairment on study is summarized as follows:

Table 6. Dose Modification Guidance for Hepatic Impaired Subjects

	Child Pugh class A (Mild hepatic impairment)*		**Child Pugh Class B (Moderate hepatic impairment)****		**Child Pugh class C (Severe hepatic impairment)**
	Ongoing at time of enrollment	Develops during study	Ongoing at time of enrollment	Develops during study	Develops during study
Ibrutinib Dose (daily)	280 mg	280mg	140 mg	140 mg	Hold until improves to moderate [Class B] or better)
* If further reduction is needed due to non-hepatic toxicity, dose may be reduced to 140 mg. In the event that additional reduction is needed, ibrutinib should be held for non-hepatic toxicity until resolution. ** If further reduction is needed due to non-hepatic toxicity, ibrutinib should be held until resolution.					

- For subjects with existing chronic mild hepatic impairment (Child-Pugh class A) at enrollment, the starting dose has to be adjusted to a level of 280 mg daily (two capsules).
- For subjects who develop mild liver impairment while on study (Child-Pugh class A), the recommended dose reduction for ibrutinib is to a level of 280 mg daily (two capsules).
- For subjects who develop moderate liver impairment while on study (Child-Pugh class B), the recommended dose reduction is to a level of 140 mg daily (one capsule).
- Subjects who develop severe hepatic impairment (Child-Pugh class C) must hold study drug until resolved to moderate impairment (Child-Pugh class B) or better.
- Subjects who develop acute hepatic toxicity with liver enzymes Grade 3 or higher while on study should be managed per standard dose modification guidelines in Section 5.4.4.

5.3.4 Other non-hematologic toxicities

Ibrutinib

- No dose adjustments are required for renal impairment.
- Hold ibrutinib for grade 3 or higher other non-hematologic toxicity associated with ibrutinib. After resolution to grade ≤ 1 or baseline, ibrutinib will be restarted as follows:

Table 7. Guideline for holding ibrutinib related non-hematologic toxicities

Occurrence	Action
1st	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (280mg daily).
2nd	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (140mg daily).
3rd	Discontinue ibrutinib.

- A high number of circulating malignant cells (>400,000/μL) may confer increased risk; these subjects should be closely monitored. Administer supportive care such as hydration and/or leukapheresis as indicated. Ibrutinib may be temporarily held, and PI should be contacted.
- In the event that ibrutinib is held for toxicity for 28 consecutive days the study drug should be discontinued. However, if the PI deems that the clinical benefit outweighs the risk of restarting treatment then patient may restart study drug.

Fludarabine

- In the event of renal impairment, dose reduction will be done as specified in section 5.1.
- For grade 3 or higher other non-hematologic toxicities fludarabine can be interrupted and resumed when the toxicity resolves to grade 2 or lower. Fludarabine can be reinitiated at a full dose, 20% dose reduced, or completely stopped depending on clinical benefit-risk assessment by the PI. In select cases where a subject has uncomfortable grade 2 toxicities, dose may be interrupted or reduced per PI discretion.

Pembrolizumab

- Adverse events (both non-serious and serious) associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic etiology. These adverse events may occur beginning shortly after the first dose or up to several months after the last dose of treatment. Pembrolizumab must be withheld or discontinued for drug-related toxicities and severe or life-threatening AEs as follows;

Table 8: Dose Modification and Toxicity Management Guidelines for Immune-related AEs (irAEs) Associated with Pembrolizumab

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent)	• Monitor participants for signs and symptoms of

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue	followed by taper • Add prophylactic antibiotics for opportunistic infections	pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with 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
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs.

5.4 Holding of study drug administration

5.4.1 Ibrutinib and surgical procedures

- Consider the benefit-risk of withholding ibrutinib for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

5.4.2 Medically necessary conditions to hold study drugs

- Ibrutinib can be held at the study team's discretion for medically necessary conditions (i.e. concurrent infection, impending workups for diagnostic and/or therapeutic purposes)
- Fludarabine or pembrolizumab infusions may be held for medically necessary reasons (i.e. concurrent infection, emergency of autoimmune cytopenia, impending workups for diagnostic and/or therapeutic purposes) and can be delayed up to 2 cycles while continuing ibrutinib until the medical reasons to hold infusion resolve or return to baseline. If the delay persists past 2 cycles, fludarabine will be omitted and the patient will continue treatment with ibrutinib. If pembrolizumab is delayed beyond 2 cycles, pembrolizumab can still be given after medical reasons to hold infusion resolve or return to baseline. Per PI discretion, patients may be given catch-up doses of pembrolizumab after cycle 17 to compensate for the missed doses as long as the medical reasons to hold the infusion have resolved or returned to baseline. Treatment should not be restarted in situations where the patient had been removed from therapy related to an adverse event that requires permanent discontinuation of pembrolizumab as described in Table 8.
- Supportive medications including allopurinol and acyclovir (if indicated) will not be started until fludarabine starts and will not be initiated if fludarabine is omitted. Weekly CBC intended for cycle -2 will be delayed until fludarabine starts and not performed if fludarabine is omitted.

5.4.3 Permanent discontinuation of study drug administration in case of treatment related adverse events

- Serious or life threatening cardiac arrhythmias
- Severe infection (requiring vasopressor support > 24h, or intubation)
- Any grade 4 toxicity excluding readily reversible metabolic or laboratory abnormalities or hematologic toxicities
- Progressive disease as defined in section 7.0

- Pregnancy or unwillingness to use acceptable method of contraception
- Other toxicities requiring permanent discontinuation of study drugs are defined in section *5.4.4. Non-hematologic toxicities.*

Patients who are not able to receive further study drug administration will be followed after resolution of the event for safety and will continue to be followed at regular intervals with reassessment of disease as outlined in section 6 and 7.

5.5 Supportive care (non-investigational)

- Patients will be transfused packed red blood cells (must be irradiated) and/or platelets (must be processed using the Intercept Blood system) as clinically indicated.
- Filgrastim or peg-filgrastim may be used to if ANC < 500/uL at the PI's discretion.
- Anti-infective agents will be used as indicated for treatment of intercurrent infections.
- Prophylactic medications will be used as defined in section *5.3. Prophylactic medications.*

5.6 Permitted and non-permitted concomitant medications

- Patients may continue most medications they were prescribed prior to study enrollment for co-morbid conditions. No formal drug-drug interaction studies have been conducted therefore we ask patients to report all medications and over the counter drugs they are taking so we can monitor for any drug-drug interactions. Treatment for autoimmune cytopenias is permitted during cycles with ibrutinib alone (during cycle -3 and -1, and after cycle 17). Treatment for autoimmune cytopenias should not exceed 14 days at doses that do not exceed 100mg per day of prednisone or equivalent.

5.6.1 Guideline for the use of CYP3A inhibitors/inducers

Dose reduction of ibrutinib will be guided by ibrutinib USPI as follows.

Patient Population	Coadministered Drug	Recommended ibrutinib dose
B-cell Malignancies	• Moderate CYP3A inhibitor	280 mg once daily
	• Voriconazole 200 mg twice daily • Posaconazole suspension 100 mg once daily, 100 mg twice daily, or 200 mg twice daily	140 mg once daily
	• Posaconazole suspension 200 mg three times daily or 400 mg twice daily • Posaconazole IV injection 300 mg once daily • Posaconazole delayed-release tablets 300 mg once daily	70 mg once daily
	• Other strong CYP3A inhibitors	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib

- After discontinuation of a CYP3A inhibitor, resume the previous dose of ibrutinib.
- A list of common CYP3A inhibitors and inducers is provided in Appendix B. For further information, please refer to the current version of the Investigator Brochure. Examples of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

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

5.6.2 Concomitant use of QT prolonging agents

Any medications known to cause QT prolongation should be used with caution; periodic ECG and electrolyte monitoring should be considered.

5.6.3 Concomitant use of antiplatelet agents and anticoagulants

Use ibrutinib with caution in subjects requiring anticoagulants or medications that inhibit platelet function. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen induced platelet aggregation were observed. Supplements such as fish oil and vitamin E preparations should be avoided during treatment with ibrutinib. Bleeding events of any grade, including bruising and petechiae, occurred in subjects treated with ibrutinib. Subjects with congenital bleeding diathesis have not been studied. Subjects requiring the initiation of therapeutic anticoagulation therapy (eg, atrial fibrillation) should be observed closely for signs and symptoms of bleeding and the risks and benefits of continuing ibrutinib treatment should be considered.

5.6.4 Concomitant use of systemic glucocorticoids

Systemic glucocorticoids should not be administered other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology or autoimmune cytopenia related to CLL. The use of physiologic doses of corticosteroids may be approved per PI decision.

5.6.5 Prohibited concomitant medications

- Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy not specified in this protocol is prohibited while the subject is receiving treatment on study.
- For patients who were newly diagnosed with a second malignancy, the study drug can be interrupted while the patient undergoes further evaluation and treatment with definitive, time-limited anti-cancer therapy (i.e. localized breast cancer requiring surgery and adjuvant chemoradiation). If the second malignancy requires long-term therapy (> 6 months) or a definite therapy is not available (i.e. metastatic solid tumor), the patient will be taken off study.

5.7 Special instructions

5.7.1 Immunizations: Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial are contraindicated. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Patients will be advised not to receive live viral vaccines . Subjects who would like to receive other routine non-attenuated vaccinations will be allowed to do so. The ability to generate an immune response to any vaccine following administration of ibrutinib has not been studied.

5.7.2 Birth control: Subjects with reproductive potential who are sexually active must use acceptable methods of contraception during the study and for 90 days after the last dose of ibrutinib. Examples of acceptable methods of contraception include condoms, implants, injectables, combined oral contraceptives, intrauterine devices, true sexual abstinence, or sterilized partner. Note that periodic abstinence, e.g., calendar, ovulation, symptothermal, post-ovulation methods or withdrawal, are not acceptable methods of contraception.

5.7.3 Guidelines for rescue medications and supportive care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance. Refer to *Section 5.3* for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

5.7.4 Immune-Infusion reactions

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Table below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 9. Infusion Reaction Treatment Guidelines

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, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids 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**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	be permanently discontinued from further trial treatment administration.	
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.		

6.0 CLINICAL MONITORING (see Appendix A. Schedule of Events)

Samples will be ordered and tracked through the CRIS screens. Should a CRIS screen not be available, the NIH form 2803-1 will be completed and will accompany the specimen and be filed in the medical record.

6.1 Study Evaluations: Screening and Baseline

Results from other NIH protocols may be used as a part of the study evaluation. Selected results (viral studies, flow cytometry, CT, FISH and karyotype) performed from outside institutions will be accepted.

Screening/Baseline: Tests will be performed from day -28 to day 0 of starting study drug, unless otherwise specified.

