Mayo Clinic Cancer Center

A Phase II Study of Anti-PD-1 Antibody (MK-3475) in Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL) and Other Low Grade B Cell Non-Hodgkin Lymphoma (NHL)

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Study Co-Investigators: [redacted]

Statistician: [redacted]

Drug Availability
Merck Supplied Investigational Agents: Anti-PD-1 antibody (MK-3475) *(IND Exempt)*
Commercially supplied agents: Idelalisib and Ibrutinib

√Study contributor(s) not responsible for patient care.

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Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	[redacted] Quality Assurance Specialist Phone: [redacted]
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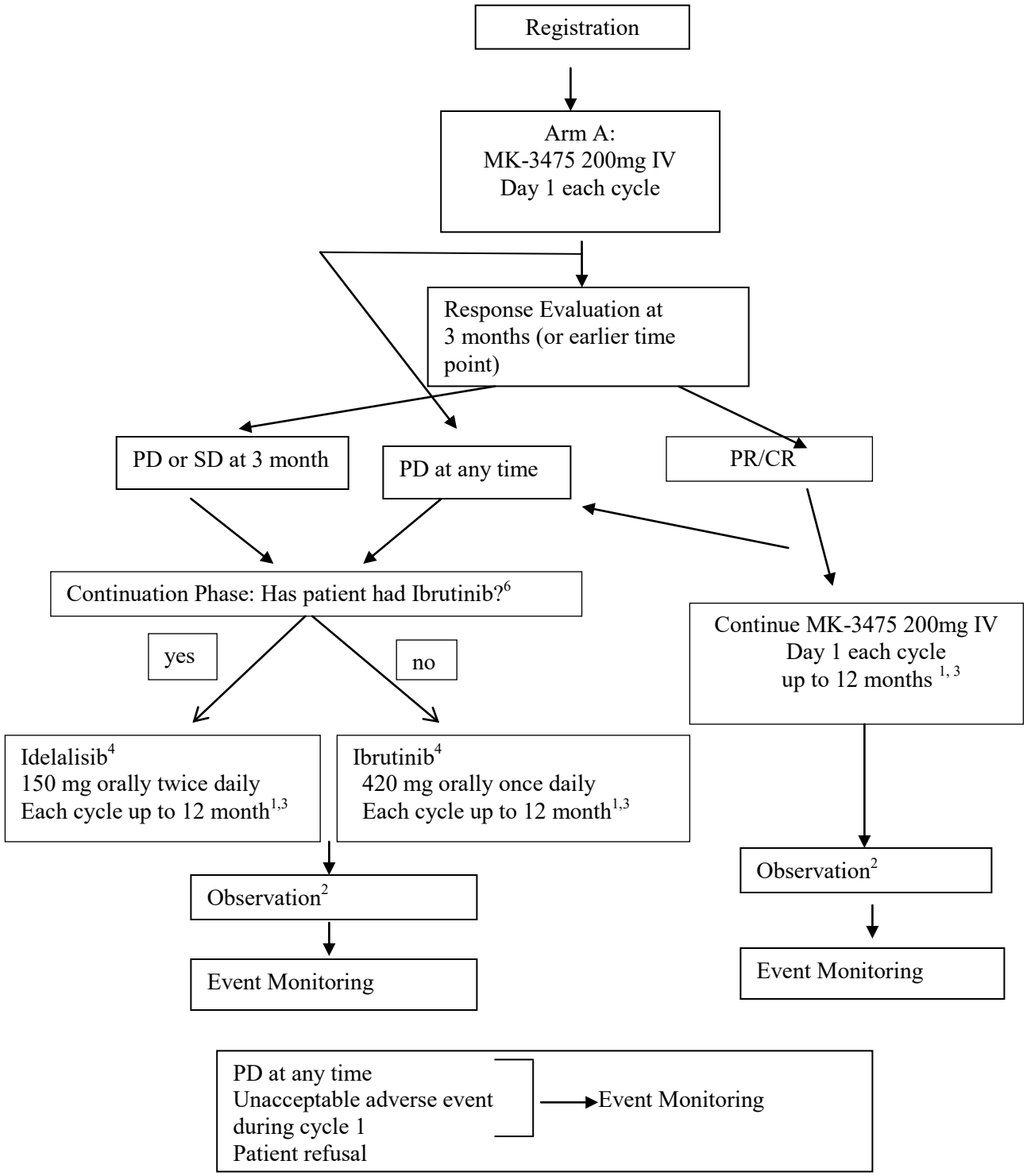
Protocol document, consent form, regulatory issues	[redacted] Senior Research Protocol Specialist [redacted]
Adverse Events (AdEERS, MedWatch, AML/MDS)	[redacted] SAE Coordinator Phone [redacted]

*No waivers of eligibility per NCI

Table of Contents

Schema for CLL (Arm A) [5]

Arm A is closed for accrual in April, 2016

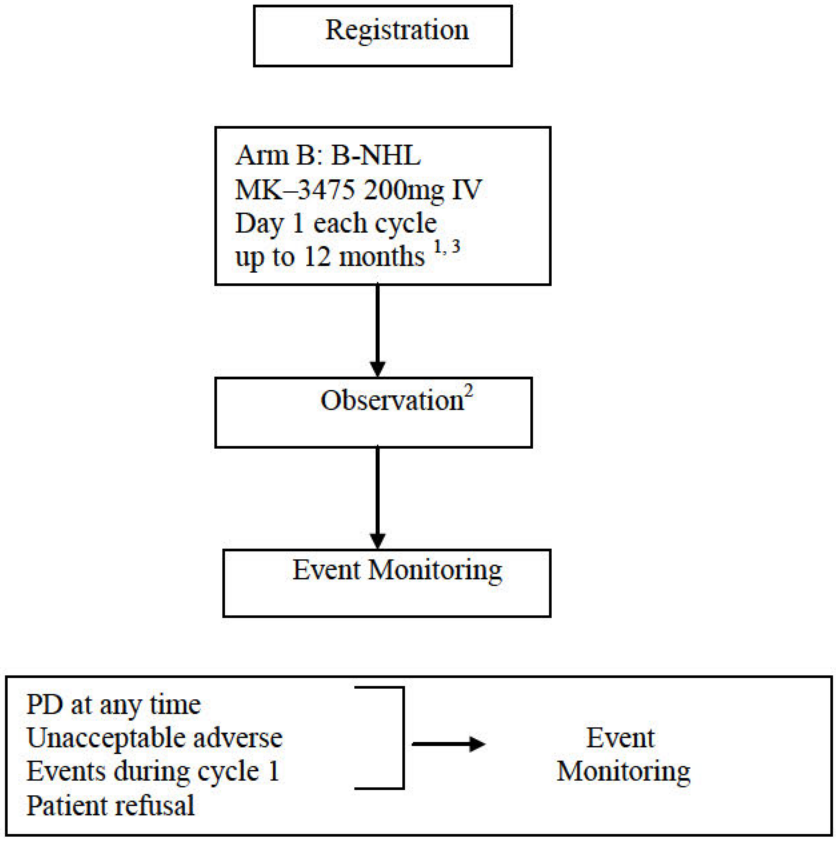


cycle length = 21 days

[1] Total duration of treatment including both single-agent or combination therapy combined is a maximum of 24 months. NOTE: If patient is continuing to benefit from treatment after 12 months, they may continue to receive treatment up to a total duration of 24 months including both single-agent and combination therapy at investigator/sponsor discretion.
[2]Q 3 months x 4
[3]If CLL patients have achieved MRD negative CR/CRi confirmed by bone marrow or PET/CT evaluation, patients could continue the treatment for 2 more cycles and stop the treatment at the discretion of the treating provider and enter observation.
[4]Signal inhibitor can be continued or stopped at the end of therapy (12 or 24 months) per treating physician discretion.
[5]Including CLL patients with Richter's transformation or Hodgkin's transformation for Arm A. As per MCCC Addendum 2: An arm (Arm C) with CLL patients with Richter's transformation only is added to the study.
[6]Disease measurements and lab parameters obtained after the last cycle of single-agent therapy are set as the baseline measurements/labs for the continuation phase.

Schema for B-NHL (Arm B)

This arm is closed for accrual in April 2017.



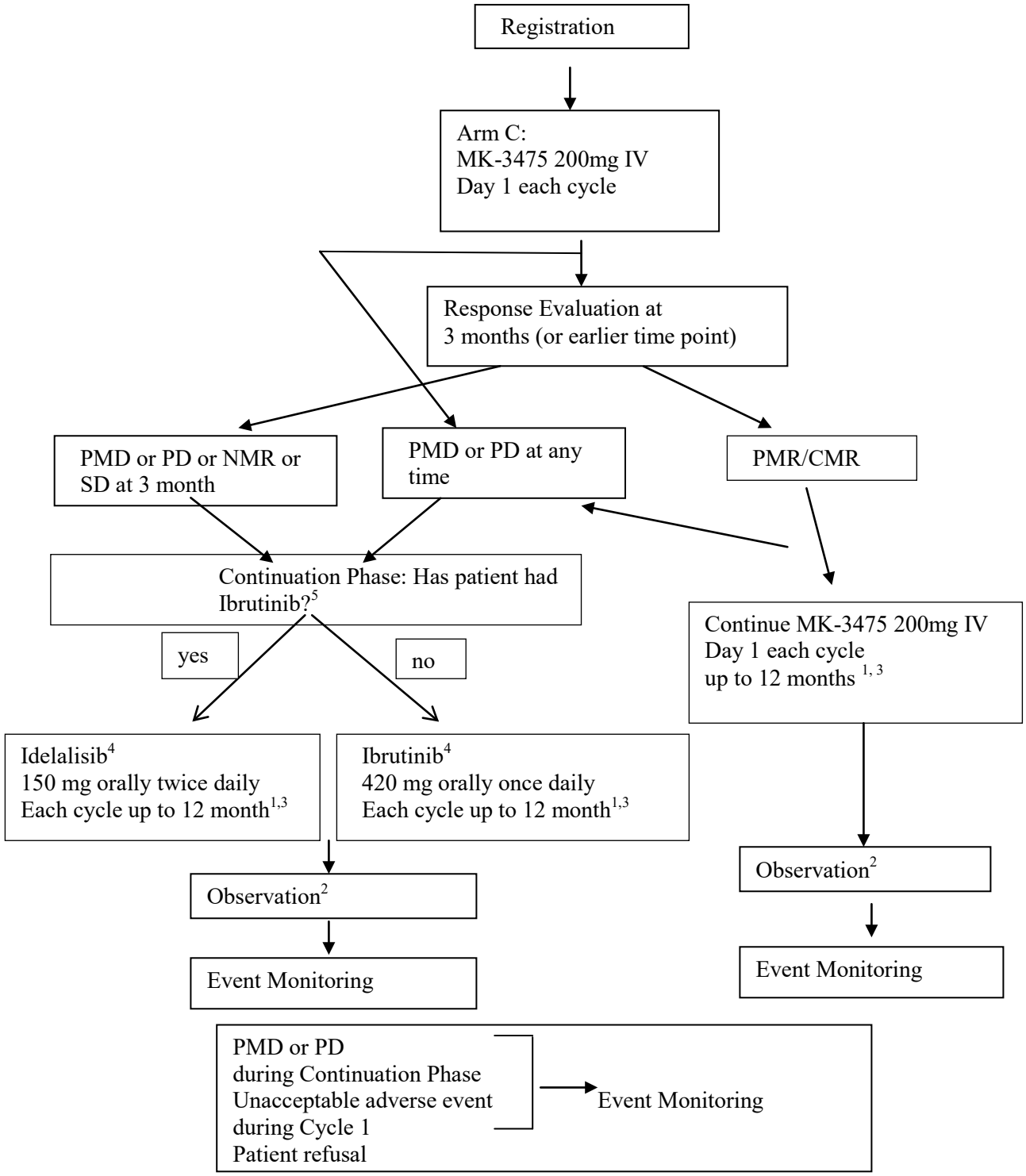
If a patient is deemed ineligible or a cancel, please refer to Section 13.0 for follow-up information.
cycle length = 21 days

[1]Duration of treatment is a maximum of 12 months. If the patient remains on cycles with a length of 21 days without treatment delays, this will be 17 cycles total. If the cycle length is increased due to dosing frequency changes or dose delays occur, the number of cycles will be reduced to not exceed 12 months (365 days) of treatment total. NOTE: If patient is continuing to benefit from treatment after 12 months, they may continue to receive treatment up to 24 months at investigator/sponsor discretion.
[2]Q 3 months x 4
[3]If NHL patients have achieved CR confirmed by bone marrow and PET/CT evaluation, patients could continue the treatment for 2 more cycles and stop the treatment at the discretion of the treating provider and enter observation.

Generic name: Pembrolizumab Brand name(s): Keytruda Mayo Abbreviation: MK-3475 Availability: Merck supplied
Generic name: Ibrutinib Brand name(s): Imbruvica® Mayo Abbreviation: IBRUTINIB

Availability: Commercially supplied
Generic name: Idelalisib Brand name(s): Zydelig® Mayo Abbreviation: IDELALISIB Availability: Commercially supplied

Schema for CLL with Richter's transformation (Arm C)



cycle length = 21 days

[1] Total duration of treatment including both single-agent or combination therapy combined is a maximum of 24 months. NOTE: If patient is continuing to benefit from treatment after 12 months, they may continue to receive treatment up to a total duration of 24 months including both single-agent and combination therapy at investigator/sponsor discretion.
[2]Q 3 months x 4
[3]If CLL with Richter's transformation patients have achieved CMR (complete metabolic response) confirmed by bone marrow and PET/CT evaluation, patients could continue the treatment for 2 more cycles and stop the treatment at the discretion of the treating provider and enter observation.
[4]Signal inhibitor can be continued or stopped at the end of therapy (12 or 24 months) per treating physician discretion.
[5] Disease measurements and lab parameters obtained after the last cycle of single-agent therapy are set as the baseline measurements/labs for the continuation phase.

1.0 Background

1.1 Overview of Chronic Lymphocytic Leukemia (CLL)

Approximately 16,000 new CLL cases are diagnosed annually and ~100,000 patients are currently alive with CLL disease in the United States. Approximately 70% CLL patients eventually progress to require treatment and a majority of these patients will ultimately die from CLL or CLL related complications. Except limited patients who underwent allogeneic stem cell transplant and achieved long term remission, CLL is an incurable disease. Chemoimmunotherapy (CIT), typically as a combination of a purine analog, cyclophosphamide and rituximab, is very effective and has been established as the front-line therapy for CLL. However, majority of treated patients will relapse. Therapies for the relapsed CLL patients are evolving. Bendamustine and rituximab combination therapies have emerged as one of the effective approaches for relapsed patients. However, only about 10% of patients achieve a complete remission and around 60% overall response rate can be achieved with this approach. Progression free survival (PFS) is typically short in the range of 1-2 years (Fischer, Cramer et al. 2011).

In the last 5 years, significant advancements have been made in the understanding of importance of B-cell receptor (BCR) signal pathway in CLL disease as well as in other B-cell lymphoma. Agents targeting BCR pathway, specifically Bruton's Tyrosine Kinase (BTK) inhibitor Ibrutinib and PI3K inhibitor Idelalisib, have been observed to achieve approximately 70% overall response rate in relapsed/refractory CLL(Byrd, Furman et al. 2013). Ibrutinib has been FDA approved for previous treated CLL patients. The longest follow-up data on Ibrutinib showed about 40-50% CLL patients relapsed after about 2.5 to 3 years of Ibrutinib treatment. CLL relapse after Ibrutinib therapy has been observed and how to manage relapsed CLL patients after Ibrutinib therapy is unknown.

1.2 Overview of low grade non-Hodgkin Lymphoma (NHL)

It is estimated that ~65,000 new NHL was diagnosed annually and ~ 500,000 people are currently living with NHL in the United States. Low grade NHL accounts for approximately one third of all cases of NHL. While introduction of CIT has improved therapy results both upfront and at relapse, the vast majority of patients with low grade NHL remains incurable and eventually will succumb to the disease. The most recent chemotherapeutic agent that has been approved by the Food and Drug Administration for use in patients with rituximab-refractory indolent non-Hodgkin's lymphoma is the alkylating agent bendamustine, which has become an important therapeutic option, although it is not curative. Bendamustine and rituximab combination achieves over 90% overall response and improved progression free survival compared to R-CHOP (Rummel, Niederle et al. 2013). Similarly rituximab maintenance after initial CIT is associated with improved progression free and overall survival (Hochster, Weller et al. 2009). However, patients continue to relapse. There is no consensus regarding the choice of salvage, second and subsequent chemotherapies in treatment of these lymphomas. Development of novel therapies for relapsed low grade NHL patients is needed.