- Complete medical history: relevant past medical history includes medical diagnoses and/or conditions; 1) that are currently ongoing, OR 2) occurred within 1 year of study enrollment, OR 3) occurred before 1 year of study enrollment and were potentially associated with major organ function or with long-term sequelae (i.e. hypertension, hyperlipidemia, diabetes, surgery of major organ system, any malignancy).
- ECOG performance status (PS) evaluation
- Physical exam will be performed and subjects will be monitored clinically for atrial fibrillation
- Concomitant medication review
- HLA typing, saliva (HLA typing performed at any timepoint, not limited to day -28 to day 0, is accepted)

- Complete blood count (CBC) with differential
- Acute care & mineral panels (includes Na, K, Cl, CO_2, creatinine, glucose, BUN, phosphorus, magnesium, albumin, and calcium)
- Total protein, CK, Uric Acid, and LDH
- Hepatic panel (includes alkaline phosphatase, ALT, AST, total bilirubin, and direct bilirubin)
- Reticulocyte count
- PT, PTT
- Serum protein electrophoresis with immunofixation (SPEP)
- Serum free light chains, quantitative immunoglobulins
- C-reactive protein (CRP)
- Beta-2 microglobulin (B2M)
- Haptoglobin, direct antiglobulin test (DAT)
- Iron panel (includes ferritin, transferrin, iron), folate, vitamin B12
- Thyroid function panel (thyroid stimulating hormone, free T4, T3)
- Viral studies (serologies for HIV 1 / 2, hepatitis B and C; HBV DNA PCR). Outside results are accepted.
- For females of childbearing potential, one negative pregnancy tests sensitive to 50 mIU within 2 weeks prior to starting study drug.
- Lymphocyte phenotyping (T, B, NK)
- *IGHV* mutation analysis (as this test does not change with time, any prior report is acceptable). Outside results are acceptable.
- PB interphase FISH within 3 months prior to starting study drug. FISH panel contains probes for *ATM* (11q22.3), *D12Z3* (12 cen), *D13S319* (13q14.3), *LAMP1* (13q34) and *TP53* (17p13.1). Outside results are acceptable.
- Karyotype within 3 months prior to starting study drug. Outside results are acceptable.
- PB or BM chromosome tests (metaphase karyotype). This is an optional test.
- Flow cytometry panel for CLL (may be done on blood, BM and/or LN) or immunohistochemistry of LN or BM demonstrating CLL/SLL within 3 months prior to starting study drug
- CT of the neck, chest, abdomen and pelvis within 3 months prior to starting study drug. IV and PO contrast will be used unless the patient has a contrast allergy or impaired renal function. Outside results are accepted.
- BM aspirate and biopsy within 3 months of starting treatment. Outside results are accepted.
- EKG within 3 months prior to starting study drug
- Lymphapheresis for research (optional)
- LN biopsy for research if the patient is willing and has an accessible LN. Outside results are accepted.
- Research blood (up to 80mL)

Pre Cycle -3 (day -5 to day 0): If pre-cycle -3 visit overlaps with screening/baseline visit, selected evaluations will be performed (marked with * below). Other evaluations are optional.

- Informed consent*
- Interval medical history
- ECOG PS
- Physical exam
- Concomitant medication review

- CBC with differential*
- Acute care & mineral panels (includes Na, K, Cl, CO_2, creatinine, glucose, BUN, phosphorus, magnesium, albumin, and calcium)*
- Total protein, CK, Uric Acid, and LDH
- Hepatic panel (includes alkaline phosphatase, ALT, AST, total bilirubin, and direct bilirubin)
- Reticulocyte count
- PT, PTT
- B2M
- Haptoglobin, DAT
- Pregnancy test for females of childbearing potential
- Research blood (up to 80ml)

6.2 On therapy evaluations

Cycle -2 until 1 year of pembrolizumab: before starting each cycle (+/- 5-day window):

Following assessments will be performed prior to each cycle.

- Interval History
- ECOG PS
- Physical exam
- Concomitant medication review
- CBC with differential
- Acute care & mineral panels (includes Na, K, Cl, CO_2, creatinine, glucose, BUN, phosphorus, magnesium, albumin, and calcium)
- Total protein, CK, Uric Acid, and LDH
- Hepatic panel (includes alkaline phosphatase, ALT, AST, total bilirubin, and direct bilirubin)
- Thyroid function panel (thyroid stimulating hormone, free T4, T3) from Cycle 1 until 1 year
- Reticulocyte count
- PT, PTT
- B2M
- Haptoglobin, DAT
- Pregnancy test for females of childbearing potential
- Research blood (up to 80ml). Research blood is required for cycles -2, -1, and 1. Research blood is optional for other cycles. If dose delay of fludarabine or pembrolizumab occurs, research blood does not have to be repeated on subsequent visits intended for delayed therapy.

After 1 year of pembrolizumab (+/- 14-day window):

Following assessments will be performed every 4 months while on therapy until disease progression or intolerable side effects. Patients with travel hardships can be followed every 8 months and draw an interim CBC with differential to substitute a missed visit and evaluations. Outside lab results are accepted for the interim lab.

- Interval History
- ECOG performance status evaluation
- Physical exam
- Concomitant medication review
- CBC with differential

- Acute care & mineral panels (includes Na, K, Cl, CO_2, creatinine, glucose, BUN, phosphorus, magnesium, albumin, and calcium)
- Total protein, CK, Uric Acid, and LDH
- Hepatic panel (includes alkaline phosphatase, ALT, AST, total bilirubin, and direct bilirubin)
- Reticulocyte count
- PT, PTT
- B2M
- Haptoglobin, DAT
- Thyroid function panel (thyroid stimulating hormone, free T4, T3; optional)
- Pregnancy test for females of childbearing potential
- Research blood (up to 80ml, optional)

Additional tests

Cycle -2

- Cycle -2 Day 14, and 22 (+/- 7 days): CBC with differential (may be performed outside). If fludarabine is delayed, these tests are also delayed until fludarabine is given. If fludarabine is omitted, interim labs will not be collected.

Cycle 1

- Prior to cycle 1 (within 14 days prior to starting pembrolizumab): CT of the neck, chest, abdomen and pelvis. IV and PO contrast will be used unless the patient has a contrast allergy or impaired renal function. Participants may waive the CT scan prior to pembrolizumab.

Others

- Up to 3 lymph node biopsies may be obtained for research at any time during therapy (optional, with at least 4 weeks between biopsies).

6.3 Response assessment

Response assessment will be performed after 6 months, 12 months, and annually thereafter (starting from cycle 1) (+/- 30-day window). Patients with travel hardships can defer assessments to subsequent clinic visits.

- Interval History
- ECOG performance status evaluation
- Physical exam
- Concomitant medication review
- CBC with differential
- Acute care & mineral panels (includes Na, K, Cl, CO_2, creatinine, glucose, BUN, phosphorus, magnesium, albumin, and calcium)
- Total protein, CK, Uric Acid, and LDH
- Hepatic panel (includes alkaline phosphatase, ALT, AST, total bilirubin, and direct bilirubin)
- Reticulocyte count
- PT, PTT
- Serum free light chains, quantitative immunoglobulins
- CRP (optional)

- B2M
- Haptoglobin, DAT
- Pregnancy test for females of childbearing potential
- Lymphocyte phenotyping (T, B, NK)
- Flow cytometry panel for CLL optional (may be done on blood, BM and/or LN)
- CT of the neck, chest, abdomen and pelvis (optional at 6 months, required at 12 months, and optional annually thereafter.) IV and PO contrast is optional and may be used unless the patient has a contrast allergy or impaired renal function.
- BM aspirate and biopsy is optional after 6 months on pembrolizumab, required at 12 months, and optional thereafter.
- Lymphapheresis for research (optional)
- Lymph node biopsy is optional and may be performed if the patient is willing and has an accessible lymph node.
- Research blood (up to 80ml) is optional past the primary endpoint.

6.4 At progression evaluation

All response assessments as listed in section *6.3 Response assessment* can be performed at progression if the patient remains available for the study (optional). Additional studies may be performed per the PI's decision.

7.0 CRITERIA FOR RESPONSE

Responses for spleen and lymphadenopathy will be assessed using CT scans. In the absence of a CT scan assessment by physical exam may be substituted. Response assessments will be made by IWCLL 2008 guidelines[13] incorporating the 2012 and 2013 clarifications for patients treated with kinase inhibitors.[74] Response includes complete response, partial response, and partial response with lymphocytosis (Table below).

Table 10. Criteria of response

Response	CR	PR[F]	PRL[F]	PD[G]
Group A				
Lymphadenopathy[A]	None >1.5cm	Decrease ≥ 50%	Decrease ≥ 50%	Increase ≥ 50% or any new lesion > 1.5cm
Splenomegaly/ Hepatomegaly[B]	None	Decrease ≥ 50%	Decrease ≥ 50%	Increase ≥ 50% or any new splenomegaly
Blood lymphocytes[BC]	< 4000/μL	Decrease ≥ 50% from baseline	Increase or <50% decrease over baseline	Increase ≥ 50% over baseline or > 5000/μL
Bone marrow[D]	Normocellular, <30% lymphocytes, no B-lymphoid nodules	Not applicable	Not applicable	Not applicable
Group B[E]				
Platelet count	>100,000/μL	> 100,000/μL or increase ≥ 50% over baseline	> 100,000/μL or increase ≥ 50% over baseline	Decrease ≥ 50% from baseline secondary to CLL

Hemoglobin	> 11.0g/dL	> 11.0 g/dL or increase ≥ 50% over baseline	> 11.0 g/dL or increase ≥ 50% over baseline	Decrease ≥ 50% from baseline secondary to CLL
Neutrophils	> 1500/μL	> 1500/μL or increase ≥ 50% over baseline	Not applicable	Not applicable

CR = complete response; CRi = CR with incomplete blood count recovery; CT = computed tomography; PD = progressive disease; PR = partial response; PRL = partial response with lymphocytosis

Footnotes

[A] Sum of the product (SPDs) of up to 6 lymph nodes as evaluated by CT scans. If CT is unavailable, the absence of enlarged lymph nodes (> 1.5cm) documented by physical exam is acceptable.

[B] Splenomegaly assessed by CT scan. In the absence of a CT scan assessment by physical exam may be substituted. New splenomegaly or hepatomegaly is assessed by physical exam.

[C]Patients with treatment-related lymphocytosis remain on study unless associated with other signs of progressive disease. Treatment-related lymphocytosis may occur at the start of treatment or at any time when resuming treatment after a dose interruption.

[D]Complete response requires confirmation with bone marrow biopsy. In the absence of a confirmatory bone marrow biopsy the response can be classified as CRu. In case of a hypocellular marrow the response can be classified as CRi.

[E] PR or PRL, at least one Group B criterion has to be met. CR, all criteria in A and B must be met. In subjects meeting Group A criteria for CR but not Group B, the response can be classified as CRi.

[F] PR and PRL criteria refer to changes from baseline.

[G] PD criteria refer to changes from baseline in subjects who never responded and to changes from best response (nadir) in subjects who responded.

Complete Response (CR)

• Is defined as meeting all criteria in A and B.
• Meet all criteria in A and B but bone marrow confirmation is pending: unconfirmed complete response (CRu).
• Meet all criteria in A but bone marrow is hypocellular, or criteria in B are not met: complete response with incomplete blood count recovery (CRi).

Partial Response (PR)

• Is defined by 2 criteria in Group A if abnormal before therapy and at least 1 Group B criterion.
• In subjects with just 1 involved Group A site (e.g., lymphadenopathy in a subject with SLL), the response is PR when the criterion for that site is met.
• If criteria for PR, except for a decrease in the number of blood lymphocytes by 50% or more from the value before therapy, are met, then assessment will be PRL.
• SLL subjects need to have both ALC >50% and ALC >5k to be PRL.

Progressive Disease (PD)

Progressive disease is defined by:
• Progressive lymphocytosis ≥50% from nadir, confirmed due to expansion of CLL cells by flow cytometry (≥5,000 B lymphocytes/μL).
• or an increase ≥50% in the sum of the products of at least two lymph nodes with at least one lymph node >1.5 cm in greatest diameter,
• or the appearance of a new pathologic lymph node >1.5 cm in greatest diameter,
• or new onset splenomegaly or hepatomegaly on physical exam, or other new CLL organ infiltrates,
• or an increase ≥50% in splenomegaly or hepatomegaly when occurring in the absence of a confounding process (e.g., infection), and that is maintained or continues to progress over a period of at least 3 months.