1.3 Overview of PD-1 pathway

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily

member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2)(Talmadge, Donkor et al. 2007; Francisco, Sage et al. 2010). PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade(Galon, Costes et al. 2006; Talmadge, Donkor et al. 2007). The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells(Kloor 2009), as well as subsets of macrophages and dendritic cells(Hillen, Baeten et al. 2008). The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors(Hiraoka 2010). Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. 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(Hiraoka 2010). Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

1.31 PD-1 is a marker of exhaustion in CLL and other B-NHL T cells

T-cells in low-grade lymphomas as well as chronic lymphocytic leukemia (CLL) are dysfunctional and PD-1 expression on these cells is higher than on normal T cells (Ramsay, Clear et al. 2012). Blocking the interaction of PD-1 with its ligands can reenergize the defective CLL T cell function (Nunes, Wong et al. 2012; Ramsay, Clear et al. 2012; Riches, Davies et al. 2013). We have shown that PD-1 expression is detected in follicular lymphoma (FL) T cells and its diffuse pattern of staining is associated with worse survival(Smeltzer, Jones et al. 2013). PD-1 expression in FL T cells is increased when FL transformed into diffuse large cell lymphoma (DLBCL). In FL T cells, dim PD-1 surface expression represents an exhausted T cell phenotype and is associated with worse progression free survival (Yang, Grote et al. 2013). PD-1 expression is also detected in T cells from almost all types of non-Hodgkin lymphoma (NHL)(Xerri, Chetaille et al. 2008; Muenst, Hoeller et al. 2010; Nunes, Wong et al. 2012; Riches, Davies et al. 2013) and is likely a marker of exhaustion in other types of NHL.

1.32 Role of PD-1 in regulating B cell immunity using mouse model

In contrast to the established function of PD-1 in regulation of T cell tolerance, the potential role of PD-1 in regulating human B cell survival and activation have

not been clearly studied. Data generated using a PD-1 or PD-1 ligand knock-out mouse model revealed that PD-1 regulates late germinal center B cell survival and the formation of long-lived plasma cells(Good-Jacobson, Szumilas et al. 2010). PD-1 is also believed to regulate antibody diversification and B cell immunity (Kawamoto, Tran et al. 2012; Cubas, Mudd et al. 2013). Thus these latter studies support a direct role of PD-1 pathway in regulating B cell survival and immunity.

1.33 Expression of PD-1 in neoplastic B cells in CLL and other B-NHL

Accumulating evidence has emerged in regards to the expression of PD-1 in multiple types of non-Hodgkin lymphoma (NHL). We detected PD-1 expression on tumor B cells from FL, marginal zone lymphoma and Waldenstrom Macroglobulinemia (WM) patients (preliminary data). When the PD-1 on WM cell line (BCWM) was ligated with PD-1 ligands, increased proliferation and survival of WM tumor B cells were observed and these increases of cell proliferation and survival were abrogated by blocking the PD-1 pathway(Grote, Ziesmer et al. 2013). PD-1 expression is detected on neoplastic B cells from small lymphocytic lymphoma (SLL)/chronic lymphocytic leukemia (CLL) (Xerri, Chetaille et al. 2008). In CLL, PD-1 expression is increased in CLL B cells compared to normal B cells (preliminary data). Additionally CLL activation by CD40L/CPG/IL-2 stimulation can promote further expression of PD-1(Xerri, Chetaille et al. 2008) and PD-L1(Brusa, Serra et al. 2013). In a co-culture system using CLL peripheral blood mononuclear cells (PBMC) and CLL marrow stromal cells (MSC, expressing PD-L2 and PD-L1, see below) to mimic cellular interactions in the bone marrow, CLL neoplastic B cells are selectively promoted for survival with the sacrifice of CLL T cell apoptosis (preliminary data). These data suggest that the PD-1 pathway can play a major role in supporting B cell lymphoma survival in the tumor microenvironment.

1.34 Expression of PD-1 ligands in lymph node and bone marrow in B cell lymphoma

In addition to the evidence of PD-1 expression in B cell lymphoma, expression of PD-1 ligands are detected in the tissue sites of B cell lymphoma. PD-L1 expression in the CLL tumors in the lymph node tissue is much higher than its counterpart in reactive lymph nodes (Ramsay, Clear et al. 2012; Brusa, Serra et al. 2013). PD-L2 is constitutively expressed and PD-L1 expression is induced in CLL bone marrow derived stromal cells (preliminary data). PD-L1 expression is increased in tumor B cells in FL lymph nodes compared to its counterpart in reactive nodes (Ramsay, Clear et al. 2012). Additionally, soluble PD-L1 levels in the peripheral blood in diffuse large B cell lymphoma impacts the patient's overall survival (Fest, Rossille et al. 2013).

1.4 Research Hypothesis

Given the evidence of PD-1 and its ligands expression in neoplastic lymphoma cells and the tumor microenvironment, we hypothesize that ***the PD-1 pathway can play a major role in B cell lymphoma progression in lymph node and bone marrow, key tissue sites of tumor microenvironment. Blocking the interactions of PD-1 with its ligands will not only activate T cell function, but also directly block the survival/proliferating signal of neoplastic B cells***

Preliminary clinical activity of PD-1 blockade in B cell lymphoma
To support our hypothesis, clinical benefits of blocking PD-1 in lymphoma have been observed. In relapsed diffuse large B cell lymphoma (DLBCL), PD-1 blockade after

autologous stem cell transplant achieved ~50% overall response rate in patients who had residual disease after transplant (Armand, Nagler et al. 2013). In relapsed follicular lymphoma (FL), an ~66% ORR and ~50% CR were observed with the combination therapy of rituximab and anti-PD-1 antibody (Westin, Chu et al. 2012). However, the potential activity of PD-1 blockade on CLL and other types of indolent B-NHL have not been studied. The relationship of expression of PD-1 and its ligands in tumor and their microenvironment with the clinical activity of PD-1 blockade have not been investigated. Thus in this proposal, we wish to test the potential activity and safety of MK-3475 in relapsed CLL/SLL, FL, WM and marginal zone lymphoma.

1.5 Treatment (MK-3475), 200 mg intravenous, every three week

MK-3475 (previously known as SCH 900475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

1.51 Clinical Trial Data

As of 18-Oct-2013, 1,000 patients have been treated with MK-3475 at several dose schedules, including 10 mg/kg every 2 weeks. MK-3475 has been generally well tolerated, as expected based on preclinical findings and other anti-PD-1 monoclonal antibodies. As of 18-Oct-2013 no serious infusions reactions have been reported in the first human clinical trial (PN001). Less than 1% of patients thus far assayed had confirmed positive anti-drug antibody (ADA) samples and among these, no or no clear impact on exposure has been observed. There is no contraindication to further clinical investigation with MK-3475. Pharmacokinetics were as expected, based on MK-3475 being an IgG mAb and based on preclinical data, which support dosing once every 2 or 3 weeks. MK-3475 monotherapy induces an ORR of 25%/27% in patients with ipilimumab exposed melanoma by central independent RECIST and oncology review/investigator assessed irRC, respectively. MK-3475 monotherapy induces an ORR of 39%/43% in patients with ipilimumab-naive melanoma by central independent RECIST and oncology review/investigator assessed irRC, respectively. These responses are remarkably durable.

The preliminary 1-year survival rate for patients, many of whom have had multiple therapies, including ipilimumab, who receive MK-3475 is 81%. MK-3475 monotherapy induces an ORR of 21%/24% in patients with previously-treated NSCLC by central independent RECIST/investigator assessed irRC, respectively, with these responses also remarkably durable. Preliminary data suggest higher levels of PD-L1 expression in tumors of NSCLC are associated with increased activity (ORR 67% by investigator assessed irRC/57% by central independent RECIST); additional data are required to define the optimal PD-L1 cut point. The most commonly reported treatment emergent AEs experienced are fatigue (43.8%), nausea (26.7%), cough (25.3%), pruritus (24.6%), diarrhoea (22.3%) and rash (21.5%). Immune-related adverse events were reported in 21.4% of melanoma patients; most of these events (15.8%) were considered drug-related by the investigator. The most commonly reported immune-related adverse events across the dose-schedules are rash (3.2%), pruritus (2.9%), vitiligo (2.9%), hypothyroidism (2.7%), arthralgia (2.2%), diarrhea (2.2%), and pneumonitis (1.9%). Review of the overall benefit:risk ratio of MK-3475 favors enrollment of eligible patients into clinical trials of MK-3475. The preliminary

data suggest that a dose of MK-3475 at 2 mg/kg Q3W is appropriate for patients with melanoma.

1.52 Rationale for Dose Selection/Regimen/Modification

The dose regimen of 200 mg Q3W of MK-3475 is planned for all urothelial cancer trials. Available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at a given dose among tumor types. An open-label Phase 1 trial (PN001) in melanoma subjects is being conducted to evaluate the safety and clinical activity of single-agent MK-3475. 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 maximum tolerated dose (MTD) has been identified.

In KEYNOTE-001, two randomized cohort evaluations of melanoma subjects receiving MK-3475 at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive MK-3475 at 2 mg/kg versus 10 mg/kg Q3W. The overall response rate (ORR) was 26% (21/81) in the 2mg/kg group and 26% (25/79) in the 10 mg/kg group (full analysis set (FAS)). The proportion of subjects with drug-related adverse events (AEs), grade 3-5 drug-related AEs, serious drug-related AEs, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group.

Available pharmacokinetic results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at a given dose among tumor types. Population PK analysis has been performed and has confirmed the expectation that intrinsic factors do not affect exposure to MK-3475 to a clinically meaningful extent. Taken together, these data support the use of lower doses (with similar exposure to 2 mg/kg Q3W) in all solid tumor indications. 2 mg/kg Q3W is being evaluated in NSCLC in PN001, Cohort F30 and PN010, and 200 mg Q3W is being evaluated in head and neck cancer in PN012, which are expected to provide additional data supporting the dose selection.

Selection of 200 mg as the appropriate dose for a switch to fixed dosing is based on simulation results indicating that 200 mg will provide exposures that are reasonably consistent with those obtained with 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed using available data from 476 subjects from PN001. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose, with some tendency for individual values to range slightly higher with the 200 mg fixed dose. The slight increase in PK variability predicted for the fixed dose

relative to weight-based dosing is not expected to be clinically important given that the range of individual exposures is well contained within the range of exposures shown in the melanoma studies of 2 and 10 mg/kg to provide similar efficacy and safety. The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different tumor types and indication settings.

1.6 Ibrutinib in relapsed CLL and justification of combined therapy with anti-PD-1

Ibrutinib is an irreversible inhibitor of Bruton's tyrosine kinase (BTK), a critical kinase in regulating B cell receptor signal and B cell development. As a single therapy, Ibrutinib has shown significant activity in relapsed CLL patients with an overall response rate of 70% in all groups of CLL patients {Byrd, 2013 #884}. This study has led to FDA approval of Ibrutinib in relapsed CLL in 2014 and Ibrutinib has become a standard therapy for relapsed CLL since. In addition to its activity in blocking BTK, Ibrutinib was also shown to inhibit interleukin-2-inducible kinase (ITK) in T lymphocytes of CLL patients and reverse a Th2 immune profile into a Th1 immune response {Dubovsky, 2013 #837}. Recent data generated in mouse models of lymphoma that are intrinsically insensitive to Ibrutinib showed that Ibrutinib was able to enhance the antitumor T-cell immune responses triggered by PD1/PD1-L blockade {Sagiv-Barfi, 2015 #887}. Thus Ibrutinib and anti-PD-1 antibody should be tested clinically for relapsed CLL including Richter's transformation for their combined efficacy and safety.

1.7 Idelalisib in relapsed CLL and justification of combined therapy with anti-PD-1

Idelalisib is an inhibitor of the delta isoform of phosphatidylinositol 3-kinase. The clinical efficacy of Idelalisib as a single agent or in combination with rituximab in relapsed CLL had been demonstrated in several trials and were shown to associate with 70-80% overall response rate {Furman, 2014 #894} {Brown, 2014 #892}. These studies led to FDA approval of Idelalisib for relapsed CLL in 2014. Idelalisib has become a standard therapy since that time for relapsed CLL patients. PI3K delta is critical signal to regulate the function of T regulatory cell {Patton, 2006 #899} and PI3K delta inhibition has been shown to inhibit Treg function and promote CD8 T cell activity to induce tumor regression in mouse model {Ali, 2014 #1018}. In melanoma, the combination therapy of CTLA-4 blocking antibody (ipilimumab, inhibiting Treg function) with anti-PD-1 showed increased efficacy {Larkin, 2015 #937}. Thus it is reasonable to hypothesize that Idelalisib will enhance anti-tumor response of anti-PD-1 antibody by inhibition of Treg function and the clinical combination of these two should be tested in relapsed CLL including Richter's transformation.

1.8 Correlative Research

1.81 To assess the potential association between PD-L1/PD-1/PD-L2 expression on tumor and T cells and/or PD-L1 soluble levels in plasma with clinical efficacy of PD-1 blockade.

1.82 To investigate the effects of MK-3475 on selected markers of immune modulation and immune profiles in peripheral blood and tumor samples (see laboratory correlates below).

- Analysis of the B cell subsets (naïve B, IgM-memory B and switched-memory B cells) at pre-/post- treatment and during therapy.

- T cell profiling analysis to assess the “activated” and “exhausted” T cell phenotypes both Pre-therapy, during therapy and post-therapy.
- T cell subset (naïve, central and effector memory T cells and effector memory RA T cells) and T cell repertoire analysis at pre-/post- treatment and during therapy.
- T cell functional studies by evaluating immune synapses of patients
- Analyses for immune profiles and biomarkers, including plasma multiplex cytokines, quantification of serum immunoglobulins and serum free light chains and B lymphocyte activation status, T regulatory cell, monocyte and NK cells analysis are also included in this protocol.
- Evaluation clinical responses based on the histology subtype of tumor and tumor mutation status of different patients

2.0 Goals

2.1 Primary

2.11 Test the efficacy (overall response rate) of single-agent MK-3475 in relapsed CLL/SLL (Arm A), other low grade B-NHL (Arm B), and CLL with Richter's transformation (Arm C).2.2 Secondary

2.21 Test the safety of single-agent MK-3475 in relapsed CLL/SLL (Arm A), other low grade B-NHL (Arm B), and CLL with Richter's transformation (Arm C).

2.22 Test the overall survival, progression free survival, treatment free survival, duration of response and time to next therapy of single-agent MK-3475 in relapsed CLL/SLL (Arm A), other low grade B-NHL (Arm B), and CLL with Richter's transformation
(Arm C).

2.23 Test the complete response rate of single-agent MK-3475 in relapsed CLL/SLL (Arm A), other low grade B-NHL (Arm B), and CLL with Richter's transformation (Arm C).

2.24 Test the safety of MK-3475 in combination with the signal inhibitor (either Idelalisib or Ibrutinib) in relapsed CLL/SLL (Arm A) and CLL with Richter's transformation (Arm C).

2.25 Test the progression-free survival, treatment-free survival, duration of response and time to next therapy, as well as overall survival of MK-3475 in combination with the signal inhibitor (either Idelalisib or Ibrutinib) in relapsed CLL/SLL (Arm A) and CLL with Richter's transformation (Arm C).

2.26 Test the overall and complete response rates of MK-3475 in combination with the signal inhibitor (either Idelalisib or Ibrutinib in relapsed CLL/SLL (Arm A) and CLL with Richter's transformation (Arm C).

2.3 Correlative Research

2.31 To assess the potential association between PD-L1/PD-1/PD-L2 expression on tumor and T cells and/or PD-L1 soluble levels in plasma with clinical efficacy of PD-1 blockade.

2.32 To investigate the effects of MK-3475 on selected markers of immune modulation and immune profiles in peripheral blood and tumor samples (see laboratory correlates below).

- Analysis of the B cell subsets (naïve B, IgM-memory B and switched-memory B cells) at pre-/post- treatment and during therapy.
- T cell profiling analysis to assess the "activated" and "exhausted" T cell phenotypes both Pre-therapy, during therapy and post-therapy.
- T cell subset (naïve, central and effector memory T cells and effector memory RA T cells) and T cell repertoire analysis at pre-/post- treatment and during therapy.
- Analyses for immune profiles and biomarkers, including plasma multiplex cytokines, quantification of serum immunoglobulins and serum free light chains and B lymphocyte activation status, T regulatory cell, monocyte and NK cells analysis are also included in this protocol.

- Evaluation clinical responses based on the histology subtype of tumor and tumor mutation status of different patients

2.33 Examine T-cell immune synapse function and expression/location of co-stimulatory and co-inhibitory molecules (including effector molecules) as potential biomarkers to response for anti-PD-1 immune checkpoint blockade immunotherapy. Motility assays will assess the effect of anti-PD-1 therapy on T-cell motility (mimicking extravasation into the tumor microenvironment, TME).