Other criteria for PD include:
• Transformation to a more aggressive histology (e.g., Richter syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy.
• The progression or development of cytopenia (excluding autoimmune cytopenia), as documented by a decrease of hemoglobin levels by >2 g/dL, or by a decrease of platelet counts by >50%, that persists for at least 3 months defines disease progression if a marrow biopsy supports a disease related etiology.

A rise of the lymphocyte count at the beginning of therapy or resumption of therapy after a period of drug hold in absence of other indications of progressive disease will not be considered as evidence of progressive disease because this type of agent does typically lead to a mobilization of tumor cells into the peripheral blood.

Transient increases of lymph node size during treatment with novel inhibitors may occur and should not be counted as progression**.**

8.0 ANCILLARY LABORATORY RESEARCH STUDIES

8.1 Collection of samples

- **Blood samples:** A volume not to exceed 550 ml of peripheral blood will be requested during the initial 8-week period. Subsequent research blood draws will typically consist of <100 ml of peripheral blood at follow up visits (not to exceed 550 mL in any 8-week period).
- **Lymphapheresis:** Lymphapheresis may be performed in consenting subjects.
- **BM samples:** BM biopsy cylinder and up to 10cc of BM aspirate may be obtained for research at the time of the BM biopsy as indicated in *Section 6.0.*
- **LN samples:** LN biopsies may be obtained in consenting subjects. During the course of participating on this study, an additional 10 cc of blood (NIH visits only) and 5 cc of bone marrow aspirate each time a patient has a bone marrow examination may be requested.
- **Saliva samples:** Saliva samples may be collected anytime on study.

8.2 Intended use

These samples will be used for to explore the biologic effects on B- and T-cell subsets and function, we will;

- Enumerate T (CD4, CD8), B, and NK cells in circulation
- Characterize T-cell subsets, including T-regulatory cells, Th-1, Th-2, Th-17
- Characterize T-cell activation state and differentiation
- Assess expression of checkpoint inhibitory molecules, including PD-L1 and PD-1
- Genomic profiling of the B- and T-cell repertoire by CDR3 analysis
- Measure pertinent cytokine and chemokine levels
- Genomic testing for somatic mutations in the CLL clone

These specimens will not be used for diagnostic purposes. Leftover and additional samples may be used for the descriptive or exploratory ancillary research studies, and if done, may be correlated with the presence or absence of response.

8.3 Genomic analysis

The scope of genomic analysis

- Targeted sequencing of candidate genes

- Gene expression profiling
- Genomic profiling of immune cell repertoire
- Whole genome/exome sequencing
- Sequencing cell-free DNA

Research grade genomic sequencing will be performed on banked samples to evaluate for *somatic* mutations possibly involved in the etiology and pathophysiology of blood diseases. Somatic mutation data will be obtained by subtracting germline sequencing data (saliva samples) from tumor sequencing data (blood, BM, LN samples). Banked samples collected serially from subjects enrolled on this protocol and subsequent treatment protocols may be analyzed at NHLBI, NIH, or external facilities, which will be specified to the IRB.

Protection of privacy and confidentiality of biological specimen

- Each sample is assigned a unique number. Vials holding patient samples are labeled with the sequential laboratory accession ID number that does not contain any protected health information (PHI). An electronic database is used to store patient information related to the coded samples. The laboratory is located in a controlled access building and laboratory doors are kept locked. Visitors to the laboratory are required to be accompanied by laboratory staff at all times. Hard copy records or electronic copies of documents containing patient information are kept in the locked laboratory or other controlled access locations.
- Pedigrees will not be published.
- Personally identifiable information will not be released to third parties.
- Clinical data (i.e. demographics and clinical outcome) and samples may be shared with other researchers once a research agreement is established and the amended protocol specifying the collaboration is approved by the IRB.
- Genomic data will be deposited in a genomic database prior to publication.

Secondary findings

Subjects will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for the purpose of this study are defined as disorders appearing in the American College of Medical Genetics and Genomics (ACMG) recommendations for the return of incidental findings that is current at the time of primary analysis. Secondary (incidental) findings analysis will be performed by the NHGRI-NIHCC Secondary Genomic Findings Service (SGFS) team under its CLIA license.

The SGFS process will evaluate exomes/genomes for secondary findings for each submitted exome or genome file. The PI will submit periodic datasets to the SGFS, comprising either full exome files, exome or genome variant files that encompass only the coding regions of the then current genes for which the SGFS provides analysis (e.g., the ACMG 59 gene list). These files will be configured per the specification of the NHGRI Bioinformatics Core and each file will include a coded individual identifier (no personally identifiable information) for which the PI retains the key.

If there is a secondary variant identified, the PI will be notified and should discuss the approach for validating this variant with the SGFS. Currently, the 2014 estimated yield is that 2 to 3% of participant will have such relevant findings. The SGFS will contact the PI to inform them of the finding and the PI will provide the PII (Name and contact information) of the individual with the finding.

The research participant will be contacted by either the primary team or the SGFS team to inform them that a secondary finding may be present, that it is potentially highly medically actionable, and that it is strongly

recommended that the participant submit a follow up sample (typically Oragene saliva DNA kit) to allow confirmation and clinical validation of this finding. The nature of the disease and the putatively mutated gene will not be disclosed in this call. If the participant presses, it may be disclosed that most of the findings relate to either heart disease or cancer susceptibility for which there are effective interventions to reduce pathogenic risk. If the participant agrees, the primary team will register the participant in CRIS (if not already registered) and enter a CRIS order for "Secondary Genomic Finding Confirmation Testing". The SGFS will then send an Oragene collection kit to the participant. Upon return of the sample, the SGFS will perform CLIA-valid Sanger PCR testing for the variant and a clinical report will be generated that either confirms or refutes the research finding. If positive, the NHGRI consult attending and genetic counselor will review the variant, meet with the participant to disclose the finding, provide medical and genetic counseling for that variant, provide referrals for further evaluation/follow-up for the proband and give recommendations for testing for his/her family members. If the participant declines traveling to the NIHCC for this result, it will be returned by telephone. The clinical testing report will be uploaded into CRIS. Individual negative secondary findings analysis reports will not be returned to the participant or PI. Instead, the service will return a list of all exomes/genomes that were analyzed to the PI and an indication of which (if any) were positive.

8.4 Storage, tracking and disposition of samples and data

Storage: All samples will be coded and stored in the laboratory of Dr. Wiestner. Collected samples will be de-identified prior to storage following current NHLBI DIR BSI Policy. Efforts to ensure protection of patient information as described in Section 8.3.

Tracking: Samples will be ordered and tracked through the CRIS Research Screens. Should a CRIS screen not be available, the NIH form 2803-1 will be completed and will accompany the specimen and be filed in the medical record. Samples will not be sent outside NIH without IRB notification and an executed MTA or CTA. De-identified human serum and/or plasma and/or tumor samples and clinical data from patients with B-cell malignancies may be sent to Dr. Dan Landau, Weill Cornell Medical College.

End of study procedures: Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed.

Loss or destruction of samples: Should we become aware that a major breech in our plan for tracking and storage of samples has occurred, the IRB will be notified.

9.0 BIOSTATISTICAL CONSIDERATIONS

9.1 Primary endpoint

To test the efficacy (CR at 12 months) and safety of combination of ibrutinib, fludarabine, and pembrolizumab in patients with high-risk and/or relapsed/refractory chronic lymphocytic leukemia (CLL) and small lymphocytic leukemia (SLL), primary endpoint is defined as the rate of complete response (CR) after 12 months from cycle 1. Response to treatment will be determined according to IWCLL 2008 criteria incorporating 2012 and 2013 clarifications pertaining to patients treated with kinase inhibitors.

9.2 Secondary endpoints

- Tolerability to the combination regimen

- Overall response rate (ORR)
- Best response
- Duration of response (DOR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Minimal residual disease (MRD) status defined by flow cytometry
- Shifts in cellular and humoral immunity on treatment (i.e., B- and T-cell counts and repertoire)
- Expression of checkpoint inhibitory molecules (i.e., PD-L1 and PD-1)

9.3 Sample size

The study will enroll 25 evaluable subjects for response assessment for primary endpoint. Up to 5 additional subjects may be enrolled to account for early discontinuation before completing 1-year on treatment due to non-treatment related reasons. Subjects who discontinue study treatment early due to non-treatment related reasons are not included in the evaluation of the primary endpoint.

For the primary endpoint, CR with ibrutinib alone has been reported to be 4-13% in a previously untreated CLL population,[47,60] and 0-2% in relapsed/refractory CLL.[45,46] When ibrutinib and rituximab were combined in high-risk CLL patients, CR rate was 8%.[49] Based on the reported data, a CR rate exceeding 30% would generate an interest for further studies. We will test the null hypothesis (H_0) that the CR rate in the study is $\leq$10% against alternative hypothesis (H_1) that CR is >10% with type I error of 0.05. A sample size of 25 evaluable patients will have 81% power to detect a 20% difference based on a one-sided binominal test. The null hypothesis is rejected if 6 or more CRs are observed in 25 subjects.

Early discontinuation within the first year due to toxicity related to the study drugs is counted as non-response towards the primary endpoint.

9.4 Statistical Methods

The planned analyses will include descriptive statistics on the proportions of overall response. The response probabilities will be estimated using the sample proportions and their inferences including confidence intervals and hypotheses testing will be evaluated using Binomial distributions. Time to response, overall survival and the PFS time will be analyzed using appropriate nonparametric tools in survival analysis such as Kaplan-Meier estimates taking consideration of random censoring.

In addition, methods based on survival analysis, cumulative incidence rates and other competing risk models will be used to evaluate the treatment effects. Graphical tools will be used to display the appropriate estimates (i.e. estimated proportions and Kaplan-Meier curves) and their corresponding 95% confidence intervals.

9.5 Study Stopping Rules

The study will be monitored to ensure that the occurrence of a specified set of treatment related serious adverse events (TRSAEs) that occur during the treatment period does not substantially exceed an anticipated rate. The following specified TRSAEs determined to be probably or definitely related to therapy will be considered for early stopping of the study:

1. Death
2. Severe infection requiring vasopressor for >24 hours or intubation
3. Any grade 4 toxicity excluding;

- Readily reversible metabolic or laboratory abnormalities, and
- Hematologic toxicities.

We anticipate the rate of these specified TRSAEs within the first year (completion of primary endpoint) to be 20% or less. Following Geller et al. (2003, "Design of Early Trials in Stem Cell Transplantation: A Hybrid Frequentist-Bayesian Approach"),[75] our stopping rule is determined by a Bayesian approach. The stopping boundary for an experiment is reached if the Bayesian posterior probability that the true probability of developing one or more of the specified TRSAE's exceeds this benchmark rate of 20% is at least 90%. We take our prior distribution to be a beta distribution so that our prior clinical opinion is worth 20% of the weight we will place on the new data. This gives prior parameters $(\alpha, \beta) = (1, 4)$. Hence, when we make decisions about stopping the study, the data from the study will dominate over the prior opinion. We begin monitoring the TRSAEs when 3 subjects are evaluable for TRSAEs within 1 year.

Number of subjects in the experiment	Stop if the number of subjects who have developed any of the specified TRSAE's reaches:
≤ 5	3
≤ 9	4
≤ 12	5
≤ 16	6
≤ 20	7
≤ 24	8
≤ 25	9

We investigated the performance of the above stopping rule by a simulation study. In each simulation run, we generated a study with 25 independent Bernoulli trials, each had a probability p for having TRSAE and q=1-p for not having TRSAE and compared the TRSAE outcomes with the above stopping boundary to determine whether the study was stopped. We repeated the simulation 100,000 times and computed the proportion of stopped studies (i.e. "number of stopped studies"/100,000) which were stopped using the above stopping rule. The following table summarizes the proportions of stopped studies under a number of scenarios for *p*:

Probability of TRSAE = *p*	0.1	0.15	0.20	0.25	0.30	0.40
Proportion of Stopped Studies	1.7%	7.9%	18.4%	35.8%	55.4%	86.2%
Average number of subjects	24.7	23.9	22.4	20.1	17.3	11.8
Average number TRSAEs	2.5	3.6	4.5	5.0	5.2	4.7

These results suggest that our stopping rule has a low probability stopping a study when the proportion of TRSAE is below the benchmark value of 20%, and the probability of stopping a study is high when the true proportion of TRSAE exceeds this benchmark value. Based on these results, we believe that our Bayesian stopping rule has satisfactory statistical properties.

9.6 Stopping rule for Mortality

In addition, we have a stopping rule for TRM (deaths that are possibly, probably or definitely related to the protocol regimen, and are not due to disease progression). We anticipate the TRM rate within one year to be

5% or less. Using the same Bayesian approach, the stopping boundary is reached if the Bayesian posterior probability that the true probability of developing TRM's exceeds 5% is at least 90%. We take our prior distribution to be a beta distribution with parameters $(\alpha, \beta) = (0.25, 4.75)$. This indicates that the relative weight we place on our prior opinion is approximately 20% of the weight we will place on the results of the new study. The following table summarizes the threshold numbers for stopping the study based on above Bayesian approach.

Number of subjects in the experiment	Stop if the number of subjects who have TRMs reaches:
≤ 9	2
≤ 21	3
≤ 25	4

We investigated the performance of the above stopping rule by a simulation study. In each simulation run, we generated a study with 30 independent Bernoulli trials, each had a probability p for having TRM and q=1-p for not having TRM and compared the TRM outcomes with the above stopping boundary to determine whether the study was stopped. We repeated the simulation 100,000 times and computed the proportion of stopped studies (i.e. "number of stopped studies"/100,000) which were stopped using the above stopping rule. The following table summarizes the proportions of stopped studies under a number of scenarios for p:

Probability of TRM = p	0.03	0.05	0.07	0.10	0.15	0.20
Proportion of Stopped Studies	4.2%	12.1%	22.9%	41.4%	68.9%	86.3%
Average number of subjects	24.4	23.3	21.9	19.4	15.2	11.6
Average number TRMs	0.7	1.2	1.5	1.9	2.3	2.3

These results suggest that our stopping rule has a low probability stopping a study when the proportion of TRM is below the benchmark value of 5%, and the probability of stopping a study is high when the true proportion of TRM exceeds this benchmark value. Based on these results, we believe that our Bayesian stopping rule has satisfactory statistical properties.

9.7 Off Study Criteria (for subject participation)

Patient choice: Subjects may be removed from the study at their request. The risks of withdrawing will be discussed, as will alternative treatment options. Subjects who opt to withdraw from the protocol will be strongly encouraged to continue to have labs monitored for two months after study withdrawal for their safety.

PI Decision: Patients will be taken off study for:

- Initiation of non-protocol treatment.
    - For patients who were newly diagnosed with a second malignancy, the study treatment can be temporarily interrupted while the patient undergoes further evaluation and treatment with definitive, time-limited systemic therapy. For pembrolizumab, drug interruptions of up to 6 weeks are allowed. For ibrutinib, drug interruptions of up to 6 months are allowed during the single-agent ibrutinib maintenance phase. Longer interruptions in investigational treatment will require removal of subjects from the protocol.
- Significant progression of disease or a concomitant condition that would make the subject ineligible

for further protocol participation
- Pregnancy or begins breast feeding
- Subject becomes significantly noncompliant with study drug administration, study procedures, or study requirements, which might increase risk or substantially compromise the interpretation of study results.

Completion of the study: Subjects will be followed indefinitely until an off study criterion is met or the study is closed to further follow up care. Once protocol participation is complete, the subject will be referred back to his or her referring physician for standard therapy or evaluated for eligibility for another branch protocol, depending on what is considered to be in the best interest of the subject.

10.0 DATA AND SAFETY MONITORING

Principal Investigator: Accrual, efficacy and safety data will be monitored by the principal investigator Adrian Wiestner, M.D., Ph.D.

NIH Intramural IRB: Prior to implementation of this study, the protocol and the proposed patient consent and assent forms will be reviewed and approved by the properly constituted Institutional Review Board (IRB) operating according to 45 CFR 46. Quality assurance and control monitoring will be consistent with the NHLBI Division of Intramural Research Clinical Research Quality Assurance and Quality Control Policy.

NHLBI DSMB: The NHLBI Data And Safety Monitoring Board (DSMB) will review the protocol, progress report, accrual, efficacy and safety data at six- or twelve-month intervals as scheduled. All AEs and SAEs observed during the clinical trial and for which there is a relationship with the use of the ibrutinib, fludarabine and pembrolizumab, or the conduct of the study will be reported to the DSMB at the regularly scheduled DSMB meeting. The DSMB may recommend early termination of the study for considerations of safety and efficacy.

Merck: Merck will approve all amendments to the protocol or informed consent prior to submission to the IRB and conduct continuing annual review so long as the protocol is open to accrual or sample and/or data analysis continues. Accrual and safety data will also be monitored and reviewed annually by the IRB. An annual progress report, any amendments to the protocol, and any change in the status of the protocol will be forwarded to Merck Global Safety facsimile number: +1-215-993-1220.

Pharmacyclics: Per the IST Agreement, any amendments to the Protocol or Informed Consent Form must be sent to Pharmacyclics for review and approval prior to submission to the IRB.

10.1 Assessment of safety

Definitions

Please refer to Policy 801: Reporting Research Events.

10.1.1. Severity

We will use the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 for grading of non-hematologic AEs (http://ctep.cancer.gov/reporting/ctc.html). We will use 2008 International Workshop for CLL grading scale for grading of hematologic AEs (Table 11).

Table 11. The grading scale for hematologic AEs in subjects with CLL[13]

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

1. Grades: 1, mild; 2, moderate; 3, severe; 4, life threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be reported as Grade 5.
2. Platelet counts must be below normal levels for Grades 1 to 4. If, at any level of decrease, the platelet count is < 20 x 10^9/L (20,000/μL), this will be considered Grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (e.g., < 20 x 10^9/L [20,000/μL]) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.

2. Hemoglobin (Hb) levels must be below normal levels for Grades 1 to 4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity, but should be documented.
3. If the ANC reaches < 1 x 10^9/L (1000/μL), it should be judged to be Grade 3 toxicity. Other decreases in the white blood cell count, or in circulating neutrophils, are not to be considered because a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was < 1 x 10^9/L (1000/μL) before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of growth factors such as granulocyte colony-stimulating factor (G-CSF) is not relevant to the grading of toxicity, but should be documented.

10.1.2 Pregnancy

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

A female subject must immediately inform the Investigator if she becomes pregnant from the time of consent to 90 days after the last dose of study drug. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of consent to 90 days after the last dose of study drug. Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus. Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 90 days after the last dose of study drug must be reported.

Reports to Pharmacyclics

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

SAE reporting timelines. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

Reports to Merck

The outcome of the pregnancy will be reported to Merck without delay and within 24 hours to the sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). Such events must be reported to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

10.1.3 Other malignancies

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival. If observed, enter data in the corresponding eCRF.

10.1.4 Causality assessments

The following general guideline will be followed:

Unrelated	Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.
Unlikely to be Related:	A temporal sequence with the onset of the adverse event and administration of the investigational product is improbable, but not impossible. Concurrent or underlying disease, or the use of other drugs or procedures provide plausible explanations for the adverse event.
Possibly Related	There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the adverse event could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible adverse event causes.
Probably Related:	There is a clinically plausible time sequence between onset of the adverse event and administration of the investigational product, and the adverse event is unlikely to be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Clinical response to withdrawal of the investigational product may indicate the adverse event is probably related. Rechallenge with the investigational drug is not required.
Definitely Related	The AE is clearly related to use of the investigational product.

10.2 Adverse Event Documentation

This study is closed for accrual as of March 9, 2021. The patients remaining on study are continuing taking ibrutinib as a single agent, consistent with the standard of care for CLL.

The protocol will no longer capture new AEs.

The protocol will continue to collect following events on study:

- SAEs and UPs defined by Policy 801

- Events of special interest (as defined in Section 10.8)

If an SAE is present at the safety follow-up visit or within 30 days of the last dose of study drug (whichever is later), it should be followed to resolution or until the Investigator assesses the subject as stable, a new anticancer

therapy is initiated, or the subject is lost to follow-up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the event.

10.3 NIH Intramural IRB and CD reporting

Expedited Reporting

Events requiring expedited reporting will be submitted to the IRB per Policy 801.

Reports to the IRB at the time of Continuing Review

The PI or designee will refer to Policy 801.

Reports to the CD

The PI or designee will refer to NHLBI DIR Policy to determine CD reporting requirements and timelines.

10.4 Reports to Merck

An SAE is any AE occurring at any dose or during any use of Merck's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event.

Any SAE, or follow up to a SAE, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the sponsor and within 2 working days to Merck Global Safety.

Additionally, any SAE, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross-reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to Merck at the time of submission to FDA.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the adverse event case report forms/worksheets.

10.5 Reports to Pharmacyclics LLC, an AbbVie Company

Special reporting situation on a Sponsor study may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of any study drug
- Suspected abuse/misuse of a study drug
- Inadvertent or accidental exposure to a study drug
- Medication error involving a product (with or without subject exposure to the study drug, eg, name confusion)

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

Pharmacyclics LLC, an AbbVie Company, will be notified for Drug Safety, or designee of any serious, unexpected, fatal or life-threatening adverse event or adverse drug reaction as soon as possible, but no later than 7 calendar days in the case of death or life-threatening serious adverse events after the Sponsor's receipt of the information or becoming aware of the occurrence. All other SAEs will be reported no later than 15 days after the Sponsor's receipt of the information or becoming aware of the occurrence. Pharmacyclics LLC may request follow-up and other additional relevant clinical records or information from the investigator. The Sponsor will submit each IND safety report in a format that complies with the FDA reporting requirements. A copy of this IND safety report must also be faxed concurrently to Pharmacyclics Drug Safety.

10.6 Reporting Period for AEs

The AE reporting period for this study begins when the patient takes the first dose of study drug and ends with the safety follow-up visit. If an SAE is present at the safety follow-up visit or within 30 days of the last dose of study drug (whichever is later), it should be followed to resolution or until the Investigator assesses the subject as stable, a new anticancer therapy is initiated, or the subject is lost to follow-up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the event.

10.7 Reporting for other malignancies

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies had been reported as SAEs until January 2019. This was based on the assumption that malignancies are medically significant events that impact patient survival. However, non-melanoma skin cancer, such as squamous cell or basal cell carcinoma of skin, is most often managed with local resection only and has minimal impact on long-term survival. As of February 2019, this protocol no longer considers non-melanoma skin cancer as a SAE. Other malignancies, including malignant melanoma and other solid tumors, will be continued to be reported as SAEs.