3.0 Patient Eligibility

3.1 Inclusion Criteria

A. Inclusion criteria for CLL/SLL patients (Arm A) only:

3.11 Diagnosis of CLL according to the NCI criteria (Cheson, 1996 and Hallek 2008) or SLL according to the WHO criteria (Harris, 1999).

This includes **previous** documentation of:

- Biopsy-proven small lymphocytic lymphoma (Harris, 1999)
  or
- Diagnosis of CLL according to NCI working group criteria (Cheson, 1996 and Hallek 2008) as evidenced by <u>all</u> of the following:

  ✓ Peripheral blood B cell count of $> 5 \times 10^9$/L consisting of small to moderate size lymphocytes

  ✓ Immunophenotyping consistent with CLL defined as:
  - The predominant population of lymphocytes share both B-cell antigens [CD19, CD20 (typically dim expression), or CD23] as well as CD5 in the absence of other pan-T-cell markers (CD3, CD2, etc.)
  - Clonality as evidenced by κ or λ light chain expression (typically dim immunoglobulin expression) or other genetic method (e.g. IGHV analysis)

NOTE: Splenomegaly, hepatomegaly, or lymphadenopathy are not required for the diagnosis of CLL

✓ Before diagnosing CLL or SLL, mantle cell lymphoma must be excluded by demonstrating a negative FISH analysis for t(11;14)(IgH/CCND1) on peripheral blood or tissue biopsy or negative immunohistochemical stains for cyclin D1 on involved tissue biopsy.

3.12 Patients <u>must be previously treated</u> with at least one prior line of therapy.
EXCEPTION: CLL patients with Richter's transformation or Hodgkin transformation do not need prior therapy to enroll.
NOTE:

a. Prior chemotherapy or biologic novel therapy or anti-cancer monoclonal antibody based therapy for treatment of CLL will be considered prior therapy. Nutraceutical treatments with no established benefit in CLL (such as epigallocatechin gallate or EGCG, found in green tea or other herbal treatments) will not be considered "prior treatment".
b. Prior oral corticosteroid therapy for an indication other than CLL will not be considered "prior treatment".
c. Previous use of corticosteroids in the combination with other therapy for treatment of autoimmune complications of CLL does constitute prior therapy for CLL.

3.13 Patient must meet one of the following:

- CLL/SLL patients must have progressive disease with any one of the following characteristics based on standard criteria for treatment as defined by the NCI-WG 1996 (Cheson, 1996 and Hallek, 2008).
  1. Symptomatic CLL characterized by any one of the following:
     a. Weight loss ≥ 10% within the previous 6 months
     b. Extreme fatigue attributed to CLL
     c. Fevers ≥100.5^{o}F for 2 weeks without evidence of infection
     d. Drenching night sweats without evidence of infection
  2. Evidence of progressive bone marrow failure with hemoglobin ≤ 11 g/dL or platelet count ≤ 100 x 10^{9}/L
  3. Symptomatic or progressive lymphadenopathy, splenomegaly, or hepatomegaly

Note: Marked hypogammaglobulinemia or the development of a monoclonal protein in the absence of any of the above criteria for active disease are <u>not</u> sufficient for protocol therapy.

OR

- Biopsy proven Richter's transformation or Hodgkin transformation of the CLL. **NOTE:** Both untreated and previously treated patients in this category can be enrolled. They do not need to meet the progressive disease criteria in first bullet as long as measurable disease can be detected by PET/CT or CT (≥1.5 cm in diameter).

B. Inclusion Criteria for low grade B-NHL patients only:

3.14 Histologically confirmed relapsed (response to last treatment ≥ 6 months duration) or refractory (no response to last treatment or response duration < 6 months) indolent/low grade B cell NHL. NOTE: If patient has received previous anti-PD-1 or anti-PDL-1 consult with study chair.

- Follicular lymphoma, grades 1, 2 and 3
- Extranodal marginal zone B-cell lymphoma of MALT type
- Splenic and nodal marginal zone lymphoma
- Lymphoplasmacytic lymphoma including Waldenstrom Macroglobulinemia

NOTE: Criteria for diagnosis can be found in the following reference: J Clin Oncol 17(4):1244-53, 1999.

3.15 Measurable disease (at least 1 lesion of ≥ 1.5 cm in diameter) as detected by CT or the CT images of the PET/CT. NOTE: Patients with Waldenstrom Macroglobulinemia are not required to have measurable disease by CT or PET/CT if monoclonal protein is detectable by serum protein electrophoresis and/or IgM level is at least 2 times upper limit of normal.

C. Inclusion Criteria for CLL with Richter's transformation (Arm C) only:

3.16 **CLL diagnosis confirmed as 3.11 have biopsy –proven Richter's transformation. NOTE:** Both untreated and previously treated patients in this category can be enrolled as long as measurable disease can be detected by PET/CT or CT (≥1.5 cm in diameter).

D. Inclusion Criteria for all patients:

3.17 Age ≥18 years.

3.18 ECOG Performance Status (PS) 0 or 1 (Appendix III).

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

- Creatinine ≤ 1.5 X upper limit of normal (ULN) OR Creatinine Clearance ≥ 60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
- Platelet count ≥25 x 10^9/L
- Absolute neutrophil count ≥ 0.5X10^9/L
- Total bilirubin ≤1.5 x upper limit of normal (ULN) unless due to Gilbert's disease. If total bilirubin is >1.5 x ULN, a direct bilirubin should be performed and must be ≤ upper limit of normal
- AST (SGOT) or ALT (SGPT) ≤ 2.5 X ULN

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

3.19b Provide informed written consent.

3.19c Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

Note: During the **Active Monitoring** Phase of a study (i.e., active treatment and observation), participants must be willing to return to the consenting institution for follow-up.

3.19d Willing to provide bone marrow, tissue, and blood samples for correlative research purposes (see Sections 6.2, 14.0, and 17.0).

3.19e Must have failed or be unable to tolerate or refused other available FDA approved effective therapies. NOTE: Patients should not have other treatment options considered curative.

3.2 Exclusion Criteria

3.21 Currently participating in or has participated in a study of an investigational agent or using an investigational device ≤ 28 days prior to registration.

3.22 Receiving systemic steroid therapy or any other form of systemic immunosuppressive therapy ≤ 7 days prior to registration.
EXCEPTIONS:

- Low doses of steroids (≤ 20 mg of prednisone or equivalent dose of other steroid/day).
- Previous use of corticosteroids is allowed.
- After initiation of MK-3475 therapy, steroid can be used for management of potential immune mediated AE for less than 8 weeks of therapy.
- Topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption) are permitted.

3.23 Prior anti-cancer monoclonal antibody ≤ 28 days prior to registration or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

3.24 Prior chemotherapy or radiation therapy ≤ 14 days prior to registration or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent..

Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3.25 Known additional malignancy that is progressing or requires active treatment. EXCEPTIONS (these following exceptions are permitted to enroll in this trial):

- Basal cell carcinoma or squamous cell carcinoma or melanoma of the skin that has undergone or will undergo potentially curative therapy.

- In situ cervical cancer that has undergone or will undergo potentially curative therapy.

3.26 Active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease/syndrome difficult to control in the past.

EXCEPTIONS:

- Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule.
- Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study.
- Subjects with hypothyroidism stable on hormone replacement, diabetes or Sjorgen's syndrome are permitted for the study.
- Patients who have a positive Coombs test but no evidence of hemolysis are permitted for participation.
- Patients with psoriasis not requiring systemic treatment are permitted for participation.
- Conditions not expected to recur in the absence of an external trigger are permitted to enroll.

3.27 Evidence of interstitial lung disease or active, non-infectious pneumonitis.

3.28 Active infection requiring systemic therapy. NOTE: When the infection is controlled, patients are permitted for this study.

3.29a Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

3.29b Any of the following because this study involves an investigational agent whose genotoxic, mutagenic, and teratogenic effects on the developing fetus and newborn are unknown:
- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment

3.29c Known to be HIV positive.

3.29d Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected). NOTE: Patients with active hepatitis B defined by hepatitis B surface antigen positivity or core antibody positivity in the presence of hepatitis B DNA are not eligible for this study. Patients with a positive hepatitis B core antibody but with negative hepatitis B DNA may participate, but must have hepatitis serologies and hepatitis B DNA monitored periodically by the treating physician.

NOTE: IVIG can cause a false positive hepatitis B serology. If patients receiving routine IVIG have core antibody or surface antigen positivity without evidence of active viremia (negative hepatitis B DNA) they may still participate in the study, but should have hepatitis serologies and hepatitis B DNA monitored periodically by the treating physician.

3.29e Received a live vaccine ≤ 30 days prior to registration.

3.29f New York Heart Association Classification III or IV cardiovascular disease (Appendix I) or Recent myocardial infarction or unstable angina pectoris or unstable cardiac arrhythmia (<30 days).

3.29g Active CNS lymphoma or cerebrospinal fluid involvement with malignant lymphoma cells that requires therapy.

3.29h Has a clinically significant coagulopathy per investigator's assessment.

3.29i Has received an allogenic stem cell transplant.

3.3 Continuation Phase Exclusion Criteria

A. Exclusion criteria for patients enrolling on the CLL Arms (Arm A and Arm C) for the combination therapy including IBRUTINIB or IDELALISIB:

3.31 Is chronically taking **a strong CYP3A inhibitor or inducer** and cannot be switched to an alternative agent at least 7 days prior to Idelalisib or Ibrutinib initiation (See Appendix VII for examples) that in the opinion of investigator/treating physicians precludes utilization of either Ibrutinib or Idelalisib. Caution is recommended for patients taking moderate inhibitors of CYP3A.

B. Exclusion criteria for patients enrolling on the CLL arms (Arm A and Arm C) for the

combination therapy including IDELALISIB arm:

3.32 Is chronically taking **a sensitive CYP3A substrate** or **a CYP3A substrate with a narrow therapeutic index** and cannot be switched to an alternative agent at least 7 days prior to study initiation (See Appendix VII for examples) that in the opinion of investigator/treating physicians precludes utilization of Idelalisib

3.33 A history of chronic diarrhea, colitis, or intestinal perforation that in the opinion of the investigator precludes utilization of Idelalisib.

4.0 Test Schedule

4.1 MK-3475 single-agent therapy for both CLL (Arms A and C) and B-NHL (Arm B)

	Active Monitoring Phase					
Tests & Procedures	Days Prior to Registration (Screening phase) ≤30 days	≤14 days	Prior to each cycle, beginning with cycle 2[1, 13]	Response Evaluation[1] at 3, 6, and 12 months of therapy	Observation (every 90 days ± 14 days)	At time of progression[19]
Complete medical history	X					
Adverse event assessment		X	X [13]	X	X	X
Physical exam, including weight, and vital signs, ECOG PS		X	X[13]	X	X	X
Height		X				
Tumor measurement by physical exam (CLL/SLL arm only) [2]		X[2]	X[13]	X	X	X
Peripheral blood immunophenotyping by flow cytometry	X[3]					
CBC with differential and reticulocytes[16]		X	X[13]	X	X	X
Serum pregnancy test		X[4]				
Peripheral smear		X				
Chemistry group (SGOT [AST], SGPT [ALT], total bilirubin[T-Bil], serum creatinine, alkaline phosphatase, direct bilirubin only when T-Bil elevated)		X	X	X	X	X
Uric acid, phosphate, calcium, potassium, sodium		X				
HBsAg, Hep C Ab, HB core antibody		X				
IGHV (CLL/SLL arm only)	X[5]					
Bone marrow biopsy/aspirate	X[6]			X [7]		
Serum protein electrophoresis (SPEP)		X[8]		X[8]		

	Active Monitoring Phase					
Tests & Procedures	Days Prior to Registration (Screening phase) ≤30 days	≤14 days	Prior to each cycle, beginning with Cycle 2[1, 13]	Response Evaluation[1]: at 3, 6, and 12 months of therapy	Observation (every 90 days ± 14 days)	At time of progression[19]
Beta-2-microglobulin (CLL/SLL arm only)		X				
Serum quantitative immunoglobulins (IgG, IgA, IgM)		X[8]	X (IgM only)[15]	X[8]		X[8]
Coombs test (monospecific direct coombs IgG and C3)		X				
TSH and Free T4		X		X[17]		
CD4 T cell number and LDH		X		X		X
CT scan chest, abdomen, pelvis (may use CT portion of the PET/CT)[14]	X			X		X
Mayo confirmation of tumor diagnosis (NHL arm only) or CLL with Richter/Hodgkin transformation	X[9]					
Mandatory tissue/node biopsy (see Section 17.0)	X[18, R]					X[18, R]
Evaluation of MRD by sensitive flow cytometry (CLL/SLL arm only)				X[10]		
Mandatory blood specimens (see Section 14.0)[R]		X[11]	For cycles 2 and 3, and 18 and 24 months (if therapy is beyond 12 months)[11]	X[11]		X[11]
Mandatory research bone marrow aspirate specimens (see Section 14.0)	X[12,R]			X[12,R]		
Rochester CLL/SLL Patients Only: Research bone marrow core sample as per 1827-00	X			X		

1. All scheduled visits will have a window of -2 days to +7 days unless otherwise stated. Response will be evaluated after approximately 3, 6, and 12 months of treatment. If the patient remains on cycles with a length of 21 days without treatment delays, this will be at the end of cycles 4, 9, and 17 (approximately days 189 and 357). If the cycle length is increased due to dosing frequency changes or dose delays occur, the response evaluations should occur where the end of the cycles are closest to 3, 6 and 12 months (days 183 and 365), keeping in mind that this may occur slightly before 3, 6, or 12 months. Response evaluation at 3, 6, and 12-month time points unless treatment has been stopped/completed and then the response evaluation can be performed between 2-8 weeks after last therapy.
   Note: all patients who received at least 2 cycles of treatment should be evaluated for formal clinical response either during the interval of 2-8 weeks after the last dose of therapy or at 3, 6, and 12-month time points since therapy start, whichever occurs first.
   If patient is continuing to benefit from treatment after 12 months determined by investigator, they may continue to receive treatment up to a total duration of 24 months including both single-agent and combination therapy at investigator/sponsor discretion.
2. Physical exam should measure the spleen and liver noting the maximal distance below the respective costal margins and should record the bidimensional diameter of the largest palpable node in each area of involvement including the following sites: left neck (sub-mandibular, cervical, supra-clavicular), right neck (sub-mandibular, cervical, supra-clavicular), left axillary, right axillary, left groin (inguinal, femoral) and right groin (inguinal, femoral).
3. Only applicable for CLL/SLL, marginal zone and Lymphoplasmacytic lymphoma patients, not for follicular lymphoma patients. For patients who have previously had full flow immunophenotyping consistent with CLL or low grade NHL performed at Mayo Clinic or other academic centers, repeat flow immunophenotyping is not necessary.
4. For women of childbearing potential only. Must be done ≤7 days prior to registration.
5. If patient has previously had done clinically at Mayo Clinic or other academic centers, this does not need to be repeated.
6. Bone marrow biopsy/aspirate is required. Baseline bone marrow biopsy/aspirate is not required if the patient has had a bone marrow biopsy/aspirate obtained for clinical purposes ≤90 days prior to registration however, this should be discussed with the study chair.
7. For CLL patients only who had bone marrow involvement at baseline, a bone marrow biopsy is required at 6-months and 12 months for all patients with evidence of response (CR, CRi, nPR, and PR) but is not required for those with disease progression/stable disease. For NHL patients, only required at 6-month and at 12-month visits for patients who have achieved clinical response and had bone marrow involvement at baseline.
8. For CLL/SLL, lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia and marginal zone lymphoma patients only. For SPEP, only required at 6-month and 12-month time points
9. Central review of pathology is required for confirmation of diagnosis for NHL patients or CLL patients with Richter/Hodgkin transformation unless patient has had a documented tissue pathology for low grade B cell NHL or Richter/Hodgkin transformation confirmed by Mayo pathologist or other academic centers in the history (anytime in the history).
10. MRD testing on 6-month and on 12-month visit only for CLL patients who have a very good response (CR/CRi/CCR/nPR) only. If marrow samples are available, marrow MRD testing is preferred.
11. Blood specimens will be collected and submitted at the following time points: registration, prior to cycle 2, prior to cycle 3, at 3-month, 6-month, and 12-month time points from start of therapy, as well as at disease progression. If patient continues therapy (single or combination) beyond 12 months, blood specimens will be collected at 18-month and 24-month time points from start of therapy, as well as disease progression.