10.8 Events of clinical interest

Merck

Selected non-serious and serious AEs are also known as Events of Clinical Interest (ECI) and must be recorded as such on the AE case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220). Events of clinical interest for this trial include:

Overdose: An overdose of pembrolizumab is defined a as any dose of 1,000 mg or greater ($\geq$5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. If an AE is associated with the overdose of pembrolizumab, the AE is reported as a serious adverse event, even if no other seriousness criteria are met. If a dose pembrolizumab 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 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 to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

Elevation of AST, ALT, bilirubin, alkaline phosphatase: An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal (ULN) and an elevated total bilirubin lab value that is greater than or equal to 2X the ULN and, at the same time, an alkaline phosphatase lab value that is less than 2X the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

Pharmacyclics

Adverse Events of Special Interest (AESI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities by the Sponsor. These events (regardless of seriousness) will be reported to Pharmacyclics Drug Safety, or designee within 15 days of awareness.

Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic adverse events of Grade 3 or higher. All hemorrhagic events requiring transfusion of red blood cells should be reported as grade 3 or higher AE per CTCAE v4.03
- Any treatment-emergent serious adverse events of bleeding of any grade
- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade

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

10.9 Data management

The principal investigator will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate

investigators/research nurses and/or a contracted data manager will assist with the data management efforts to ensure that data is verifiable and evaluable. Data will be abstracted from Clinical Center progress notes as well as from progress notes forwarded from the subjects' home physician. Laboratory data from NIH will be imported electronically from CRIS into an in-house clinical trial database. Laboratory values from referring home physicians will be entered into the system.

We will maintain the confidentiality of identifiable private information collected in this Clinical Trial and protect the privacy of the individual human subjects. Primary data containing individually identifiable information obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH information security standards. Neither individual personal identifiers nor the key linking coded data to individuals will be released to Merck without prior IRB approval and an executed CDA or MTA. Identifiable data will not be sent outside NIH without prior IRB approval or appropriate conditions for disclosure outlined in the executed CDA or MTA.

End of study procedures: Data will be stored in locked cabinets and in a password protected database until it is no longer of scientific value. Upon completion of the data analysis, the investigator will send to Merck a copy of the de-identified data set and final Clinical Study Report as requested.

Loss or destruction of data: Should we become aware that a major breech in our plan to protect patient confidentiality and trial data has occurred, the IRB will be notified.

10.10 Protocol Amendments

Per the IST Agreement, any amendments to the protocol or informed consent form must be sent to Merck and Pharmacyclics for review and approval prior to submission to the IRB. Written verification of IRB approval will be obtained before any amendment is implemented.

Publication Policy: Given the research mandate of the NIH, patient data including the results of testing and responses to treatment will be entered into an NIH-authorized and controlled research database. Any future research use will occur only after appropriate human subject protection institutional approval such as prospective NIH IRB review and approval or an exemption from the NIH Office of Human Subjects Research Protections (OHSRP).

Per the IST Agreement, the Investigator is required to submit to Merck and Pharmacyclics a copy of a planned publication (abstract, poster, oral presentation or manuscript) prior to the submission thereof for publication or disclosure. Merck and Pharmacyclics may provide scientific comments and suggestions understanding that the Investigator has sole editorial responsibility, and retains the authority to make the final determination on whether or not to incorporate Merck and Pharmacyclics comments or requests for additional information.

10.11 Protocol Monitoring

As per ICH-GCP 5.18 and FDA 21 CFR 312.5, clinical protocols are required to be adequately monitored by the study sponsor. The monitoring of this study will be conducted by Clinical Research Associates (CRAs)/Monitors working under an agreement with NHLBI to monitor aspects of the study in accordance with the appropriate regulations and the approved protocol. The objectives of a monitoring visit will be: 1) to verify the existence of signed informed consent form (ICF) and documentation of the ICF process for each monitored subject; 2) to verify the prompt and accurate recording of all monitored data points, and prompt reporting of all SAEs; 3) to compare abstracted information with individual subjects' records and source documents (subject's

charts, laboratory analyses and test results, physicians' progress notes, nurses' notes, and any other relevant original subject information); and 4) to help ensure investigators are in compliance with the protocol. The monitors also will inspect the clinical site regulatory files to ensure that regulatory requirements (Office for Human Research Protections-OHRP), FDA and applicable guidelines (ICH-GCP) are being followed. During the monitoring visits, the investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit.

The investigator (and/or designee) will make study documents (e.g., consent forms and pertinent hospital or clinical records readily available for inspection by the local IRB, the FDA, the site monitors, and the NHLBI staff for confirmation of the study data.

11.0 HUMAN SUBJECT PROTECTION

The investigator(s) accept their responsibilities for protecting the rights and welfare of human research subjects and will permit, with reasonable advance notice and at reasonable times, the designated research monitors to monitor the conduct of the research, as well as to audit source documents to the extent necessary to verify compliance with FDA Good Clinical Practice and the approved protocol.

11.1 Rationale for subject selection

11.1.1 Predicted distribution by gender, age and race

CLL is a rare neoplasm that comprises a substantial proportion of all leukemia in middle-aged persons and is the most common type among elderly persons in western populations. Epidemiologic studies suggest that distribution by gender will be 66% males and 33% females.[13] CLL is more common in Caucasian and African-American but rare in Hispanics and very rare in the Asian population. This study will be open to all patients who fit the inclusion criteria and provide informed consent to protocol participation. We would predict that distribution should be comparable to that seen on the NHLBI Hematology Branch screening protocol as follows:

- by gender: 33% females; 66% males
- by age: ages 23-79, median 60
- by race: 2% Asian, 11% Black, 8% Hispanic, 79% White

11.1.2 Special Populations

Justification for inclusion of high-risk and/or relapsed/refractory CLL: Ibrutinib is FDA-approved for the treatment of high-risk CLL with deletion 17p regardless of treatment status and for relapsed/refractory CLL. However, treatment with a single-agent ibrutinib lacks the depth of response, and resistant mutations can occur. By combining ibrutinib with short-course fludarabine and pembrolizumab, this study aims to augment the quality of response and prevent drug resistance in patients with high-risk cytogenetic mutations or who have relapsed/refractory CLL.

Justification for exclusion of children: CLL is uncommon in patients less than 45 years of age and is virtually unknown in patients less than 20 years of age. At the time of diagnosis, more than 95% of patients are 45 years old and above.[11] CLL may also be, biologically, a different disease in children. Ibrutinib has not been studied in human subjects under 18 years of age. For these reasons, individuals < 18 years old have been excluded from protocol participation.

Justification for exclusion of pregnant women: There are no clinical studies that were done on pregnant women, and it is unknown whether ibrutinib, pembrolizumab or their metabolites are excreted in human milk. In addition, it is highly unlikely that a woman of pre-menopausal age will present with CLL or SLL at the Clinical Center. CLL/SLL is a malignancy of B cells that predominantly affects the elderly population. Diagnosis is typically made in adults over the age of 50 and more than half of the people with CLL/SLL are over the age of 70.

Justification for exclusion of patients with impaired hepatic or renal function: No specific clinical studies have been conducted to date in patients with impaired hepatic or renal function. To minimize risks, patients enrolled must have adequate hepatic and renal function as defined in eligibility and exclusion criteria.

Adults with decisional impairment: Adults unable to give consent are excluded from enrolling in the protocol. However, reconsent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. Because there is a prospect of direct benefit from research participation those subjects will be allowed to continue study participation. For this reason all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will follow Policy 403 and contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation to assess ongoing capacity of the subjects and to identify an LAR as needed.

Please note that if a subject loses the ability to consent due to an adverse event/serious adverse event, the subject will remain on study until that event resolves and will be allowed to continue to participate in this trial.

Recruitment: A Strategic Recruitment Plan (SRP) has been developed in conjunction with the NHLBI Patient Recruitment Office. Recruitment strategies that will be ongoing throughout recruitment period of trial may include 1) distribution of a recruitment flyer in the NIH campus, patient advocacy organizations and the community; 2) updating study information on clinicaltrials.gov, NIH Search the Studies, and a dedicated recruitment page on the Clinical Center Office of Patient Recruitment website; 3) the use of ResearchMatch for identification of study candidates; 4) promoting the study on the official NIH social media account with IRB approved language and images; 5) distribution of a recruitment information on NIH listservs; and 7) distribution of a physician-to-physician letter to local hematologists/oncologists.

Payment for participation: $0 – Subjects will not be compensated for their participation in this study. There is no payment for the blood samples obtained for research.

Reimbursement for protocol participation travel, food, and lodging will be consistent with NIH guidelines.

For travel from home: Travel from home for the first NIH visit will not be reimbursable. If the patient consents to protocol participation travel home following the first visit will be reimbursable. Subjects will be reimbursed 100% of government rate for travel once the subject has been determined eligible to participate and signs consent.

Local travel (car/taxi/shuttle/train/bus): Subjects will be reimbursed for local train/bus and/or shuttle costs consistent with NIH guidelines. Car mileage will be reimbursed $0.41/mile when the distance from home is

greater than 50 miles. Reimbursement for mileage less than 50 miles from home is not provided. Subjects will not be reimbursed for rental car cost beyond the car mileage rate. Taxi will be paid only when medically necessary and authorized by the PI.

Meals: Subjects will not be reimbursed for meals.

Lodging: Will be consistent with NIH guidelines.

Competition with other Branch protocols: There is no active treatment protocol specifically designed for treatment-naïve CLL/SLL patients with high-risk genetic markers. Approximately 10% of treatment-naïve CLL patients will be eligible for the current protocol.

11.2 Risks and discomforts related to research

11.2.1 Risks related to ibrutinib

Bleeding-related events

There have been reports of bleeding events in subjects treated with ibrutinib both with and without thrombocytopenia. These include primarily minor bleeding events such as contusion, epistaxis, eye hemorrhage, and petechiae; and major bleeding events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage and hematuria. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. Use of either anticoagulant or antiplatelet agents concomitantly with ibrutinib increases the risk of major bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with ibrutinib. Monitor for signs and symptoms of bleeding. Supplements such as fish oil and vitamin E preparations should be avoided.

Subjects with congenital bleeding diathesis have not been studied. See Section 5.6.3 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery, depending upon the type of surgery and the risk of bleeding. See Section 5.4.1 for guidance on ibrutinib management with surgeries or procedures.

Cardiac arrhythmias

Fatal and serious cardiac arrhythmias or cardiac failure have occurred in patients treated with ibrutinib. Patients with significant cardiac comorbidities may be at greater risk of events, including sudden fatal cardiac events. Atrial fibrillation, atrial flutter, ventricular tachyarrhythmia and cardiac failure, have been reported, particularly in subjects with acute infections, or cardiac risk factors, including hypertension, diabetes mellitus, and a previous history of cardiac arrhythmia.. Appropriate clinical evaluation of cardiac history and function should be performed prior to initiating ibrutinib. Patients should be carefully monitored during treatment for signs of clinical deterioration of cardiac function and clinically managed. Consider further evaluation (e.g., ECG, echocardiogram), as indicated for patients in whom there are cardiovascular concerns. For signs and symptoms that persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guideline (see Section 5.4.2).

Cerebrovascular accidents

Although causality has not been established, cases of cerebrovascular accident, transient ischemic attack, and ischemic stroke including fatalities have been reported with the use of ibrutinib in the post-marketing setting, with and without concomitant atrial fibrillation and/or hypertension. Regular monitoring and appropriate treatment of conditions that can contribute to the occurrence of these events is recommended.

Cytopenias

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

Gastrointestinal disorders

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, dyspepsia, and constipation. These events are rarely severe and are generally managed with supportive therapies including antidiarrheals and antiemetics. Subjects should be monitored carefully for gastrointestinal AEs and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation may include tests to rule out other etiologies such as Clostridium difficile or other infectious agents. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 5.4).

Hypertension

Hypertension has occurred in subjects treated with ibrutinib. Regularly monitor blood pressure in subjects treated with ibrutinib and initiate or adjust antihypertensive medication throughout as appropriate.

Infections

Infections (including sepsis, bacterial, viral, or fungal infections such as Pneumocystis pneumonia and aspergillosis) were observed in subjects treated with ibrutinib therapy. Some of these reported infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) and hepatitis B reactivation and pneumocystis pneumonia have occurred in patients treated with ibrutinib. Cases of hepatitis E, which may be chronic, have occurred in patients treated with ibrutinib. Subjects should be monitored for signs and symptoms (such as fever, chills, weakness, confusion, vomiting, jaundice, and abnormal liver function tests) and appropriate therapy should be instituted as indicated

Tumor lysis syndrome (TLS)

There have been reports of tumor lysis syndrome (TLS) events in subjects treated with single-agent ibrutinib or in combination with chemotherapy. Subjects at risk of TLS are those with high tumor burden prior to treatment.

Non-melanoma skin cancer

Non-melanoma skin cancers have occurred in patients treated with ibrutinib. Monitor patients for the appearance of non-melanoma skin cancer.

Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. Most rashes were mild to moderate in severity. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) have been reported in subjects treated with

ibrutinib. Neutrophilic dermatosis has been reported in postmarketing surveillance. Subjects should be closely monitored for signs and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events including erythema, urticaria, and angioedema have been reported.

Interstitial lung disease
Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Subjects should be monitored and evaluated for symptoms indicative of ILD (eg, dyspnea, cough or pyrexia). If symptoms develop, interrupt ibrutinib and manage ILD appropriately. If symptoms persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines.

Leukostasis
There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes (>400,000/μL) may confer increased risk of leukostasis. Consider temporarily withholding ibrutinib. Subjects should be closely monitored. Administer supportive care such as hydration and/or leukapheresis as indicated.

Lymphocytosis
Upon initiation of single-agent treatment with ibrutinib, a reversible increase in lymphocyte counts (i.e., ≥50% increase from baseline and an absolute count >5000/μL), often associated with reduction of lymphadenopathy, has been observed in most subjects (66%) with CLL/SLL. This effect has also been observed in some subjects (33%) with mantle cell lymphoma (MCL) treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first month of ibrutinib therapy and typically resolves within a median of 8 weeks in subjects with MCL and 14 weeks in subjects with CLL/SLL (range, 0.1 to 104 weeks).

When ibrutinib was administered in combination with BR or with obinutuzumab in subjects with CLL/SLL, lymphocytosis was infrequent (7% with ibrutinib + BR versus 6% with placebo + BR and 7% with ibrutinib + obinutuzumab versus 1% with chlorambucil + obinutuzumab). Lymphocytosis was not commonly observed in subjects with Waldenström's macroglobulinemia treated with ibrutinib.

Long-term safety
The long-term safety data over 5 years from 1,284 subjects (treatment-naïve CLL/SLL n = 162, relapsed/refractory CLL/SLL n=646, relapsed/refractory MCL n = 370, and WM n=106) treated with ibrutinib were analyzed. The median duration of treatment for CLL/SLL was 51 months (range, 0.2 to 98 months) with 70% and 52% of subjects receiving treatment for more than 2 years and 4 years, respectively. The median duration of treatment for MCL was 11 months (range, 0 to 87 months) with 31% and 17% of subjects receiving treatment for more than 2 years and 4 years, respectively. The median duration of treatment for WM was 47 months (range, 0.3 to 61 months) with 78% and 46% of subjects receiving treatment for more than 2 years and 4 years, respectively. The overall known safety profile of ibrutinib-exposed subjects remained consistent, other than an increasing prevalence of hypertension, with no new safety concerns identified. The prevalence for Grade 3 or greater hypertension was 4% (year 0-1), 6% (year 1-2), 8% (year 2-3), 9% (year 3-4), and 9% (year 4-5). The overall incidence for the 5-year period was 11%.

Potential for drug-drug interactions

Ibrutinib is primarily metabolized by CYP3A4.. Of the 3,838 subjects with hematologic malignancies in the RSI pool, 51.9% took at least one CYP3A inhibitor at any time during a study; 9.2% used a strong CYP3A inhibitor, 28.5% used a moderate CYP3A inhibitor, and 32.6% used a weak CYP3A inhibitor (Appendix H of the IB v.15). The strong CYP3A inhibitors used were clarithromycin (5.0%), voriconazole (3.2%), posaconazole (0.7%), itraconazole (0.5%), and ketoconazole (0.1%). The most commonly used moderate CYP3A inhibitors (≥1% of subjects) were fluconazole (5.2%), ciprofloxacin (15.4%), diltiazem (2.4%), and aprepitant (1.6%). The most commonly used weak CYP3A inhibitors (≥2% of subjects) were amlodipine (8.2%), atorvastatin (6.5%), ranitidine (6.1%), alprazolam (4.6%), amiodarone (3.0%), ranitidine hydrochloride (2.7%), amlodipine besilate (2.2%), atorvastatin calcium (2.0%).

Of the 214 subjects with cGVHD in the RSI pool, 98.6 % took at least 1 CYP3A inhibitor; 60.3% used a strong CYP3A inhibitor, 46.7% used a moderate CYP3A inhibitor, and 90.7% used a weak CYP3A inhibitor. The strong CYP3A inhibitors used were posaconazole (33.2%), voriconazole (29.0%), clarithromycin (3.7%), and itraconazole (3.7%). The most commonly used moderate CYP3A inhibitors (≥1% of subjects) were fluconazole (30.4%), ciprofloxacin (9.8%), imatinib (8.4%), isavuconazonium (2.3%), and erythromycin (1.9%). The most commonly used weak CYP3A inhibitors (≥2% of subjects) were tacrolimus (52.8%), ciclosporin (39.7%), amlodipine (21.0%), ranitidine (6.5%), atorvastatin (5.6%), alprazolam (3.3%), amiodarone (3.3%), and tacrolimus monohydrate (3.3%).

Agents that may increase ibrutinib plasma concentrations (CYP3A inhibitors):

Concomitant use of ibrutinib and drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure and strong CYP3A inhibitors should be avoided.

Strong CYP3A inhibitors

Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects, increased exposure (Cmax and $AUC_{0\text{-last}}$) of ibrutinib by 29- and 24-fold, respectively. In a dedicated drug-drug interaction study in subjects with B-cell malignancies, co-administration of voriconazole increased ibrutinib Cmax and AUC by 6.7-fold and 5.7-fold, respectively. In clinical studies, the maximal observed ibrutinib exposure (AUC) was ≤ 2-fold in 37 subjects treated with mild and/or moderate CYP3A inhibitors when compared with the ibrutinib exposure in 76 subjects not treated concomitantly with CYP3A inhibitors. Clinical safety data in 66 patients treated with moderate (n=47) or strong CYP3A inhibitors (n=19) did not reveal meaningful increases in toxicities. Voriconazole and posaconazole can be used concomitantly with ibrutinib as per the dosing guidance described in the specific clinical study protocol. All other strong inhibitors of CYP3A (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazodone and cobicistat) should be avoided, and an alternative with less CYP3A inhibitory potential should be considered. If the benefit outweighs the risk and a strong CYP3A inhibitor must be used, see the recommended dose modifications described in the specific clinical study protocol.

Moderate and mild CYP3A inhibitors

In subjects with B-cell malignancies, co-administration of the CYP3A inhibitor erythromycin increased Cmax and AUC by 3.4-fold and 3.0-fold, respectively. Follow dose modifications described in the ibrutinib USPI.

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

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

Drugs that may have their plasma concentrations altered by ibrutinib
In vitro studies indicated that ibrutinib is a weak reversible inhibitor of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 and does not display time--dependent CYP450 inhibition. The dihydrodiol metabolite of ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, and CYP2D6. Both ibrutinib and the dihydrodiol metabolite are at most weak inducers of CYP450 isoenzymes in vitro. However, in a drug interaction study in patients with B cell malignancies, a single 560 mg dose of ibrutinib did not have a clinically meaningful effect on the exposure of the CYP3A4 substrate midazolam. In the same study, 2 weeks of treatment with ibrutinib at 560 mg daily had no clinically relevant effect on the pharmacokinetics of oral contraceptives (ethinyl estradiol and levonorgestrel), the CYP3A4 substrate midazolam, nor the CYP2B6 substrate bupropion.

In vitro studies indicated that ibrutinib is not a substrate of P-gp, nor other major transporters, except OCT2. The dihydrodiol metabolite and other metabolites are P-gp substrates. Ibrutinib is a mild inhibitor of P-gp and breast cancer resistance protein (BCRP). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp and BCRP after a therapeutic dose. There are no clinical data available. To minimize the potential for an interaction in the GI tract, narrow therapeutic range P-gp or BCRP substrates such as digoxin or methotrexate should be taken at least 6 hours before or after ibrutinib. Ibrutinib may also inhibit BCRP systemically and increase the exposure of drugs that undergo BCRP -mediated hepatic efflux, such as rosuvastatin.

Based on preliminary data from the combination studies of ibrutinib and venetoclax, venetoclax exposure (AUC_{0-24}) at 400 mg daily was approximately 1.8-fold higher with 420 mg ibrutinib in one study (Study 1142, CLL, N=131) and approximately 3-fold higher with 560 mg ibrutinib in another study (Study 1143, MCL, N=18) compared to available venetoclax single agent 400 mg daily exposure data. In the ibrutinib and venetoclax combination study CLL3011, venetoclax trough concentrations were higher in combination with ibrutinib (1,765 ng/mL) compared with monotherapy based on historical data (mean range of 630 to 810 ng/mL) (NDA/BLA Multi-disciplinary Review and Evaluation Supplemental 2016). It must be noted that the variability in pharmacokinetic parameters observed in Study 1142 (%CV of 66%), Study CLL3011 (%CV of 89%) and reported in Roberts et al (%CV of 57% and 66% in 2 different 400 mg cohorts) was high. No apparent effect on ibrutinib exposure has been noted in Study 1142, while in Study 1143 a higher mean ibrutinib exposure has been observed; however, the exposure was within the exposure range of 560 mg ibrutinib observed with monotherapy. To date, no new safety signals have been identified in these ongoing combination therapy studies. Subjects should be closely monitored for signs of toxicity.

Contraindications
Ibrutinib is contraindicated in subjects with clinically significant hypersensitivity to any of the compound's structural components. Ibrutinib has not been used in subjects with biliary obstruction, acute hepatitis, severe liver failure, or severely impaired renal function; hence, avoid use of ibrutinib in patients with these conditions.

Registration and marketing experience

The company reviewed safety data from clinical trials and postmarketing reports as part of routine surveillance. Eye hemorrhage and dyspepsia were recently identified as new adverse reactions in the postmarketing setting since the last version of the IB.

11.2.2 Risks related to fludarabine

Safety data for fludarabine is generated from treatment trials using fludarabine for up to 6 cycles in CLL. In the current study, fludarabine is given as a short-course over two cycles only. Nevertheless, all of the known adverse events related to fludarabine are listed based on available data. Details of the adverse events can be found in the FDA-approved label for fludarabine.

Common side effects: The most common side effects, reported in 1 out of every 3-4 patients, are anorexia, nausea, vomiting, muscle pain, tiredness, weakness, and general body discomfort.