12. Research bone marrow aspirate specimens must be collected at the same time when clinical bone marrow tests are required (e.g. baseline, 6 and 12 months of therapy or other time when performed) and submitted. If bone marrow was performed prior to consenting the patient for this study, a repeat bone marrow is not required to obtain the research aspirate sample at baseline.
13. Adverse events, CBC, Cr and LFTs must be evaluated every cycle. For patients who tolerated therapy and have clinical benefits, they will be followed at each cycle for the first 6 months. Clinical response will be evaluated at 3 and 6 months. After 6 months of therapy, responsive or stable patients can be followed every other cycle by treating physician/provider until one or two years of total duration of therapy. However, patient will be followed by nurse at each cycle of treatment for adverse event assessment. They will be seen as needed by provider. Physical exam and tumor measurements are required only on cycles where the patient is evaluated by the treating physician. All patients who received at least 6 months of therapy and have shown clinical benefit will be evaluated again at 12 months for clinical response. For patients who continue therapy beyond 12 months, the above schedule is recommended. Further formal response evaluation is only required if there is clinical sign of disease progression. Other response evaluation is per discretion of treating physician.
14. For Follicular lymphoma grade 3 and CLL patients with Richter's transformation or Hodgkin transformation, PET/CT scan will be performed to replace CT at baseline, at 3, 6, and 12 months for response evaluation. Scans after baseline are not required for patients with lymphoplasmacytic lymphoma (Waldenstrom Macroglobulinemia) if utilizing IgM as the criteria for response. If patient had measurable nodes at baseline, then scans should be repeated.
15. For patients with lymphoplasmacytic lymphoma (Waldenstrom Macroglobulinemia) only when this is being used as the criteria for measurable disease.
16. Reticulocytes are required at baseline for all patients. After baseline may be ordered at physician discretion.
17. At 6 month visit. If there is no change from baseline, further testing is not required.
18. Research tissue/node biopsy- tissue block or slide submission is required for correlative research described in section 17.0. Repeat tissue/node biopsy solely for the purpose of correlative study is not required pre-registration. If a tissue biopsy is done to make a clinical diagnosis per the treating physician, then the tissue block (preferred) or slides should be submitted for correlative research.
19. For Arm A and Arm C patients who go on to combination treatment, this is considered the baseline visit and lab tests before continuing to follow test schedule in Section 4.2.

R Research funded (see Section 19.0). Will be charged to study and not to patient's account.

4.2 Continuation Phase: Combination therapy of MK-3475 with a signal inhibitor (Idelalisib or Ibrutinib) for CLL (Arm A) and CLL with Richter's transformation only (Arm C)

	Active Monitoring Phase			
Tests & Procedures	Prior to each cycle, beginning with 2nd cycle of combination therapy[1, 8]	Response Evaluation[1]: at 3, 6, and 12 month of combination therapy	Observation (every 90 days ± 14 days)	At time of progression
Adverse event assessment	X [8]	X	X	X
Physical exam, including weight, and vital signs, ECOG PS	X[8]	X	X	X
Tumor measurement by physical exam (CLL/SLL arm only) [2]	X[8]	X	X	X
CBC with differential and reticulocytes[10]	X[8]	X	X	X
Chemistry group (SGOT [AST], SGPT [ALT], total bilirubin[T-Bil], serum creatinine, alkaline phosphatase, direct bilirubin only when T-Bil elevated)	X	X	X	X
Bone marrow biopsy/aspirate		X [3]		
Serum protein electrophoresis (SPEP)		X[4]		
Serum quantitative immunoglobulins (IgG, IgA, IgM)		X[4]		X
CD4 T cell number and LDH		X		X
CT scan chest, abdomen, pelvis (may use CT portion of the PET/CT)[9]		X		X
Mandatory tissue/node biopsy (see section 17.0)				X[11, R]
Evaluation of MRD by sensitive flow cytometry (CLL/SLL arm only)		X[5]		
Mandatory blood specimens (see Section 14.0)[R]	For cycles 2 and 3 of combination therapy and 18 and 24 months of combination therapy[6]	X[6]		X[6]

Mandatory research bone marrow aspirate specimens (see Section 14.0)		X[7,R]		
Rochester CLL/SLL Patients Only: Research bone marrow core sample as per 1827-00		X		

1. All scheduled visits will have a window of - 2 days to +7 days unless otherwise stated. Response will be evaluated after approximately 3, 6, and 12 months of combination treatment. Disease measurements and lab parameters obtained after the last cycle of single-agent therapy are set as the baseline measurements for this phase. If the cycle length is increased due to dosing frequency changes or dose delays occur, the response evaluations should occur where the end of the cycles are closest to 3, 6, and 12 months of combination treatment, keeping in mind that this may occur slightly before 3, 6 or 12 months. Response evaluation at 3, 6, and 12-month time point unless treatment has been stopped/completed and then the response evaluation can be performed between 2-8 weeks after last dose of pembrolizumab therapy.
   Note: all patients who received at least 2 cycles of treatment should be evaluated for formal clinical responses either during the interval of 2-8 weeks after the last dose of pembrolizumab therapy or at 3, 6, and 12-month time point since therapy start, whichever occurs first.
   If patient is continuing to benefit from treatment after 12 months determined by investigator, they may continue to receive treatment up to a total duration of 24 months including both single-agent and combination therapy at investigator/sponsor discretion.
2. Physical exam should measure the spleen and liver noting the maximal distance below the respective costal margins and should record the bidimensional diameter of the largest palpable node in each area of involvement including the following sites: left neck (sub-mandibular, cervical, supra-clavicular), right neck (sub-mandibular, cervical, supra-clavicular), left axillary, right axillary, left groin (inguinal, femoral) and right groin (inguinal, femoral).
3. For CLL patients only who had bone marrow involvement at baseline, a bone marrow biopsy is required at 6-months and 12-months for all patients with evidence of response (CR, CRi, nPR, and PR) but is <u>not</u> required for those with disease progression/stable disease.
4. For CLL/SLL, lymphoplasmacytic lymphoma patients only. For SPEP, repeat only is required at 6 and 12 months.
5. MRD testing on 6-month and on 12-month visit only for CLL patients who have a very good response (CR/CRi/CCR/nPR) only. If marrow samples are available, marrow MRD testing is preferred.
6. Blood specimens will be collected and submitted at the following time points: prior to cycle 2, prior to cycle 3, at 3, 6, and 12- month time point for combination therapy, as well as at the disease progression. If patient continues therapy (single or combination) beyond 12 months, blood specimens will be collected at 18-month and 24-month time points from start of therapy, as well as disease progression.
7. Research bone marrow aspirate must be collected at the same time when clinical bone marrow tests are required (e.g. 6 and 12 months of therapy or other time when performed) and submitted.
8. Adverse events, CBC, Cr and LFTs must be evaluated every cycle. For patients who tolerated therapy and have clinical benefits, they will be followed at each cycle for the first 6 months. Clinical response will be evaluated at 6 months. After 6 months of therapy, responsive or stable patients can be followed every other cycle by treating physician/provider until one year of total duration of therapy. However, patient will be followed by nurse at each cycle of treatment for adverse event assessment. They will be seen as needed by provider. Physical exam and tumor measurements are required only on cycles where the patient is evaluated by the treating physician. All patients who received at least 6 months of combination therapy and shown clinical benefit will be evaluated again at 12 months for clinical response. For patients continuing

therapy beyond 12 months, the above schedule is recommended. Further formal response evaluation is only required if there is clinical sign of disease progression. Other response evaluation is per discretion of treating physician.

9. For CLL patients with Richter's transformation or Hodgkin transformation, PET/CT scan will be performed to replace CT at all time points (month 3, 6, and 12 of the combination therapy) and disease progression for response evaluation.
10. Reticulocytes are required at baseline for all patients. After baseline, may be ordered at physician discretion.
11. Research tissue/node biopsy tissue block or slide submission is required for correlative research described in section 17.0. If a tissue biopsy is done to make a clinical diagnosis per the treating physician, then the tissue block (preferred) or slides should be submitted for correlative research.

R Research funded (see Section 19.0). Will be charged to study and not to patient's account.

5.0 Grouping Factor:

5.1 Treatment Arm: Arm A (CLL/SLL and CLL with Richter's transformation) vs Arm B (low grade NHL) vs. Arm C (CLL with Richter's transformation)

Note: CLL patients with Richter's transformation or Hodgkin's transformation will be included in Arm A and C.

As per MCCC Addendum 2: An arm (Arm C) with CLL patients with Richter's transformation only is added to the study.

6.0 Registration Procedures

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

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

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

6.2 Correlative Research

A mandatory correlative research component is part of this study. The patient will be automatically registered onto this component (see Sections 3.19c, 14.0, and 17.0).

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

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

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

6.4 Prior to accepting the registration, registration application will verify the following:

- IRB approval at the registering institution

- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

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

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

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

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

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

6.8 Treatment on this protocol must commence at Mayo Clinic Rochester, Mayo Clinic in Florida, or Mayo Clinic in Arizona under the supervision of a Hematologist.

6.9a Study drug is available on site.

6.9b **Continuation Phase (Combination Treatment with MK-3475 and Ibrutinib/Idelalisib):** To register a patient fax [redacted]) a completed continuation phase eligibility checklist to the Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

7.0 Protocol Treatment

7.1 Treatment Schedule for all three arms

Agent	Dose Level	Route	Day	Cycle Length
MK-3475	200 mg	IV	Day 1	21 days
CLL/SLL patients only: Bactrim DS*	1 tablet once daily	Oral	Three times per week while on treatment	

*If a patient has sulfa allergy or could not tolerate Bactrim, alternative PCP prophylaxis is allowed at the discretion of treating provider. For patients continuing on combination therapy, PCP prophylaxis is optional. Bactrim can be changed to alternative PCP prophylaxis.

Note: Tumor lysis syndrome has not been observed with MK-3475 therapy. Standard prophylaxis for tumor lysis syndrome can be considered prior to therapy.

Note: Each cycle of treatment is 21 days. If patient experienced adverse events which required dosing delay (see Section 8.0), the new dosing interval (increased interval) can be defined as a new cycle length. If CLL or NHL patients have achieved CMR/CR/CRi (MRD negative CR for CLL patients) confirmed by bone marrow or CT/PET evaluation, patients could continue the treatment for 2 more cycles and stop the treatment at the discretion of the treating provider. If patient experiences disease relapse after stopping therapy due to CMR/CR, the previous treatments can be restarted. The designed maximum length of treatment is 12 months (365 days).

Note: If patient is continuing to benefit from treatment after 12 months, they may continue to receive treatment up to 24 months at investigator/sponsor discretion

7.2 Timing of Dose Administration for all three arms

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the test schedule (Section 4.0). Trial treatment may be administered up to 2 days before or 7 days after the scheduled Day 1 of each cycle due to administrative reasons.

Note: For patients who tolerated therapy and have clinical benefits, they will be followed at each cycle for the first 6 months. Clinical response will be evaluated at 3 and 6 months. After 6-months of therapy, responsive or stable patients can be followed every other cycle by treating physician/provider until one year of total duration of therapy. However, patient will be followed by nurse at each cycle of treatment for adverse event assessment. They will be seen as needed by provider. All patients who received at least 6 months of therapy and shown clinical benefit will be evaluated again at 12 months for clinical response. For patients continuing therapy beyond 12 months, the above schedule is recommended. Further formal response evaluation is only required if there is clinical sign of disease progression. Other response evaluation is per discretion of treating physician.

7.3 For CLL patients with or without Richter's transformation (Arm A and Arm C), if a patient developed progressive disease (not tumor flare) at any time of the single-agent (MK-3475) therapy, or has stable disease without partial remission at the response

evaluation at month 3 of the single-agent (MK-3475) therapy, a commercially available FDA-approved CLL signal inhibitor can be added to MK-3475 (remain at the dose 200mg IV every 3 weeks). In this clinical scenario, if the patient had not used Ibrutinib in the past, Ibrutinib is recommend to be added using the standard FDA approved dose. However, the dose of Ibrutinib can be modified by treating physician based on concomitant medications or other clinical status. If the patient had progressed or had intolerable adverse events on Ibrutinib, Idelalisib is recommended to be added using the standard FDA approved dose. The dose of Ibrutinib or Idelalisib can be reduced/adjusted due to adverse events or concomitant medications according to the package inserts of the individual agent. If the patient had used both Ibrutinib and Idelalisib in the past, it is at the discretion of investigator/treating physician to decide which FDA-approved oral CLL therapy to use according to the package inserts of the individual agent and clinical status of the patient.

Treatment Schedule for Combination Therapy with MK-3475 and Ibrutinib

Agent	Dose Level	Route	Day	Cycle Length
MK-3475	200 mg	IV	Day 1	21 days**
Ibrutinib	420 mg	Oral	Once daily	

**If the dosing interval was increased due to adverse events while receiving single-agent MK-3475, continue with the increased dosing interval the patient was receiving for the last cycle of single-agent MK-3475

Treatment Schedule for Combination Therapy with MK-3475 and Idelalisib

Agent	Dose Level	Route	Day	Cycle Length
MK-3475	200 mg	IV	Day 1	21 days**
Idelalisib	150 mg	Oral	Twice daily	

**If the dosing interval was increased due to adverse events while receiving single-agent MK-3475, continue with the increased dosing interval the patient was receiving for the last cycle of single-agent MK-3475.

7.4 For patient who received ibrutinib previously:

Note: due to the observed ibrutinib withdrawal syndrome in selected CLL patients who had received ibrutinib before, steroid use in the format of 0.5 mg to 2 mg per kilogram body weight prednisone or equivalent is allowed with a gradual taper to overcome the ibrutinib withdrawal syndrome. The duration of high dose steroid use should be within the first 1-3 months when patients were off ibrutinib

7.5 If CLL or NHL patients have achieved CMR/CR (MRD negative CR for CLL patients) confirmed by bone marrow or CT/PET evaluation, patients could continue the treatment for 2 more cycles and stop the treatment at the discretion of the treating provider. If patient experiences disease relapse after stopping therapy due to CMR/CR, the previous treatments can be restarted. The designed maximum length of active treatment with MK-3475 is 12 or 24 months.

7.6 Total duration of treatment including both single-agent and combination therapy is a maximum of 12 months. If the patient remains on cycles with a length of 21 days without treatment delays, this will be 17 cycles total. If the cycle length is increased due to dosing frequency changes or dose delays occur, the number of cycles will be reduced to not exceed 12 months (365 days) of treatment total. NOTE: If patient is continuing to benefit from treatment after 12 months, they may continue to receive treatment up to a total duration of 24 months including both single-agent and combination therapy at

investigator/sponsor discretion.

7.7 At the end of the trial therapy with MK-3475, signal inhibitor can be continued or stopped at the discretion of the treating physicians.

8.0 Dose modification based on Adverse Events

8.1 MK-3475 Dose Levels

Dose Level	MK-3475**
0*	200 mg IV Day 1 every 21 days

*Dose level 0 refers to the starting dose.
**If dose modifications are needed, the dosing interval may be increased by 7 days each time, the maximal dosing interval allowed is 8 weeks.
Note: This study will not allow dose reduction of MK-3475, only dose interval changes

8.2 Arms A and C Dose Modifications – NOTE: Dose hold/modification of Ibrutinib or Idelalisib will be based on the package insert of the individual medicine. If the patient is on a moderate cytochrome P450 inhibitor or inducer (see Appendix VII), caution is recommended and close monitoring of toxicity or efficacy of therapy is warranted. Providers should consult the package insert for recommendations on dose adjustment in the setting of drug interactions. In case an adverse event cannot be easily attributed to either MK-3475 or the signal inhibitor, strongly recommend to discuss with study chair and/or sponsor for subsequent decision.

8.3 MK-3475 Dose Modifications only-see table below. In case an adverse event cannot be easily attributed to either MK-3475 or the signal inhibitor, strongly recommend to discuss with study chair and/or sponsor for subsequent decision.

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←			
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT (at least possibly related)	AGENT	ACTION**
AT TIME OF RETREATMENT			
Gastrointestinal disorders[1]	Enterocolitis Grade 2	MK-3475	Hold study treatment and consider infection evaluation with C. diff toxin. If rule out c.diff, anti-diarrheal treatment should be started. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours with oral hydration until diarrhea free (maximum 16 mg/day). If symptoms are persistent for more than one week or complicated with rectal bleeding, GI consultation and endoscopy is recommended. Systemic corticosteroids or budesonide 9 mg daily should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started. If AE improves to grade 1 or less within 4 weeks, study treatment should be restarted at the same dose with the same cycle length for the first occurrence. The cycle

			interval will increase by one week for each occurrence of the same adverse events. If the treatment is delayed ≥ 8 weeks from last therapy, study treatment should be discontinued and go to observation if at least 2 cycles of therapy were given, otherwise, go to event monitoring.