Serious side effects: Most of the side effects seen in patients taking fludarabine are mild to moderate in severity. However, severe side effects have occurred, and some had been severe enough to stop fludarabine, modify the dose of fludarabine, or led to hospitalization, disability, or death. The following rare but serious side effects have been reported in less than 1 in 100 patients; severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); abnormal thinking; black, tarry, or bloody stools; blood in the urine; changes in strength or walk; chest pain; confusion; coughing or vomiting blood; difficult or painful urination; fainting; hearing loss; irregular heartbeat; lower back or side pain; mental or mood changes (i.e. agitation, confusion); numbness or tingling in the hands or feet; red, swollen, blistered, or peeling skin; seizures; severe or persistent tiredness or weakness; signs of infection (i.e. fever, chills, cough, or sore throat); shortness of breath; skin changes; sores on the mouth or lips; swelling of the fingers, hands, or feet; unusual bruising or bleeding; vision changes or blindness; yellowing of the eyes or skin. Patients will be advised to contact the research team immediately in the event of a severe side effect.

11.2.3 Risks related to pembrolizumab

Immune-mediated pneumonitis

Pneumonitis occurred in 139 (3.6%) patients, including Grade 2, 3, 4 or 5 cases in 56 (1.5%), 38 (1.0%), 9 (0.2%) and 5 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of pneumonitis was 3.7 months (range 2 days to 21.3 months). The median duration was 2.1 months (range 1 day to 17.2+ months). Pneumonitis led to discontinuation of pembrolizumab in 60 (1.6%) patients. Pneumonitis resolved in 81 patients, 1 with sequelae.

Immune-mediated colitis

Colitis occurred in 71 (1.9%) patients, including Grade 2, 3 or 4 cases in 15 (0.4%), 44 (1.1%) and 3 (<0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of colitis was 3.6 months (range 7 days to 16.2 months). The median duration was 1.3 months (range 1 day to 8.7+ months). Colitis led to discontinuation of pembrolizumab in 18 (0.5%) patients. Colitis resolved in 61 patients. .

Immune-mediated hepatitis

Hepatitis occurred in 23 (0.6%) patients, including Grade 2, 3 or 4 cases in 4 (0.1%), 16 (0.4%) and 2 (<0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hepatitis was 1.3 months (range 8 days to 21.4 months). The median duration was 1.5 months (range 8 days to 20.9+ months). Hepatitis led to discontinuation of pembrolizumab in 7 (0.2%) patients. Hepatitis resolved in 19 patients.

Immune-mediated nephritis
Nephritis occurred in 15 (0.4%) patients, including Grade 2, 3 or 4 cases in 3 (0.1%), 10 (0.3%) and 1 (<0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of nephritis was 4.9 months (range 12 days to 12.8 months). The median duration was 1.8 months (range 10 days to 10.5+ months). Nephritis led to discontinuation of pembrolizumab in 7 (0.2%) patients. Nephritis resolved in 9patients.

Immune-mediated endocrinopathies
Hypophysitis occurred in 21 (0.5%) patients, including Grade 2, 3 or 4 cases in 6 (0.2%), 12 (0.3%) and 1 (<0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hypophysitis was 3.7 months (range 1 day to 17.7 months). The median duration was 3.3 months (range 4 days to 12.7+ months). Hypophysitis led to discontinuation of pembrolizumab in 6 (0.2%) patients. Hypophysitis resolved in 10 patients, 2 with sequelae.

Hyperthyroidism occurred in 135 (3.5%) patients, including Grade 2 or 3 cases in 32 (0.8%) and 4 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hyperthyroidism was 1.4 months (range 1 day to 21.9 months). The median duration was 2.1 months (range 10 days to 15.5+ months). Hyperthyroidism led to discontinuation of pembrolizumab in (0.1%) patients. Hyperthyroidism resolved in 104 (77%) patients, 1 with sequelae.

Hypothyroidism occurred in 345 (9.0%) patients, including Grade 2 or 3 cases in 251 (6.6%) and 4 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hypothyroidism was 3.5 months (range 1 day to 18.9 months). The median duration was not reached (range 2 days to 29.9+ months). One patient (< 0.1%) discontinued pembrolizumab due to hypothyroidism. Hypothyroidism resolved in 81 (23%) patients, 6 with sequelae. In patients with cHL (n=241) the incidence of hypothyroidism was 14.1% (all Grades) with 0.4% Grade 3.

Out of a total of 1562 subjects, adrenal insufficiency was reported for 2 subjects (0.1%). Both events were identified as Grade 3 acute event and were considered by the Investigators to be serious and not drug related.

Severe skin reactions
Immune-related severe skin reactions occurred in 63 (1.6%) patients, including Grade 2 or 3 cases in 4 (0.1%) and 52 (1.4%) patients, respectively, receiving pembrolizumab. The median time to onset of severe skin reactions was 2.5 months (range 4 days to 21.5 months). The median duration was 2.0 months (range 3 days to 17.8+ months). Severe skin reactions led to discontinuation of pembrolizumab in 6 (0.2%) patients. Severe skin reactions resolved in 41 patients. Rare cases of SJS and TEN, some of them with fatal outcome, have been observed.

Complications of allogeneic HSCT in classical Hodgkin lymphoma
Of 23 patients with classic Hodgkin lymphoma who proceeded to allogeneic HSCT after treatment with pembrolizumab, 6 patients (26%) developed GVHD, one of which was fatal, and 2 patients (9%) developed severe hepatic VOD after reduced-intensity conditioning, one of which was fatal. The 23 patients had a median follow-up from subsequent allogeneic HSCT of 5.1 months (range: 0-26.2 months).

Immunogenicity
In clinical studies in patients treated with pembrolizumab 2 mg/kg every three weeks, 200 mg every three weeks, or 10 mg/kg every two or three weeks, 36 (1.8%) of 2,034 evaluable patients tested positive for

treatment-emergent antibodies to pembrolizumab, of which 9 (0.4%) patients had neutralizing antibodies against pembrolizumab. There was no evidence of an altered pharmacokinetic or safety profile with anti-pembrolizumab binding or neutralizing antibody development.

Other immune-mediated adverse reactions
The following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% of patients treated with pembrolizumab in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010: uveitis, myositis, Guillain-Barré syndrome, pancreatitis, encephalitis, sarcoidosis, myasthenic syndrome, myelitis, and vasculitis. The following were reported in other clinical studies with pembrolizumab or in post-marketing use: myocarditis and sclerosing cholangitis. Cases of these immune-mediated adverse reactions, some of which were severe, have been reported in clinical trials or in post-marketing use. Cases of arthritis/arthralgia, hemophagocytic lymphohistiocytosis (HLH) and Vogt-Koyanagi-Harada syndrome were identified based on post-marketing reports. These side effects were voluntarily reported from a group of people of unknown size who received pembrolizumab. It is not possible to estimate the frequency of these side effects.

Transplant-related adverse reactions
Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with pembrolizumab. Treatment with pembrolizumab may increase the risk of rejection in solid organ transplant recipients. Consider the benefit of treatment with pembrolizumab versus the risk of possible organ rejection in these patients.

Infusion-related reactions
Severe infusion reactions, including hypersensitivity and anaphylaxis, have been reported in 6 (0.2%) of 2799 patients receiving pembrolizumab in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010. For severe infusion reactions, stop infusion and permanently discontinue pembrolizumab. Patients with mild or moderate infusion reaction may continue to receive pembrolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered.

Potential for Drug-Drug Interactions
No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab.

Contraindications
None.

11.2. 3 Risks related to blood draws and saliva collection
No major risks are involved with blood draws. Minor complications including bleeding, pain, and hematoma formation at the site of blood draws, vasovagal reactions or infections may rarely occur. There is no risk or discomfort associated with saliva collection.

11. 2. 4 Risks related to CT Scan
CT (computed tomography) uses special x-ray equipment to obtain image data from different angles around the body and then uses computer processing of the information to show a cross-section of body tissues and organs. Oral and/or intravenous contrast agents will be used and are usually well tolerated. However, some subjects will experience allergic reactions to intravenous contrast. To lower the risk of allergic reactions, low allergenic contrast agents are administered at NIH clinical center. In addition, subjects will be advised that approximately

2-7% of patients who receive contrast agents will experience a temporary reduction in kidney function lasting up to 2 weeks following infusion and that in rare instances, permanent renal damage can result from the use of the IV contrasting agent. Therefore, in subjects with impaired kidney function, we will not use intravenous contrast. The amount of radiation subjects will receive from the research scans in this study is 3.8 rem of radiation annually. All female subjects will receive pregnancy testing prior to radiation exposure.

11. 2. 5 Risks related to pregnancy and nursing mothers

There are no clinical studies in pregnant women, and it is unknown whether ibrutinib, pembrolizumab, or their metabolites are excreted in human milk. Men and women of child-bearing potential must use highly effective contraceptive (e.g., condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence, or sterilized partner) protection while on study and for 30 days after the last dose of study drug. If a female subject or the partner of a male subject becomes pregnant, the sponsor must be notified. Male subjects should refrain from sperm donation.

11. 2. 6 Risks related to bone marrow biopsy

The anesthetic can cause some temporary stinging and burning. A pulling sensation and discomfort may be felt as the marrow is withdrawn. Although rare, there is a potential for bleeding at the site and local infection. Bleeding can be stopped by applying local pressure, and infection can be treated with antibiotics.

11.3 Risks in relation to benefit

The benefits to the adult patient could be a reduction or a control of the CLL/SLL resulting in an improved quality of life, a decreased susceptibility to infections, and foremost a significant improvement in survival time. Potentially, treatment with other therapies could also be avoided or postponed.

11.4 Informed consent processes and procedures

The investigational nature and research objectives of this trial, the procedure and its attendant risks and discomforts will be carefully explained to the subject and a signed informed consent document will be obtained prior to entry onto this study.

At any time during participation in the protocol, should new information become available relating to risks, adverse events, or toxicities, this information will be provided orally or in writing to all enrolled or prospective patient participants. Documentation will be provided to the IRB and if necessary the informed consent amended to reflect relevant information.

If there is an unexpected enrollment of a research participant for which there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent.

Refer to Section 11.1.2 for consent process for adults with decisional impairment.

Note: Effective January 21, 2019, a witness to the signature of the written long form research consent at an NIH site (whether initially approved by an IRB before or after January 21, 2019) is no longer a requirement.

Consent processes using telephone or telehealth platform

Participants may be contacted by telephone and or Telehealth (NIH approved platform) to obtain informed consent. It may be used for subjects actively participating in the study who may need to be re-consented. The telephone consents will be obtained by those investigators designated as authorized to obtain inform consent on the Study Personnel page. Telehealth procedure will follow the NIH-approved policy. Procedures for obtaining telephone consent are as follows:

- The informed consent document will be sent to the patient either by mail (U.S. Postal Service or Fed-Ex), fax, or e-mail prior to the phone conversation. If mailed, a pre-addressed return envelope may be included.
- A telephone call or telehealth appointment will be scheduled between the participate and designated investigator to allow time for the participate to thoroughly read over the consent. The protocol will be discussed and explained during the scheduled call or telehealth appointment and any questions will be answered.
- If the patient agrees to participate, the patient will print (if email was used to send the consent), sign and date the informed consent document with the date of the telephone/telehealth conversation.
- The patient is to return the signed document by mail or fax to the investigator. Upon receiving consent, the investigator will sign and date the consent with date of receipt of the consent document. This document will be designated as both the original and telephone consent.
- A copy of the fully executed document will be returned to the patient by mail or secure email for the patient's record. The signed consent will be sent to medical records to be placed in the patients electronic chart.
- The informed consent process will be documented on a CRIS progress note (Progress Note - Documentation of Consent) by the investigator.

11.5 Conflict of interest

Merck is providing pembrolizumab for this study to NIH without charge. No NIH investigator involved in this study receives any payment or other benefits from Merck. The principal investigator assures that each associate investigator listed on the protocol title page received a copy of the NIH's Guide to preventing conflict of interest. No members of the research team reported a potential conflict of interest.

11.6 Technical Transfer Agreements

The protocol has the following associated CRADA: between NHLBI and Merck, between NHLBI and Pharmacyclics, an AbbVie Company, LLC.

12.0 PHARMACEUTICALS

12.1 Ibrutinib

Product description: Ibrutinib is commercially available. Note for more detailed and comprehensive background information please refer to the ibrutinib Package Insert. Chemical name of ibrutinib is PCI-32765-00, which is 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4 d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one. PCI-32765-00 is a white to off-white crystalline solid, and given as an oral formulation containing micronized PCI-32765-00.

Formulation, Packaging, and Storage: Ibrutinib is provided as a gray, immediate-release hard gelatin capsule containing 140 mg of ibrutinib. The capsules are packaged in blister pack with aluminum lidding foil or opaque high-density polyethylene (HDPE) plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All study drug will be dispensed in child-resistant packaging. The drug product is manufactured for Pharmacyclics LLC, an AbbVie Company, by a contract manufacturer. All formulation excipients are compendial and are commonly used in oral formulations. Each bottle contains 92 capsules.

Dosage and Administration: The investigator must ensure that patients receive ibrutinib only from personnel who fully understand the procedures for administering the drug.

At any given visit, up to 4-month supply of ibrutinib can be dispensed. In cases where there are patient scheduling conflicts, additional doses of ibrutinib may be given to accommodate visits within the window specified in the protocol. Drug dispensed will be recorded in ID MRS for drug accountability. Missed or held doses will be recorded at every clinic visit. If the patient is taken off from the study, unused ibrutinib capsules must be returned to ID MRS for local destruction according to institution's standard operating procedures. Returned capsules must not be re-dispensed.

Ibrutinib 420 mg (3 capsules at 140-mg per capsule) is intended to be administered orally once daily with 8 ounces (approximately 240 mL) of water (avoid GRAPEFRUIT JUICE and SEVILLE ORANGES due to CYP450 3A4 inhibition). The capsules should be swallowed intact and patients should not attempt to open capsules or dissolve them in water.

If a dose is missed, it can be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If it has been greater than 6 hours, the dose should not be taken and the patient should take the next dose at the scheduled time the next day. The missed dose will not be made up.

Overdose: Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any Serious Adverse Event criterion must be reported as a Serious Adverse Event in the appropriate time frame and documented as clinical sequelae to an overdose. There is Limited data on the effects of ibrutinib overdose. No maximum tolerated dose (MTD) was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1400 mg/day). Healthy subjects were exposed up to single dose of 1680 mg. In a separate study, one healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. There is no specific antidote to ibrutinib. Subjects who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment. Refer to Section 10.3.1 for further information regarding AE reporting.

Supply: The drug product ibrutinib is manufactured and supplied by Pharmacyclics LLC, an AbbVie Company.

Shipping:

National Institutes of Health
Investigational Drug Management and Research Section
Clinical Center Pharmacy Department, Room 1C230
10 Center Drive, MSC1196, Building 10
Bethesda, MD 20892-1196
Phone: (301) 496-1031

12.2 Fludarabine:

Product description: Fludarabine phosphate is commercially available as both a lyophilized powder for injection in vials containing 50 mg of fludarabine phosphate with mannitol 50 mg and sodium hydroxide for pH adjustment and a solution for injection in 2 mL vials containing 50 mg of fludarabine phosphate (25 mg/mL

of fludarabine) with 25 mg/mL mannitol and sodium hydroxide for pH adjustment.

Preparation: Fludarabine lyophilized powder for injection should be reconstituted with 2 mL of sterile water for injection, up to a concentration of 25 mg/mL. The prescribed dose of fludarabine should be diluted in 100 mL of either 0.9% sodium chloride or 5% dextrose in water for intravenous administration over 30 minutes.

Storage and Stability: Fludarabine vials should be stored under refrigeration between 2-8 ^{o}C (36- 46 ^{o}F). Reconstituted fludarabine phosphate is chemically and physically stable for 24 hours at room temperature or for 48 hours if refrigerated. The manufacturer recommends use of either the reconstituted powder for injection or the solution for injection (once diluted for administration) within 8 hours because neither product contains an antimicrobial preservative.

Administration: The prescribed dose of fludarabine should be diluted in 100 mL of either 0.9% sodium chloride or 5% dextrose in water for intravenous administration over 30 minutes.

Supply: Commercially available.

12.3 Pembrolizumab

Background Information: Note for more detailed and comprehensive background information please refer to the Investigator's Brochure.

Investigational Product Name and Description: 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.

Preparation: The vials contain 4 mL of sterile solution for IV infusion, 25 mg/mL pembrolizumab, and a total of 100 mg protein/vial. Pembrolizumab Solution for Infusion 100 mg/vial is a liquid drug product (DP) (manufactured using the fully formulated drug substance with L-histidine as a buffering agent, polysorbate 80 as a surfactant, and sucrose as a stabilizer/tonicity modifier and water for Injection as Solvent). The DP is manufactured using facilities and practices under GMP requirements.

Packaging, and Storage: Pembrolizumab DP is a sterile-filtered liquid and is aseptically filled into single-use vials. stored under refrigerated conditions at 2°C to 8°C (36°F to 46°F).

Administration: The liquid product is intended for IV administration. The liquid DP can be further diluted with normal saline or 5% dextrose in the concentration range of 1 to 10 mg/mL in IV containers made of polyvinyl chloride (PVC) or non-PVC material. At the point of use, pembrolizumab DP is diluted with 0.9% sodium chloride injection, USP (normal saline) or 5% dextrose injection, USP (5% dextrose) to 1 to 10 mg/mL before IV administration through an infusion filter.

Reconstituted vials should be used immediately to prepare the infusion solution in the IV bag, and the infusion solution should be administered immediately. If the diluted pembrolizumab solution is not used immediately, it may be stored for no more than 24 hours at 2°C to 8°C. This 24-hour hold time from reconstitution may include up to 6 hours at room temperature (at or below 25°C). If refrigerated, the vials and/or IV bags must be allowed to come to room temperature before to use.

Supply: The drug product pembrolizumab is manufactured and supplied by Merck.

Shipping:

National Institutes of Health
Investigational Drug Management and Research Section
Clinical Center Pharmacy Department, Room 1C230
10 Center Drive, MSC1196, Building 10
Bethesda, MD 20892-1196

12.4 Accountability procedures

Drug accountability records will be maintained for all clinical supplies. All empty and partially used vials and clinical trial supplies will be destroyed locally according to the institution's standard operating procedures for drug destruction. The pharmacy will maintain detailed documentation of the number and identification of vials which are destroyed, and copies of these documents will be provided to the sponsor. Disposition of all unused boxes of study drug will be carried out according to instructions provided by the sponsor at the end of the study after drug accountability is performed by the study monitor.

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APPENDIX A: Schedule of Events

Study Day/NAME:	**Screening/Baseline**	**Pre C-3 & -1**	**C-2 (28-day)**						**C1 to 17 (21-day)**	**After cycle 17 (every 4 months)@**	**Response at 6 months (from cycle 1)**	**Response at 1 year (from cycle 1) and annually**	**At progression**
Days (Plus/Minus)	N/A	±5	±5						±5	±14	±30	±30	N/A
Day of the cycle	N/A	N/A	D1	D2	D3	D4	D5	D14 D21	D1	N/A	N/A	N/A	N/A
NIH visit	[R]	X	X	X	X	X	X		X	X	X	X	[R]
Clinical													
Consent		X											
History, ECOG PS	X	X	X						X	X	X	X	[R]
Physical Exam	X	X	X						X	X	X	X	[R]
Medication Review	X	X	X						X	X	X	X	[R]
Specific Labs/Other Tests													
HLA Typing*, Saliva	X												
CBC with Differential	X	X	X					[X]	X	X	X	X	[R]
Acute Care & Mineral Panels	X	X	X						X	X	X	X	[R]
Tot. protein, CK, Uric Acid, LDH	X	[R]	X						X	X	X	X	[R]
Hepatic Panel	X	X	X						X	X	X	X	[R]
Reticulocyte Count	X	[R]	X						X	X	X	X	[R]
PT, PTT	X	X	X						X	X	X	X	[R]
SPEP with IFE													[R]
SFL, qIG											X	X	[R]
CRP													[R]
β2 microglobulin	X	[R]	X						X	X	X	X	[R]
Haptoglobin, DAT	X	[R]	X						X	X	X	X	[R]
Iron panel, folate, B12 level	X												
Thyroid function panel	X								X	[R]			
Viral Studies (HIV, hepatitis)	X												
EBV, CMV PCR													[R]
BKT and PLCg2 mutation analysis													[R]
Pregnancy test	X	X	X						X	X	X	X	[R]
TBNK	X	X							X*		X	X	[R]
IGHV mutation analysis	[X]												[R]
CLL/ FISH (w/in 3 mo of starting)	[X]												[R]
Karyotype (w/in 3 mo of starting)	[X]												
Flow CLL (w/in 3 mo of starting)	X										X	X	[R]
CT Neck, CAP (w/in 3 mo of starting)	[X]								X#*		[R]	[R]	[R]

Bone Marrow (w/in 3 mo of starting)	[X]										[R]	-[R]	[R]
EKG (w/in 3 mo of starting, then if medically indicated)	X												
Research Samples													
Lymphapheresis	[R]										[R]	[R]	[R]
Lymph node biopsy***	[R]										[R]	[R]	[R]
Research blood##	X	X	X						X/[R]	[R]	X	[R]	[R]

Footnotes for Schedule of Events*:*

* Prior to cycle 1 only. No need test before other cycles.

** Can be CT or PET/CT of neck, chest, abdomen, and pelvis at progression

*** Up to 3 lymph node biopsy can be performed in consented patients.

Patient may choose to waive CT scan prior to pembrolizumab.

Research blood is mandatory at cycle -3, -2, -1, 1, and at response assessments. Research blood is optional for other timepoints.

@ Patients with travel hardships can be followed every 8 months and draw an interim CBC with differential to substitute a missed visit and evaluations. Outside lab results are accepted for the interim lab.

[R] Optional, at discretion of clinical team

X Will be done on study

[X] Outside labs are accepted

Appendix B. Inhibitors and Inducers of CYP3A

Inhibitors and inducers of CYP3A enzymes are defined as follows. Further information can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/main-table/.

Inhibitors of CYP3A

Strong inhibitors:

boceprevir
clarithromycin
cobicistat
indinavir
itraconazole
ketoconazole
mibefradil
nefazodone
nelfinavir
posaconazole[a]
ritonavir
saquinavir
suboxone
telaprevir
telithromycin
troleandomycin

Moderate inhibitors:

amiodarone
amprenavir
aprepitant
atazanavir
ciprofloxacin
crizotinib
darunavir
diltiazem
dronedarone
erythromycin
fluconazole
fosamprenavir
grapefruit juice
imatinib
Seville orange juice
verapamil
voriconazole[a]

Weak inhibitors:

cimetidine
fluvoxamine

All other inhibitors:

chloramphenicol
delaviridine
diethyl-dithiocarbamate
gestodene
mifepristone
norfloxacin
norfluoxetine
star fruit

Inducers of CYP3A

carbamazepine
barbiturates
efavirenz
glucocorticoids
modafinil
nevirapine
oxcarbazepine
phenobarbital
phenytoin
pioglitazone
rifabutin
rifampin
St. John's Wort
troglitazone

a. Classification based on internal data.

Appendix C. Child-Pugh Score for Subjects with Liver Impairment

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

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

Source:

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