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←			
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT (at least possibly related)	AGENT	ACTION**
AT TIME OF RETREATMENT			
Gastrointestinal disorders	Enterocolitis ≥ Grade 3	MK-3475	Discontinue study treatment, GI consultation and endoscopy is recommended. Go to observation if ≥ 2 cycles were given, otherwise go to event monitoring. Treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started.
Respiratory, thoracic and mediastinal disorders[1]	Pneumonitis		Subjects with symptomatic pneumonitis should immediately stop receiving study treatment and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection. If the subject is determined to have study drug associated pneumonitis, treat as follows:
	Grade 2		Hold study treatment and treat with systemic corticosteroids and taper when the symptoms improve to grade 1 or less. For first occurrence, restart at the same dose with the same cycle length if AE improves to Grade 1 or less within 4 weeks when systemic steroid reduced to ~ prednisone 10 mg oral daily dose or less. If the symptoms improve to grade 1 or less between 4 to 8 weeks, discontinue therapy or consult with study chair. For second occurrence, discontinue study treatment and go to observation if ≥ 2 cycles of therapy were given, otherwise go to event monitoring.
	≥ Grade 3		Discontinue study treatment and go to observation if ≥ 2 cycles of therapy were given, otherwise go to event monitoring. Recommend pulmonary evaluation including bronchoscopy and pulmonary function tests to rule out other causes. Treat with systemic

			corticosteroids. The use of infliximab may be indicated as appropriate. May consult study chair.

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←			
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT (at least possibly related)	AGENT	ACTION**
AT TIME OF RETREATMENT			
General disorders and administration site conditions	Infusion related reaction ≥ Grade 3 (see Section 9.9a for treatment guidelines)		Discontinue study treatment and go to observation if ≥ 2 cycles of therapy were given, otherwise go to event monitoring.
Immune system disorders	Immune system disorders – Other, specify Events of Clinical Interest & Immune-related Adverse Events (irAEs) (see Section 9.9b supportive care guidelines) Grade 2	MK-3475	May hold study treatment. Steroid treatment may be indicated. Clinical AE resolves to grade 1 or less within 4 weeks: Same dose and schedule. Clinical AE does not resolve to grade 1 or less within 4 weeks: hold therapy until AE improves to grade 1 or less and may prolong the dosing interval to maximal 8 weeks. May increase the dosing interval by 1 week. May increase the dosing interval by 1 week for each occurrence. If AE does not resolve within 8 weeks of last therapy discontinue study treatment and go to observation if ≥ 2 cycles of therapy were given, otherwise go to event monitoring.
	≥ Grade 3[2]		Hold study treatment and discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 8 weeks of adverse event. Consult with study chair as needed. If treatment is discontinued, go to observation if ≥ 2 cycles of therapy were given, otherwise go to event monitoring.

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←			
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT (at least possibly related)	AGENT	ACTION**
AT TIME OF RETREATMENT			
Investigations	Neutrophil count decreased Grade 4	MK-3475	Hold study treatment and restart when resolved to Grade 0-1 or baseline. May increase dosing interval by 1 week. If adverse event does not resolve to grade 0-1 or baseline within 8 weeks from last therapy, discontinue study treatment and go to observation if ≥ 2 cycles of therapy were given, otherwise go to event monitoring.
Endocrine disorders	Adrenal Insufficiency Hyperthyroidism Hypothyroidism Endocrine disorders - Other, Hypopituitarism, Thyroiditis, Hypophysitis Grade 2		Monitor hormonal levels in the appropriate frequency by the discretion of treating physician until returned to baseline values. Hormonal replacement or other necessary therapy is recommended. Consider endocrine consultation as needed. Hold treatment until AE improves to grade 1or baseline. If AE improves to grade 1 or baseline within 4 weeks, study treatment should be restarted at the same dose with the same cycle length for the first occurrence. The cycle interval will increase by one week for each occurrence of the same adverse events. If the treatment is delayed ≥8 weeks, study treatment should be discontinued and go to observation if ≥2 cycles of therapy were given, otherwise go to event monitoring.
	≥ Grade 3		Hold study treatment, consider endocrine consultation and discussion. Rule out infection and sepsis with appropriate cultures and imaging. Consider treatment with corticosteroids 1 to 2 mg/kg daily. When symptoms improved to grade 1 or less, steroid taper may be started. Replacement of appropriate hormones may be required. Discuss with study chair for the option of continuation of treatment when the AE improves to grade 1 or baseline within 8 weeks from last therapy. If treatment is discontinued, go to observation if ≥ 2 cycles were given, otherwise go to event monitoring.

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←			
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT (at least possibly related)	AGENT	ACTION**
AT TIME OF RETREATMENT			
Eye disorders	Uveitis Grade 1- 2	MK-3475	Hold treatment. Evaluation by an ophthalmologist is strongly recommended. Infectious causes will need to be ruled out. Treat with topical steroids is recommended. For the first occurrence, if AE resolves within 4 weeks, study treatment should be restarted at the same dose with the same cycle length. If AE resolves between 4-8 weeks from the last therapy, the cycle interval will increase by one week. Discontinue treatment if symptoms persist despite topical therapies. Discontinue treatment for the second occurrence. If the treatment is delayed ≥8 weeks, study treatment should be discontinued and go to observation if ≥2 cycles of therapy were given, otherwise go to event monitoring.
	≥ Grade 3		Discontinue treatment. Evaluation by an ophthalmologist is strongly recommended. Infectious causes will need to be ruled out. Treat with topical or systemic steroids is recommended. When symptoms improve to grade 1 or less, systemic steroid taper should be started.
Cardiac disorders	Myocarditis Grade 1	MK-3475	Hold all treatment. Consult study chair. Resume when resolved and corticosteroids have been tapered, if applicable. If not resolved within 12 weeks of last dose or if corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks, discontinue treatment and go to observation if ≥ 2 cycles of therapy were given, otherwise go to event monitoring. Ensure adequate evaluation to confirm etiology and/or exclude other causes. .
	≥Grade 2		Discontinue all treatment and go to observation if ≥ 2 cycles of therapy were given, otherwise go to event monitoring. Ensure adequate evaluation to confirm etiology and/or exclude other causes. May administer corticosteroids.

Metabolism and nutrition disorders	Glucose intolerance (Type 1 diabetes mellitus [if new onset] or Hyperglycemia Any Grade	MK-3475	Hold treatment of MK-3475. Consult with endocrinology to decide if T1DM is confirmed. If T1DM confirmed, initiate insulin replacement therapy. Administer anti-hyperglycemic in participants with hyperglycemia. Monitor for hyperglycemia or other signs and symptoms of diabetes. Prior to restarting, consult with PI or treating physician to assess whether further treatment is indicated.

→ → Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified ← ←			
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT (at least possibly related)	AGENT	ACTION**
AT TIME OF RETREATMENT			
Other non-hematologic	Grade 2 Exception: Grade 2 alopecia and fatigue do not require any action.	MK-3475	Consider holding study treatment for persistent significant clinical symptoms until AE resolves to Grade 0-1 or baseline. Clinical AE resolves to grade 0-1 or baseline within 4 weeks: Same dose and schedule Clinical AE does not resolve to grade 0- 1 or baseline within 4 weeks: May increase the dosing interval to maximal 8 weeks. May increase the dosing interval by 1 week for each occurrence. If AE does not resolve to grade 0-1 or baseline within 8 weeks, discontinue study treatment and go to observation if ≥ 2 cycles of therapy were given, otherwise go to event monitoring.
	≥ Grade 3		Hold study treatment until AE resolves to Grade 0-1 or baseline. May increase the dosing interval by 1 week for each occurrence. Consult with study chair as needed. If AE does not resolve to grade 0-1 or baseline within 8 weeks from last therapy, discontinue study treatment and go to observation if ≥ 2 cycles of therapy were given, otherwise go to event monitoring. For any severe or life-threatening AE, consider discontinuing study treatment.

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

** Use the following to describe actions in the Action column:

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

NOTES:

- In case toxicity does not resolve to Grade 0-1 or baseline within 8 weeks after last infusion, trial treatment should be discontinued after consultation with the study chair. With study chair and Sponsor agreement, subjects with a laboratory or non-significant adverse event still at Grade 2 or baseline after 8 weeks may continue treatment in the trial only if asymptomatic and controlled with appropriate supportive care.
- Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of MK-3475 should be discontinued from trial treatment.

1. Consideration should be given to MK-3475 or Idelalisib as the causative agent in the setting of enterocolitis/pneumonitis, if both agents are being utilized. Consultation with the study chair is warranted.
2. In case of autoimmune hepatitis, when grade 3 (AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN), discontinue MK 3475 or combination therapy. Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury. If necessary, treat with high-dose intravenous or oral glucocorticosteroids (prednisone equivalent 1-2 mg/kg) for 24 to 48 hours. When symptoms improve to grade 1 or less, a steroid taper should be started and continued. If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given.

MK-3475 will be withheld for drug-related Grade 4 hematologic toxicities per table in 8.4, non-hematological toxicity ≥ Grade 3 including uncontrolled laboratory abnormalities, and severe or life-threatening AEs as per Tables in 8.3 and 8.4

8.4 MK-3475 Dose Modification for Hematological Toxicities (Platelet and Hemoglobin only) for MK-3475.

Note: hematological toxicity is not based on CTCAE 4.0 except neutrophil, but based on CLL specific hematological toxicity (this table and Appendix IV).
Dose modification guidelines for drug-related hematological (hemoglobin and platelets) adverse events[1, 2, 3]

Toxicity	Grade [1, 2, 3]	Decrease from pretreatment[4]	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with PI)
CLL/NHL specific Hematological Toxicity (appendix IV)	1	11-24% decrease in HGB or PLT	No	N/A	N/A	N/A
	2	25-49% decrease in HGB or PLT				
	3	50-74% decrease in HGB or PLT	Yes	Toxicity resolves to Grade 0-2 or baseline	May increase the dosing interval by 1 week	Toxicity does not resolve within 8 weeks of last infusion Permanent discontinuation should be considered for any severe or life-threatening event. Go to observation if ≥ 2 cycles of therapy were given, otherwise go to event monitoring
	4	≥75% decrease in HGB or PLT	Yes	Toxicity resolves to Grade 0-2 or baseline	May increase the dosing interval by 1 week	

[1]If, at any level of decrease the platelet count is < 20,000/μL, this will be considered grade 4, unless the initial platelet count was ≤ 20,000 μL in which case the patient is inevaluable for toxicity referable to platelet counts.
[2]If, at any level of decrease from the baseline value the platelet and/or hemoglobin counts are within normal limits or platelet count is still ≥ 100,000/μL, this will be considered a grade 0.
[3]If patient has persistent cytopenia, it is recommended to repeat bone marrow evaluation to test if there is disease progression.
[4]For patients initiated on combination therapy of a signal inhibitor with MK-3475, the pretreatment value is the value before addition of the signal inhibitor.

9.0 Ancillary Treatment/Supportive Care

9.1 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (42) Update of Recommendations for the Use of Hematopoietic Colony-Stimulating Factors: Evidence-Based, Clinical Practice Guidelines. J Clin Oncol 24 (19): 3187 -3205, 2006.

9.2 Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, and antiemetics when appropriate. **Any blood transfusions administered must be irradiated blood products to reduce risk of transfusion mediated graft versus host disease in CLL and NHL patients receiving T-cell suppressive therapy. Leukocyte reduction of all blood products for patients on protocol is also required.** All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.3 Concomitant Medications/Vaccinations (allowed & prohibited): Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or medication/vaccination may be required. The provider should discuss any questions regarding this with the investigator. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, the provider, and the subject.

9.4 Acceptable Concomitant Medications: All treatments that the provider/investigator considers necessary for a subject’s welfare may be administered at the discretion of the provider/investigator in keeping with the community standards of medical care.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. If changes occur during the trial period, documentation of the changed medication should be recorded.

Note: IVIG replacement therapy for CLL patients is permitted, but recommend to discuss with study chair for continuation.

9.5 Prohibited Concomitant Medications: Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Anti-cancer systemic chemotherapy
- Immunotherapy not specified in this protocol. Note: IVIG replacement is permitted.
- Radiation therapy. Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Investigator.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza and pneumonia vaccines for injection are

generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Ongoing chronic steroid therapy with a dose more than equivalent prednisone dose ≥30mg daily for longer than 2 months.

Subjects may receive other medications that the investigator deems to be medically necessary.

9.6 Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

9.7 Diarrhea: Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered. Steroid therapy should be strongly considered per table 8.3

- All subjects who experience diarrhea 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.
- If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.8 Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice. **For CLL patients, it is highly recommended to start PCP and viral prophylaxis while patients are on treatment.**

9.9a Management of Infusion Related Reactions: Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting or Diarrhea.

Treatment guidelines for subjects who experience an infusion related reaction associated with administration of MK-3475.

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 Corticosteroids 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 two hours 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 3 toxicity despite adequate	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of MK-3475 with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic). Additional pre-medication as needed per treating provider's discretion.

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	premedication should be permanently discontinued from further trial treatment. If ≥ 3 cycles of therapy was given, patients will go to observation, otherwise event monitoring.	
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.** If ≥ 2cycles of therapy was given, patients will go to observation, otherwise event monitoring.	No subsequent dosing, discontinue the treatment.

9.9b Supportive Care Guidelines for Events of Clinical Interest and Immune-related Adverse Events (irAEs)

Events of clinical interest of a potential immunologic etiology (irECIs) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. irAEs may be predicted based on the nature of the MK-3475 compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Subjects who develop a Grade 2 or higher irAE should be discussed immediately with the Investigator/Sponsor.

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

General Approach to Handling irAEs

irAE	Withhold/Discontinue MK-3475	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold MK-3475	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3 and Grade 4	Withhold MK-3475 Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 8 weeks of toxicity If ≥ 2 cycles of therapy was given, patients will go to observation, otherwise event monitoring.	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered gradually.

10.0 Adverse Event (AE) Reporting and Monitoring

NOTE: References to grade will always be per CTCAE throughout section 10.0.

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web [redacted]

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.5). With this information, determine whether the event must be reported as an expedited report (see Section 10.). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). Grade is an essential element of the Guidelines and, in general, relates to **severity** for the purposes of regulatory reporting to NCI.

NOTE: A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

- The determination of whether an AE is expected is based on agent-specific information provided in Section 15.0 of the protocol and the study specific consent form.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of the protocol and the study specific consent form.

NOTE: "Unexpected adverse experiences" means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).

Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.4 Expedited Reporting Requirements for IND/IDE Agents

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

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:
Death
A life-threatening adverse event
An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
A congenital anomaly/birth defect.
Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

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

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour 3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>7 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in section 10.41 of the protocol.
Expedited AE reporting timelines are defined as:
"24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.

"7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:
All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:
Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization

Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.
Effective Date: May 5, 2011

Additional instructions:
1. Contact: Merck Global Safety. (Attn: Worldwide Product Safety; FAX [redacted])
2. Use MedWatch form, Form FDA 3500a, available on the FDA website at [redacted]
   Following completion of the FDA electronic form, print for signature and submission.
   Submit to Merck Global Safety. (Attn: Worldwide Product Safety; FAX [redacted])

Mayo Clinic Cancer Center (MCCC) Institutions: Provide copies, along with the UPIRTSO cover sheet, by fax ([redacted]) to the MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist who will determine and complete IRB reporting. The RAU will submit to the MCCC SAE Coordinator and the MCCC IND Coordinator to determine if FDA submission is needed

10.41 Special Situations for Expedited Reporting

Exceptions to Expedited Reporting: EXPECTED Serious Adverse Events

An expedited report may not be required for specific Grade 1, 2, 3 and 4 Serious Adverse Events where the AE is EXPECTED. Any protocol specific reporting procedures MUST BE SPECIFIED BELOW and will supercede the standard Expedited Adverse Event Reporting Requirements. Note: These adverse events must still be reported through the routine reporting mechanism [i.e. Nadir/Adverse Events Form]; see footnote 1.

CTCAE Category	Adverse Event	CTCAE Grade
Blood and lymphatic system disorders	Anemia	3 or 4
Investigations	Platelet count decreased	3 or 4
	Neutrophil count decreased	3 or 4
	Lymphocyte count decreased	3 or 4

	White blood cell decreased	3 or 4

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators ONLY if they exceed the expected grade of the event.

10.5 Other Required Reporting

10.51 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormities or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.52 Death

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

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

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE need to be reported. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

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

10.55 **Reporting of Pregnancy and Lactation to the Cancer Center Compliance Unit and to Merck**

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to Cancer Center Compliance Unit at [redacted] and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; [redacted])

10.6 Required Routine Reporting

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

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Investigations	Platelet count decreased*	X	X
	Neutrophil count decreased	X	X
Blood and lymphatic system disorders	Anemia*	X	X
Gastrointestinal disorders	# of stools	X	
	Diarrhea		X
	Nausea	X	X
	Vomiting	X	X
Respiratory, thoracic and mediastinal disorders	Cough	X	X
	Dyspnea	X	X
	Pneumonitis	X	X
Skin and subcutaneous tissue disorders	Rash maculo-papular	X	X

* Grading will be performed by the study statisticians at the time of analysis based on the CLL toxicity grading scale for blood counts in Appendix IV. CTCAE grades for platelet count decreased and anemia will also be recorded for reporting purposes.

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

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

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

10.613 Grade 5 AEs (Deaths)

10.6131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6132 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

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

11.0 Treatment Evaluation

Response will be evaluated after approximately 3, 6, and 12 months of single or combination treatment. (Note: Disease measurements obtained after the last cycle of single-agent therapy are set as the baseline measurements for the combination therapy phase.) If the patient remains on cycles with a length of 21 days without treatment delays, this will be at the end of cycles 4, 9, and 17 (approximately days 84, 189, and 357). If the cycle length is increased due to dosing frequency changes or dose delays occur, the response evaluations should occur where the end of the cycles are closest to 3, 6, and 12 months (days 92, 183, and 365), keeping in mind that this may occur before 3, 6, or 12 months. Response evaluation at 3, 6, and 12-month time points unless treatment has been stopped/completed and then the response evaluation can be performed between 2-8 weeks after last therapy.

Arm A : CLL/SLL patients without Richter's transformation or Hodgkin transformation

Note: For CLL patients with Richter's transformation or Hodgkin transformation, see Section 11.5 (Arm A) or Section 11.6 (Arm C) for response evaluation for the transformed (lymphoma) phase of the disease, but their CLL phase of the disease will still be evaluated based on Section 11.1-4.

Note: Formal response evaluation should occur at the end of 3, 6, and 12 months with the first response evaluation occurring at the end of cycle 4 and before the start of cycle 5 or at the end of the cycle closest to 3 months of therapy, whichever occurs first. Objective status should be classified as PD vs. Not PD on cycles when a formal response evaluation does not occur.

11.1 Schedule of evaluations: For the purposes of this study, patients should be reevaluated for progression during each cycle assessment during the first 3 months of therapy with MK3475. After 3 months, patients who do not have evidence of PD or SD will continue on therapy and these patients will be evaluated for disease progression every other cycle. Formal response evaluation will occur at 3, 6, and 12 months since therapy start. For patients who discontinued the therapy due to adverse events, but have received at least 3 cycles of therapy and do not have evidence of PD, they should have formal response evaluation at about 2-8 weeks after the last dose of therapy or at the 3, 6, and 12-month time point since therapy start which ever occurs first. Prior to the first formal response evaluation, baseline on study measurements will be used to determine disease progression (e.g. **not** cycle by cycle comparisons). Once patients undergo formal response evaluation, the nadir value at either baseline or time of response evaluation will be used for evaluating future disease progression. In addition to a baseline scan, confirmatory scans should also be obtained as needed to document objective response at sites of non-palpable lymphadenopathy or organomegaly as indicated in Section 4 or as needed clinically.

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

11.2 Definitions

The NCI Working Group criteria (Hallek, 2008) will be used to assess response to therapy.

11.21 COMPLETE RESPONSE (CR) requires all of the following for a period of at least

2 months. The first formal response evaluation for CR should occur no sooner than the end of cycle 3.

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

11.212 No hepatomegaly or splenomegaly by physical examination.

11.213 Absence of constitutional symptoms.

11.214 CBC demonstrating:

- Neutrophils >1500/ul.
- Platelets >100,000/ul (untransfused).
- Hemoglobin >11.0 gm/dl (untransfused).
- Peripheral blood lymphocytes <4000/uL.

Note: Patients who fulfill all criteria for a CR but who have a persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity rather than residual CLL will be classified as **CR with incomplete marrow recovery (CRi)** according to the international criteria (Hallek, 2008).

11.215 Bone marrow aspirate and biopsy should be performed at the end of the cycle closest to 6 months or 12 months of therapy or at the same time for response evaluation for patients who received ≥ 3 cycles of treatment and are off therapy due to AE (see note in section 4.0), which ever occurred sooner. The marrow sample should ideally be at least normocellular with <30% of nucleated cells being lymphocytes. Samples are to be analyzed by a pathologist and the presence or absence of nodules noted. Repeat bone marrow aspirate and biopsy are not necessary to document sustained CR.

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

In a subset of patients who are otherwise in a complete response, bone marrow nodules can be identified histologically. In such cases, special stains will be performed to determine whether such nodules represent "regenerative nodules" or residual "clonal nodules". The presence of regenerative nodules is consistent with CR while the presence of residual clonal nodules will be classified as an **nPR (nodular PR)** which is a sub-classification of PR. Per the PR criteria, patients must fulfill one or more of the blood count parameters (Section 11.224, 11.225, 11.226) but are not required to meet all 3 of these conditions.

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

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

response but will be recorded for clinical correlations.

11.218 For patients whose only measurable disease at the time of enrollment is on CT scan (i.e. SLL with no palpable nodes), a CT scan showing absence of lymphadenopathy (e.g. lymph nodes >1.5 cm) is required before classifying patients a CR.

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

11.221 ≥50% decrease in peripheral blood lymphocyte count from the pretreatment baseline value.

11.222 ≥50% reduction in the sum of the products of the maximal perpendicular diameters of the largest measured node or nodal masses in the right and left cervical, axillary, and inguinal lymph node regions on physical examination.

11.223 ≥50% reduction in size of liver and/or spleen as measured by physical exam noting the maximal distance below the respective costal margins of palpable hepatosplenomegaly during rest.

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

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

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

11.227 For patients whose only measurable disease at the time of enrollment is on CT scan (i.e. SLL with no palpable nodes), a CT scan demonstrating > 50% reduction of target nodes enlarged at baseline is required before classifying patients a PR.

11.228 For patients whose only measurable disease at the time of enrollment is on CT scan (i.e. SLL with no palpable nodes), a CT scan is required before classifying patients PR.

11.23 PROGRESSION (PD):

11.231 Patients will receive protocol therapy unless they have evidence of disease progression according to the NCI criteria (Hallek, Cheson et al. 2008) as evidenced by: ≥ 50% increase in the sum of the products of at least 2 lymph nodes on 2 consecutive determinations 4 weeks apart (at least one node must be ≥2 cm) or the appearance of new palpable lymph nodes >1.5 cm not due to a tumor flare for lasting more than 4 weeks. Enlargements or the appearance of new nodes due to a tumor flare do NOT qualify as progression.

11.232 ≥ 50% increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin on 2 consecutive determinations 4 weeks apart and with a minimum of a ≥ 2 cm increase in size from baseline; or appearance of hepatomegaly or splenomegaly which was not previously present at baseline and not due to a tumor flare on 2 consecutive determinations 4 weeks apart

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

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

11.234 ≥ 50% increase in the absolute number of circulating lymphocytes NOT due to infection or tumor flare or reactive process to complications or potential clinical response associated with novel therapies **for at least 2 different time points at least 4 weeks apart** (taking as reference for progressive disease the smallest absolute lymphocyte count recorded since the treatment started). The absolute lymphocyte count must be at least 5000/mm^3 to qualify as potential disease progression. The increase of absolute lymphocyte count also has to be associated with increase of either lymph node or spleen/liver size for at least 2 different occasions at least 4 weeks apart.

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

11.236 In the case where progression is confirmed on at least 2 occasions at least 4 weeks apart, the objective status will be entered as unconfirmed progression (uPD) on the measurement form at the time this criteria is first met. Once this criteria is confirmed at least 4 weeks later, the objective status will be entered as PD. If confirmed, the date of first evidence of progression (date of first uPD) will be considered the progression date (and should be entered on the event monitoring form).

11.237 Patients whose only evidence of disease recurrence is by sensitive evaluation of MRD will NOT be considered PD.

11.24 STABLE DISEASE (SD): Patients who do not meet criteria for CR, CRi, nPR, CCR, PR, or PD will be classified as having "stable disease". The first formal response evaluation should occur no sooner than the end of cycle 3.

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

Note: Formal response evaluation should occur at 3, 6, and 12 months with the first response evaluation occurring at the end of cycle 4 or at the end of the cycle closest to 3 months of therapy, whichever occurred earlier. For patients who have received more than 2 cycles of treatment and off therapy due to AE, they should have formal response evaluation between 2-8 weeks from the last therapy as long as they do not have evidence of PD. Objective status should be classified as PD vs. Not PD on cycles when a formal response evaluation does not occur.

11.3 EVALUATION OF MINIMAL RESIDUAL DISEASE (MRD): An important aspect of this trial is evaluation of minimal residual disease using a sensitive flow cytometry method capable of detecting approximately 1 CLL cell per 10,000 leukocytes following induction.

An International, standardized approach for flow cytometric evaluation of residual disease in patients with CLL was recently developed (Rawstron, Villamor et al. 2006). This approach reliably detects residual CLL B-cells at the level of 1 leukemic cell per 10,000 leukocytes. Notably, analysis of peripheral blood was equally or more sensitive to marrow in 92% of samples except when patients had received treatment with monoclonal antibodies within 3 months of evaluation.

This approach uses a pre-antibody ammonium chloride red cell lysis approach to separate peripheral blood white blood cells from RBCs followed by staining of 1-2 x 10^6 leukocytes with a panel of antibodies for flow cytometry analysis. For each test, 300,000 to 500,000 events were collected to ensure the desired sensitivity of the assay.

While the 4 color based strategy was the standard proposed by the international group, 5- to even 8-color flow cytometry based assays are being used in many laboratories and are expected to have a similar degree of sensitivity (level of 1 leukemic cell per 10,000 leucocytes) while enhancing the accuracy of the assay.

These assessments for MRD in the present study will be conducted in the Mayo Clinic's campus in Rochester Department of Hematopathology under the direction of [redacted] using a flow cytometry strategy able to detect residual leukemia at the level of 1 leukemic cell per 10,000 leukocytes in accord with the International Standard (Rawstron, Villamor et al. 2006). The antibody panel includes: CD45, CD19, CD20, CD5, and anti-kappa and anti-lambda immunoglobulin light chains. For each test, 300,000 to 500,000 events are collected to ensure the desired sensitivity of the assay.

All patients with evidence of response (CR, CRi, CCR, nPR) will undergo assessment of MRD using sensitive flow cytometry at the completion of MK3475 therapy. If bone marrow samples are available, marrow MRD testing is preferred.

11.4 Summary Definition of objective response for patients with B–CLL/SLL

	CCR[1]	CR[2, 9]	CRi[3, 9]	nPR[4, 9]	PR[5]	PD[6]
Physical Exam						
Nodes[7]	None	None	None	None	≥50% ↓	≥50% ↑, new nodes
Liver/spleen[8]	Not palpable	Not palpable	Not palpable	Not palpable	≥50% ↓	≥50% ↑, newly palpable
Symptoms	None	None	None	None	N/A	N/A
PERIPHERAL BLOOD						
ANC	>1500/µL	>1500/µL	See footnote 3	>1500/µL or >50% improvement from baseline	>1500/µL or >50% improvement from baseline	See footnote 6
Platelets	>100,000/µL	>100,000/µL	See footnote 3	>100,000/µL or >50% improvement from baseline	>100,00/µL or >50% improvement from baseline	Decrease of ≥ 50% from baseline secondary to CLL See footnote 6
Hemoglobin	>11.0 g/dL without transfusion	>11.0 g/dL without transfusion	See footnote 3	>11.0 g/dL or >50% improvement from baseline without transfusion	>11.0 g/dL or >50% improvement from baseline without transfusion	Decrease ≥ 2g/dL from baseline secondary to CLL See footnote 6
Lymphocytes	<4000/µL	<4000/µL	<4000/µL	<4000/µL	≥50% ↓	≥50% ↑ to at least 5,000/µL due to clear progression, not other reasons
BONE MARROW	N/A	Normocellular[3]; <30% lymphocytes; no nodules	<30% lymphocytes; no nodules	<30% lymphocytes; bone marrow nodules[4]	N/A	N/A

1. Clinical complete response (CCR) requires fulfillment of all physical exam and peripheral blood criteria as noted in the table above. No bone marrow biopsy is required to call a patient a CCR; however, patients should have a bone marrow around the same time of the formal response evaluation as instructed in the test schedule to confirm CR.
2. Complete response (CR) requires fulfillment of all physical exam and peripheral blood criteria for a duration of ≥2 months. A bone marrow aspirate and biopsy are required to document the response as a complete within one month of the formal response evaluation where clinical and laboratory evidence of complete response was first seen (see Section 11.21).
3. Patients who fulfill all criteria for a CR but who have a persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity rather than residual CLL or have hypocellular marrow will be classified as CR with incomplete marrow recovery (CRi).
4. Nodular partial response (nPR) is essentially a patient in who it appeared that CR had been obtained but nodules are present in the bone marrow. It requires fulfillment of all physical exam and lymphocyte criteria for CR; however, when the bone marrow is done to confirm CR, nodules of malignant lymphocytes are found. Patients must fulfill one or more of the blood count parameters (ANC, Platelets, Hemoglobin) but are not required to meet all 3 of these conditions. See Section 11.215 regarding the distinction between clonal and regenerative nodules.
5. Partial response (PR) requires fulfillment of at least two of the above-noted decrease in circulating lymphocytes, regression in adenopathy and regression in hepatosplenomegaly, and at least one other parameter listed above for a duration of ≥ 2 months. See Section 11.22.
6. Progression: Fulfilling the criteria as noted in section 11.23. Prior to the formal response evaluation, baseline on study measurements will be used to determine disease progression (e.g. not cycle by cycle comparisons). Once patients undergo formal response evaluation, the nadir value at either baseline or time of response will be used for evaluating future disease progression. In the absence of other indices of clinical progression, the presence of a ≥2 g/dL decrease in hemoglobin or a ≥50% decrease in platelet count and/or absolute neutrophil count will not exclude a patient from continuing on the study. Although not mandatory, bone marrow aspirate and biopsy are strongly encouraged to better define the cause of the suppressed counts (i.e. treatment- versus disease-related). In case worse cytopenia is secondary to CLL marrow progression, this is confirmed PD. In the case where progression due to nodal progression is confirmed on at least 2 occasions at least 4 weeks apart, the objective status will be entered as unconfirmed progression (uPD) on the measurement form at the time this criteria is first met. Once this criteria is confirmed at least 4 weeks later, the objective status will be entered as PD. If confirmed, the date of first evidence of progression (date of first uPD) will be considered the progression date (and should be entered on the event monitoring form).
7. Measurement of lymphadenopathy will be determined on physical exam by adding the sum of the products of the maximal perpendicular diameters of measured lesion(s). No simultaneous increase in the size of any lesions or the appearance of any new lesions may occur for more than 2 consecutive cycles. Minor fluctuations are acceptable as long as they don't exceed 50% of previous measurement. However, if they do exceed 50% of the previous measurement it should be held for 2 consecutive cycles to rule out the possibility of nodes that wax and wane. For purposes of determining CCR and nPR, all nodes on physical exam need to be ≤1.5 cm in maximal dimension or documented to be free of CLL by biopsy. NOTE: Information from CT scans regarding lymphadenopathy is not considered in the standard classification of response with the exception of the patients fitting criteria of section 11.218 and 11.228.
8. Measurement of hepatosplenomegaly will be determined by noting the maximal distance below the respective costal margins of palpable hepatosplenomegaly during rest (e.g., not during deep inspiration). NOTE: Information from CT scans regarding hepatosplenomegaly is not considered in the standard classification of response with the exception of the patients fitting criteria of section 11.218 and 11.228.

Note : See Section 11.7 for patients on Arm B with Waldenstrom macroglobulinemia

11.5 Arm B: Low grade NHL patients

Response Considerations

Definitions for clinical response for patients with lymphoma are from the Cheson et al. Revised Response Criteria for Malignant Lymphoma (Cheson, Pfistner et al. 2007). Lymph node measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. Measurement of lymphadenopathy will be determined by adding the sum of the products of the maximal perpendicular diameters of measured lesions (SPD). Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically and pathologically negative. Disease assessable by physical exam only (e.g. skin lymphoma) will be recorded as either measurable diseases using targeted lesions or photography at the baseline and subsequent visits for response assessment.

Response is based on CT alone or the CT component of PET/CT or MRI where applicable and the PET.

PET/CT scans are required at baseline for all Follicular lymphoma grade 3

Follicular lymphoma grade 3 PET scans are required at response assessments for these patients. These patients should be followed by the FDG-avid or PET positive criteria (part a).

Follicular lymphoma grade 1 or 2 and marginal zone lymphoma: Response will be determined by CT (PET/CT or dedicated CT). These patients should be followed by the variably FDG-avid or PET negative criteria (part b).

Waldenstrom macroglobulinemia: For patients with Waldenstrom macroglobulinemia, response will be assessed according to Section 11.6.

Response criteria, modified from Cheson et al. 2007.

Response Category	Definition	Nodal Masses[1]	Spleen, liver	Bone Marrow
CR	Disappearance of all evidence of disease.	a) FDG-avid or PET positive prior to therapy: Mass of any size permitted if PET negative b) Variably FDG-avid or PET negative: Regression to normal size on CT or resolve of measurable disease by physical exam only (e.g. skin lymphoma)	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses or ≥50% decrease of other measurements (e.g. skin lymphoma) only measurable by physical exam; no increase in size of other nodes and a) or b): a) FDG-avid or PET positive prior to therapy: one or more PET positive at previously involved sites b) Variably FDG-avid or PET negative: regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	a) FDG-avid or PET positive prior to therapy: PET positive at prior sites of disease and no new sites on CT or PET b) Variably FDG-avid or PET negative: no change in size of previous lesions on CT		
Relapse/ Progressive disease [2]	Any new lesion or increase by ≥50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥50% increase from nadir in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node > 1 cm in short axis not due to tumor flare and persistent for 4 weeks apart. Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy persistent for 4 weeks apart	> 50% increase from nadir in the SPD of any previous lesions not due to tumor flare and persistent for 4 weeks apart.	New or recurrent involvement

Abbreviations: CR, complete response; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial response; SPD, sum of the product of the diameters; STAB, stable disease; PD, progressive disease.

[1] Patients will be assessed by part a or part b as specified in section 11.5. For patients with predominant skin lymphoma, skin disease should be recorded as photograph or measurable diseases as targeted lesions. Please refer to published guideline{Olsen, 2011 #547}.
[2] In the case where progression is confirmed on at least 2 occasions at least 4 weeks apart, the objective status will be entered as unconfirmed progression (uPD) on the measurement form at the time this criterion is first met. Once this criterion is confirmed at least 4 weeks later, the objective status will be entered as PD. If confirmed, the date of first evidence of progression (date of first uPD) will be considered the progression date (and should be entered on the event monitoring form).

11.51 **Complete Response (CR)**. The designation of CR requires all of the following:

11.511 Complete disappearance of all detectable clinical evidence of disease and definitely disease-related symptoms if present before therapy.

11.512 Patients will be assessed by part a or part b as specified in section 11.5.

a) In patients with pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

b) In patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (≤1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤1.0 cm in their short axis after treatment. For patients with only skin involvement, these same criteria apply to skin lesions photographed and measured with a ruler with images maintained in the medical record.

c) Resolve of measurable disease by physical exam only (e.g. skin lymphoma).

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

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

11.52 **Criteria for Partial Response (PR)**. The designation of PR requires all of the following:

11.521 At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following:

- they should be clearly measurable in at least 2 perpendicular dimensions
- if possible they should be from disparate regions of the body
- they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved or ≥.50% decrease of other measurements (e.g. skin lymphoma) only measurable by physical exam {Olsen, 2011 #547}
- ≥50% decrease of other measurements (e.g. skin lymphoma) only measurable by physical exam

11.522 No increase should be observed in the size of other nodes, liver, or spleen.

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

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

11.525 Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.
When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

11.526 No new sites of disease should be observed.

11.527 Patients will be assessed by part a or part b as specified in section 11.5.

a) For patients with pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.

In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.b) For patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used (except in patients with only skin involvement where skin lesions are photographed and measured with a ruler).

11.53 Criteria for Stable Disease (STAB)

11.531 A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR (see above), but does not fulfill those for

progressive disease (see below).

11.532 Patients will be assessed by part a or part b as specified in section 11.5.

a) The PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

b) For patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan (or on ruler measurements for patients with only skin involvement).

11.54 **Relapsed Disease (after CR)/Progressive Disease (after PR, SD):** Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes ≤1.0 x ≤1.0 cm will not be considered as abnormal for relapse or progressive disease.

11.541 Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy for at least 4 weeks apart, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities to be persistent. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation. Tumor flare reactions should be ruled out.

11.542 At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis. The above changes have to be persistent for 4 weeks apart not due to tumor flare reaction.

11.543 At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis. The above changes have to be persistent for 4 weeks apart. Tumor flare reactions should be ruled out.

11.544 If patient is being assessed by part a as specified in section 11.5: Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

11.545 Transformation to a more aggressive histology

11.546 In the case where progression is confirmed on at least 2 occasions at least 4 weeks apart, the objective status will be entered as unconfirmed progression (uPD) on the measurement form at the time this criterion is first met. Once this criterion is confirmed at least 4 weeks later, the objective status will be entered as PD. If confirmed, the date of first evidence of progression (date of first uPD) will be considered the progression date (and should be entered on the event monitoring form).

11.6 Arm C and Arm A for CLL patients with Richter's transformation

Response Considerations

Schedule of Evaluations: PET/CT scans are required at baseline for all patients. In addition to a baseline PET/CT scan, scans should also be obtained to assess clinical responses after 3, 6, and 12 months of therapy or when it is clinically needed by treating physician.
Definitions for clinical response for patients with lymphoma are from the recently revised Cheson's et al criteria published in 2014, derived from the original criteria published in 2007. (Cheson et al, 2014)(Cheson et al, 2007). Lymph node measurements should be taken from the CT portion of the PET/CT, or other dedicated CT scans where applicable. Measurement of lymphadenopathy for purposes of assessing for PR will be determined by adding the sum of the products of the maximal perpendicular diameters of measured lesions (SPD). The PPD of a single node is sufficient to evaluate for PD (see Table 11.61). Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically and pathologically negative.

Response is based on PET/CT based on the revised 2014 Lugano Classification. (Cheson et al, 2014).

Progressive disease is based on either PET-CT based (PMD) or CT based (PD) response criteria if PET is not available. PET confirmation of progressive disease is per physician discretion.

11.61 Lugano Classification Response criteria (Cheson et al, 2014)

	PET-CT Based Response	CT-Based Response
Complete Response	Complete metabolic response (CMR)	Complete radiologic response (CR) (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial Response	Partial metabolic response (PMR)	Partial remission (PR) (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm X 5 mm as the default value When no longer visible, 0 X 0 mm For a node > 5 mm X 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI	Not Applicable

	or biopsy or an interval scan	
No Response or Stable Disease	No metabolic response (NMR)	Stable disease (SD)
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not Applicable
Progressive disease	Progressive metabolic disease (PMD)	Progressive disease (PD) requires at least 1 of the following
Individual target nodes/nodal masses Extranodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	PPD progression: An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.
*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).
†PET Deauville 5PS: 1, no uptake above background; 2, uptake≤mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

11.7 Arm B: Waldenstrom Macroglobulinemia

Response considerations

11.71 Patients will be formally evaluated for response each cycle using the following criteria:

Table 11.71
Summary of Updated Response Criteria From the Third International Workshop on Waldenström's Macroglobulinemia

Response	Criteria
Complete response	Disappearance of monoclonal protein by immunofixation; no histologic evidence of bone marrow involvement and resolution of any adenopathy/organomegaly (confirmed by CT scan), along with no signs or symptoms attributable to WM; reconfirmation of the complete response status is required at least 6 weeks apart with a second immunofixation
Partial response	A ≥50% reduction from baseline of serum monoclonal IgM concentration on protein electrophoresis and ≥50% decrease in adenopathy/organomegaly on physical examination or on CT scan (if adenopathy/organomegaly present at baseline); no new symptoms or signs of active disease
Minor response	A ≥25% but < 50% reduction from baseline of serum monoclonal IgM by protein electrophoresis; no new symptoms or signs of active disease
Stable disease	A < 25% reduction and < 25% increase from baseline of serum monoclonal IgM by electrophoresis without progression of adenopathy/organomegaly, cytopenias, or clinically significant symptoms caused by disease and/or

	signs of WM
Progressive disease [1]	A ≥25% increase from nadir in serum monoclonal IgM by protein electrophoresis confirmed by a second measurement 4 weeks apart or progression of clinically significant findings as a result of disease (i.e., anemia, thrombocytopenia, leukopenia, bulky adenopathy/organomegaly) or symptoms attributable to WM (unexplained recurrent fever ≥38.4°C, drenching night sweats, ≥10% body weight loss, hyperviscosity, neuropathy, symptomatic cryoglobulinemia, or amyloidosis) Transformation to a more aggressive histology

NOTE. Data from Kimby E, Treon SP, Anagnostopoulos A, et al. Clin Lymphoma Myeloma 6:380-383, 2006.

[1] In the case where progression is confirmed on at least 2 occasions at least 4 weeks apart, the objective status will be entered as unconfirmed progression (uPD) on the measurement form at the time this criteria is first met. Once this criteria is confirmed at least 4 weeks later, the objective status will be entered as PD. If confirmed, the date of first evidence of progression (date of first uPD) will be considered the progression date (and should be entered on the event monitoring form).

12.0 Descriptive Factors

12.1 CLL Patients

12.11 Rai Stage: 0 vs. 1 vs. 2 vs. 3 vs. 4.

12.12 $CD38^+$ expression: Positive (≥30%) vs. negative (<30%).

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

12.14 IGHV mutation status: Mutated (≥2%) vs. unmutated (<2%) vs. indeterminate.

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

12.16 CD49d expression: Positive (≥45%) vs. negative (<45%).

12.17 Richter transformation: yes vs. no.

12.18 Hodgkin transformation: yes vs. no.

12.19a Prior Ibrutinib therapy: yes or no; if yes, progressed on Ibrutinib: yes or no

12.19b Prior Idelalisib therapy: yes or no; if yes, progressed on Idelalisib: yes or no

12.2 NHL patients

12.21 Histology category: Follicular Lymphoma vs. Lymphoplasmacytic Lymphoma vs. Marginal zone lymphoma.

12.22 Prior Anti-PD-1 or Anti PDL-1 agent: Yes vs. No.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

NOTE: Per addendum 3, for patients with Richter's transformation, treatment and follow-up decision will be based on the Richter's response criteria.

13.1 Arm A and Arm C: If the patient develops progressive disease (not tumor flare) at any time while on single-agent (MK-3475) therapy, or has stable disease without partial remission at the response evaluation at months 3 of the single-agent (MK-3475) therapy, a commercially available signal inhibitor can be added to MK-3475 (remain at the dose 200 mg IV every 3 weeks). If the patient develops PMD/PD at any time during active treatment with the combination of MK-3475 and a signal inhibitor or patient refuses all further study participation including refusal of observation, study treatment will be discontinued and the patient will go directly to EVENT MONITORING. Refer to Section 4.0 for required tests at PMD/PD. Patients will then be followed in event monitoring per Section 18.0.

13.2 Arm B : If the patient develops PD at any time during active treatment or patient refuses all further study participation including refusal of observation, study treatment will be discontinued and the patient will go directly to EVENT MONITORING. Refer to Section 4.0 for required tests at PD. Patients will then be followed in event monitoring per Section 18.0.

13.3 Patients not progressing on active treatment and tolerating the therapy will continue treatment per protocol for 12 months. If patient is continuing to benefit from MK-3475 treatment after 12 months, they may continue to receive treatment up to 24 months at investigator/sponsor discretion.

13.4 Observation: During observation patients will be seen every 3 months according to the test schedule in Section 4.0 for up to one year. When a subject discontinues treatment, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 10.0 - Assessing and Recording Adverse Events. Patients will discontinue study treatment and go to observation for the following reasons:

- Completion of 12 months or more therapy of MK3475 or combination treatment as determined by investigator/sponsor discretion
- An unacceptable adverse event that occurs after the patient received at least 2 cycles of treatment, which in the opinion of the Investigator, precludes further trial participation.

13.5 Event Monitoring: Patients will enter event monitoring for the following reasons:

- If the patient develops evidence of PMD/PD (For CLL Arm A and C: PMD/PD on combination therapy; For B-NHL Arm B: PD on MK-3475 single therapy) during treatment or OBSERVATION by examination, blood counts, or imaging as defined in Sections 11.23, 11.4, 11.54 and 11.61, they will be considered to have progressed and will enter EVENT MONITORING. Refer to Section 4.0 for required tests at PMD/PD.

NOTE: Patients whose only evidence of disease recurrence is by sensitive evaluation of MRD will continue under OBSERVATION in accord with standard clinical practice and will NOT be considered PD.

- Subsequent treatment for CLL or NHL
- Failure to return for an evaluation during OBSERVATION
- Patient refusal of further study treatment or noncompliance
- Patient develops an intercurrent illness that precludes further participation, or requires a prohibited concomitant treatment
- The Investigator withdraws the patient in the patient's best interests
- Administrative reasons (e.g., the patient is transferred to hospice care)
- Pregnancy
- An unacceptable adverse event that occurs during cycles 1-2

Note: When a subject discontinues treatment, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 10.0 -Assessing and Recording Adverse Events

13.6 A patient is deemed ineligible if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient will go directly to the event-monitoring phase of the study:

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

13.7 A patient is deemed a major violation, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study.

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

14.0 Body Fluid Biospecimens

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

14.11 Samples collected for correlative studies for patients on single-agent MK-4375 therapy for B-NHL and CLL arm (all three arms)

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Baseline	Prior to cycle 2[2]	Prior to cycle 3[2]	At 3 month visit[2]	At 6 and 12 month visit[2]	At 18 and 24 month visit[2]	At Disease Progression
Bone marrow aspirate	Mandatory	Bone marrow aspirate	ACD (yellow top)	6 mL (1 tube)	X[1]				X[1]		
Peripheral Blood	Mandatory	Whole blood	EDTA (purple top)	10ml (1 tube)	X	X	X	X	X	X	X
Peripheral Blood	Mandatory	Whole blood	Heparin (green top)	10ml (6 tubes)	X	X	X	X	X	X	X
Peripheral Blood	Mandatory	Whole blood	No anticoagulant (red top)	10 ml (1 tube)	X	X	X	X	X	X	X

1. Only obtained when the clinical bone marrow is needed. Bone marrow samples can be collected ≤ 90 days prior to registration. If bone marrow was performed prior to consenting the patient for this study, a repeat bone marrow is not required to obtain the research aspirate sample at baseline.
2. - 2 days to +7, the 18 and 24 month blood samples are only required for patients who continue therapy beyond 12 months

14.12 Samples collected for correlative studies for CLL patients on combination therapy of a signal inhibitor (Ibrutinib or Idelalisib) with MK-3475 (CLL Arm A and C only)

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Prior to 2nd cycle of the combination therapy[2]	Prior to 3rd cycle of the combination therapy[2]	At 3 month visit of the combination therapy[2]	At 6 and 12 month visit of the combination therapy[2]	At 18 and 24 month visit of the combination therapy[2]	At Disease Progression
Bone marrow aspirate	Mandatory	Bone marrow aspirate	ACD (yellow top)	6 mL (1 tube)				X[1]		
Peripheral Blood	Mandatory	Whole blood	EDTA (purple top)	10ml (1 tube)	X	X	X	X	X	X
Peripheral Blood	Mandatory	Whole blood	Heparin (green top)	10ml (6 tubes)	X	X	X	X	X	X
Peripheral Blood	Mandatory	Whole blood	No anticoagulant (red top)	10 ml (1 tube)	X	X	X	X	X	X

[1] Only obtained when the clinical bone marrow is needed.

[2] Days to +7, the 18 and 24 month blood samples are only required for patients who continue therapy beyond 12 month

14.2 Collection and Processing

Processing for the Blood and Marrow samples

Collection tube description and/or additive (color of tube top)	Component Available	Cell Surface Markers (Flow Cytometry)	DNA	Banking
EDTA (purple)	Plasma			X
EDTA (purple)	DNA		X	X
Na Heparin (green)	PBMCs	X		X
No anticoagulant (red)	serum			X
ACD (yellow)	Plasma (marrow)			X
ACD (yellow)	PBMCs (marrow)	X		X

Note: All collection tubes need to be labeled with the protocol number, patient initials (last name, first name), study patient ID number (if available), specimen type (bone marrow or peripheral blood) and date of collection as well as the arm of the study (A or B or C).

14.3 Shipping and Handling

14.31 Kits will be provided for non-Mayo Rochester sites for the samples collected in Section 14.1 .

The kit contains supplies and instructions for collecting, processing, and shipping specimens.

Participating institutions may obtain kits by e-mailing [redacted]. E-mail requests should include the site address, contact information and number of kits being requested.

Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. **Allow 3 to 4 business days to receive the kits.**

14.32 Label specimen tubes with the protocol number, patient initials (last name, first name), study patient ID number (if available), specimen type (bone marrow or peripheral blood) and date of collection, as well as the arm of the study (A or B or C)

14.33 Collect all specimens according to instructions in Appendix V and table above.

14.34 Shipping

Specimens must be shipped the same day they are drawn.

Ship the bone marrow and peripheral blood tubes in the kit provided. No cold pack is required. The Fed Ex air bill is pre-addressed and provided in the kit.

Ship specimens via Priority Overnight service on **Monday – Thursday Preferred** (Friday only if you must) directly to:

[redacted]

Please email [redacted] to notify the laboratory when specimens are being shipped. The message should include the study name, sample type, Fed Ex air bill tracking number, contact name and telephone number.

Shipping costs will be covered by the study if these kits and Fed Ex air bills are used for shipping specimens. Each kit contains the required tubes.

14.4 Background and Methodology

Blood/Marrow product samples will be collected for protocol specific research (see Section 2.3).

14.41 Plasma and PBMC isolated from the enrolled patients collected at baseline, prior to Cycles 2 and 3, at 3, 6 and 12 months and disease progression will be stored for biomarker analysis of soluble and cell surface PD-L1 expression to correlate with clinical response to the therapy.

14.42 Peripheral blood mononuclear cells will be isolated from the whole blood of the patients at baseline, prior to cycle 2 and 3, at 3, 6 month and 12 month, at disease progression. They will be stored for later use of analysis of immune profiles for T, B and NK, monocyte subsets.

14.43 Exome mutation in tumor and T cell repertoire, as well as single nucleotide polymorphisms (SNPs) in host immune genes: Genomic DNA from patients at on study will be obtained from peripheral blood or paraffin block/slides (Section 17.0) and cryopreserved. We have previously demonstrated our ability to analyze ES and SNPs in patients with lymphoma. For example, Cerhan et al. (Blood 109: 5439 - 46) demonstrated that host gene SNP profiles could predict prognosis in follicular lymphoma. This information is not yet available for CLL; therefore we will study that in this protocol. Genomic DNA samples will be batched and analyzed in the Mayo Clinic Cancer Center Genotyping Shared Resource.

14.44 Flow cytometry: $1x10^6$ cells will be washed in phosphate-buffered saline (PBS) containing 0.5% bovine serum albumin (BSA), incubated with specific antibodies to the marker in question and analyzed on a FACSCalibur flow cytometry (Becton-Dickinson). Isotype controls will be done for each sample.

Multiple surface and intracellular antigens will be analyzed using flow cytometric method. Apoptosis status of the leukemic cells will also be analyzed. CD38, ZAP-70 and CD49d status will be determined by flow cytometric method.

14.45 Plasma from the enrolled patients will be stored for future study of multiplex cytokine, biomarker analysis and microvesicle analysis.

14.46 RNA will also be isolated from CLL PBMC and stored for future use of analysis of gene expression profiling of the involved signal pathways. IGHV status will be assessed using RNA from CLL B-cells using previously described methods (Jelinek Br J Haematol.115 (4):854-61)

14.47 Peripheral blood CLL FISH panel (CLL/SLL arm only): may be performed using a portion of the research samples if not performed clinically.

14.5 Residual specimens: A portion of the plasma, DNA, RNA, bone marrow aspirates and white blood cells will initially be analyzed as described in 14.41. After the above correlative studies are completed and according to patient consent information (see Section 6.34), remaining blood products will be transferred to [redacted] and stored frozen by [redacted] laboratory until specific analyses are identified. Future research that is in the area of the studies outlined above will not require resubmission to the IRB; however, if a new use of the tissue or blood is requested, then this request will be presented for IRB review and approval.

15.0 Drug Information

15.1 Pembrolizumab (MK-3475, SCH 900475, Keytruda®)

15.11 **Background**: Pembrolizumab is a potent humanized IgG4 monoclonal antibody with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1.

15.12 **Formulation**: Pembrolizumab is available as a liquid 25 mg/mL, 100 mg/vial.

15.13 **Preparation and storage**: Vials should be stored in the refrigerator at temperatures between 2-8°C.

Drug concentrate is further diluted with normal saline (or 5% dextrose in the concentration range of 1 to 10 mg/mL). The infusion solution in the IV bag should be immediately administered. Diluted pembrolizumab solutions may be stored at room temperature for a cumulative period of up to 6 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. The product can also be stored under refrigeration at 2°C to 8°C for no more than 96 hours from the time of dilution. If refrigerated, the diluted solution must be allowed to come to room temperature prior to administration. The solution must be discarded after 6 hours at room temperature or 96 hours under refrigeration

15.14 **Administration:** Pembrolizumab is administered by intravenous infusion over 30 minutes via a 0.22 micron in-line filter. The final infusion volume must be between 1 and 10 mg/mL. Maximum rate of infusion should not exceed 6.7 mL/minute through a peripheral or indwelling catheter. Flush the line with 0.9% NaCL following the completion of the infusion.

15.15 Pharmacokinetic information:

a) Absorption – Because pembrolizumab is administered intravenously, it is immediately and completely bioavailable. Steady -state concentrations of pembrolizumab are reached by 16 weeks of repeated dosing with a Q3W regimen and the systemic accumulation is 2.1-fold. The peak concentration, trough concentration, and area under the plasma concentration versus time curve at steady state of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg Q3W.
b) Distribution – Pembrolizumab has a limited volume of distribution.
c) Excretion –CL is approximately 23% lower after achieving maximal change at steady state compared with the first dose. The terminal elimination half-life (t ½) is estimated to be 22 days at steady state
d) Metabolism - Pembrolizumab is catabolized through non-specific pathways; metabolism does not contribute to its CL.

15.16 **Potential Drug Interactions**: There are no known significant drug interactions.

15.17 **Very common know potential toxicities, ≥ 10%**

Gastrointestinal disorders: diarrhea, nausea, abdominal pain
Skin and subcutaneous tissue disorders: rash, pruritis
General disorders and administration site conditions: fatigue
Common known potential toxicities, ≥1 to < 10%:
Blood and lymphatic system disorders: anemia

Immune system disorders: infusion related reaction
Endocrine disorders: hyperthyroidism, hypothyroidism
Metabolism and nutrition disorders: decreased appetite
Nervous system disorders: headache, dizziness, dysgeusia
Respiratory, thoracic, and mediastinal disorders: pneumonitis, dyspnea, cough
Gastrointestinal disorders: colitis, vomiting, constipation, dry mouth
Skin and subcutaneous tissue disorders: severe skin reactions, vitiligo, dry skin, erythema
Musculoskeletal and connective tissue disorders: arthralgia, myositis, musculoskeletal pain, , pain in extremity
General disorders and administration site conditions: asthenia, edema, pyrexia, influenza like illness, chills
Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased

Uncommon known potential toxicities, ≥0.1% to <1%:
Infusion related reactions
Blood and lymphatic system disorders: neutropenia, thrombocytopenia, leukopenia, lymphopenia, eosinophilia
Endocrine disorders: hypophysitis, adrenal insufficiency, Thyroiditis, hypopituitarism
Metabolism and nutrition disorders: type I diabetes mellitus, hyponatremia, hypokalemia, hypocalcemia
Psychiatric disorders: insomnia, confusional state
Nervous system disorders: epilepsy, lethargy, peripheral Neuropathy
Eye disorders: uveitis, dry eye
Cardiac disorders: myocarditis, atrial fibrillation
Vascular disorders: hypertension
Gastrointestinal disorders: pancreatitis, dysphasia
Hepatobiliary disorders: hepatitis
Skin and subcutaneous tissue disorders: lichenoid keratosis, psoriasis, alopecia, dermatitis, dermatitis acneiform, eczema, hair color changes, papule
Musculoskeletal and connective tissue disorders: tenosynovitis, myelitis
Renal and urinary disorders: nephritis, acute kidney injury
Investigations: blood bilirubin increased, amylase increased, hypercalcemia
Respiratory: pneumonia aspiration

Rare known potential toxicities, <0.1% (Limited to important or life-threatening):
Blood and lymphatic system disorders: immune thrombocytopenic purpura, hemolytic anemia
Immune system disorders: sarcoidosis
Nervous system disorders: Guillain-Barre syndrome, myasthenic syndrome, exacerbation of myasthenia gravis
Gastrointestinal disorders: small intestinal perforation

Skin and subcutaneous tissue disorders: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema nodosum
The risk profile for pembrolizumab also includes two important potential risks: a) myasthenic syndrome, and b) an increased risk of severe complications (such as early severe graft versus host disease and venoocclusive disease) of allogeneic transplant in patients with hematologic malignancies who have previously been treated with PD-1 inhibitors.

Patients with multiple myeloma who were treated with pembrolizumab in combination with either pomalidomide or lenalidomide and dexamethasone, had an increased number of serious side effects and deaths as compared to patients who received only dexamethasone and either pomalidomide or lenalidomide. The benefit-risk profile is unfavorable for the combination of pembrolizumab, pomalidomide, and dexamethasone in relapsed refractory multiple myeloma, and the combination of pembrolizumab, lenalidomide, and dexamethasone in newly diagnosed treatment-naive multiple myeloma.

Post marketing reports identified Vogt-Koyanagi-Harada syndrome and hemophagocytic lymphohistiocytosis.

15.18 **Drug procurement:** Pembrolizumab will be provided free of charge to study participants by Merck.

15.19 Nursing Guidelines:

15.191 Pembrolizumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids.

15.192 Diarrhea can be seen however it is less common than that seen with anti-CTLA-4 agents. However it can be severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.

15.193 Rash/pruritus/dermatitis is seen. Patients should report any rash to the study team. Treat per section 9.0 and monitor for effectiveness.

15.194 Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.

15.195 Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.

15.196 Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysistis, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and "not

feeling well". Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.

15.197 Patients who are started on steroid therapy for any side effects of pembrolizumab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.

15.198 Fatigue is common and may or may not be associated with immune related side effects. Assess patient's fatigue level prior to each cycle of therapy and report any changes to the study team.

15.199a Patients should avoid receiving live vaccines within 30 days of study drug administration or per other study guidelines

15.199b Patients who have undergone an allogenic bone marrow transplant, have an increased risk of severe complications including early GVHD, and venoocclusive disease, if they have previously been treated with pembrolizumab

15.199c Myocarditis has been reported and associated with pembrolizumab. Instruct patients to report chest pain , SOB, or dyspnea to study team immediately and/or seek emergency medical attention.

15.199d Autoimmune hematologic disorders including ITP and hemolytic anemia have been reported. Monitor blood counts closely and report any abnormalities to the study team.

15.199e Rare neurologic disorders including Guillian-Barre syndrome and myasthenia gravis have been reported. Instruct patients to report any neurologic symptoms including weakness, parasthesias or numbness, tingling to the study team immediately.

15.2 Idelalisib for Oral Administration (Zydelig®)

15.21 **Background**: Idelalisib inhibits PI3Kδ kinase, which is highly expressed in malignant lymphoid B-cells and is central to multiple signaling pathways that drive proliferation. Through inhibition CXCR4 and CXCR5 signaling, Idelalisib inhibits homing and retention of malignant B-cells in the tumor microenvironment including lymphoid tissues and the bone marrow.

15.22 **Formulation**: Idelalisib is available as 100 mg or 150 mg tablets. The 150 mg tablet is oval shaped, pink, and debossed with "150" on one side and "GSI" on the other side. The 100 mg tablet is oval-shaped, orange, and debossed with "100" on one side and "GSI" on the other side.

Inactive ingredients: microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, magnesium stearate and a tablet coating. The tablet coating consists of polyethylene glycol, talc, polyvinyl alcohol, and titanium dioxide and of FD&C Yellow #6/Sunset Yellow FCF Aluminum Lake (for the 100 mg tablet) and red iron oxide (for the 150 mg tablet).

15.23 **Preparation and storage**: Dispense only in original container. Store between

20–30°C (68–86°F) with excursions permitted 15–30ºC (59–86ºF).

15.24 **Administration:** Refer to the treatment section for specific administration instructions. Idelalisib may be taken with or without food. Idelalisib should be swallowed whole. If a dose is missed by less than 6 hours, take the missed dose right away and take the next dose as usual. If a dose of Idelalisib is missed by more than 6 hours, advise the patient to wait and take the next dose at the usual time.

15.25 Pharmacokinetic information:

Absorption: Time to peak concentration in a fasting state is approximately 1.5 hours. Administration with a high fat meal increased the AUC 1.4-fold. Idelalisib exposure increases in a less than dose-proportional manner.
Distribution: 23 L at steady state
Protein binding: > 84%
Metabolism: Idelalisib is hepatically metabolized to its major metabolite, GS-563117, via aldehyde oxidase and CYP3A. GS-563117 is inactive against PI3Kδ. Idelalisib undergoes minor metabolism by UGT1A4.
Half-life elimination: Approximately 8 hours
Time to peak: 1.5 hours
Excretion: Feces (78%; 44% as GS-563117); urine (14%; 49% as GS-563117)

15.26 Potential Drug Interactions:

Idelalisib is metabolized primarily by CYP3A4. The AUC of Idelalisib was reduced by 75% when coadministered with a strong CYP3A inducer. Avoid coadministration with strong CYP3A inducers, such as rifampin, phenytoin, St. John's wort or carbamazepine.

The AUC of Idelalisib was increased 1.8-fold when coadministered with a strong CYP3A inhibitor. If patients are taking concomitant strong CYP3A inhibitors, monitor for signs of Idelalisib toxicity. Follow dose modifications in the package insert for adverse reactions.

Idelalisib is a strong CYP3A4 inhibitor. The AUC of sensitive CYP3A4 substrates was increased 5.4 fold when Idelalisib was coadministered with a sensitive CYP3A4 substrate. Avoid coadministration of Idelalisib with CYP3A4 substrates.

Idelalisib also inhibits CYP2C8, CYP2C19, and UGT1A1. GS-563117 inhibits CYP2C8, CYP2C9, CYP2C19, CYP3A, and UGT1A1 in vitro. Idelalisib and GS-563117 are not likely to inhibit CYP1A1, CYP2B6, and CYP2D6.

Idelalisib also induces CYP2B6, but does not induce CYP1A2 in vitro. GS-563117 does not induce these enzymes.

Idelalisib and GS-563117 are substrates of P-glcyoprotein (P-gp) and BCRP in vitro. Idelalisib is not a substrate of OATP1B1, OATP1B3, PAT1, OAT3, or OCT2. GS-563117 is not a substrate of OATP1B1 or OATP13.

Idelalisib inhibits P-gp, OATP1B2, and OATP1B3, and GS-563117 inhibits OATP1B1, OATP1B3 in vitro. Idelalisib is not likely to inhibit BCRP, OCT2,

OAT1, or OAT3, and GS-563117 is not likely to inhibit P-gp, BCRP, OCT2, OAT1, or OAT3.

15.27 Known potential toxicities:

Warning: Fatal and serious toxicities: Hepatic, severe diarrhea/colitis, pneumonitis, and intestinal perforation. *See full prescribing information for complete boxed warning.*

Hepatotoxicity: ALT/AST elevations >5 times ULN have occurred, and were generally observed during the first 12 weeks of therapy; transaminase elevations were reversible upon therapy interruption. Hepatotoxicity may recur upon rechallenge, even at a reduced dose; discontinue for recurrent hepatotoxicity. Avoid concomitant use with other hepatotoxic agents.

Severe diarrhea/colitis: Fatal and/or serious and severe diarrhea or colitis occurred in 14% of Idelalisib-treated patients. Monitor for the development of severe diarrhea or colitis. Grade 3 or higher diarrhea or colitis has been reported in clinical trials. Diarrhea may occur at any time during therapy and responds poorly to antidiarrheal (antimotility) medications. The median time to resolution of diarrhea was 1 week to 1 month (following therapy interruption); corticosteroids were used in some cases to manage toxicity. Avoid concomitant use with other promotility agents.

Pneumonitis: Fatal and serious pneumonitis can occur in Idelalisib-treated patients. Monitor for pulmonary symptoms and bilateral interstitial infiltrates. Symptoms such as cough, dyspnea, hypoxia, interstitial infiltrates, or an oxygen saturation decrease of more than 5% should be promptly evaluated.

Intestinal perforation: Fatal and serious intestinal perforation can occur in Idelalisib-treated patients across clinical trials. In some patients, perforation was preceded by moderate to severe diarrhea. Monitor closely for new or worsening abdominal pain, chills, fever, nausea, or vomiting. Discontinue Idelalisib for intestinal perforation.

Very common toxicities (≥10%):
Central nervous system: Fatigue, insomnia, headache
Dermatologic: Skin rash (, night sweats
Gastrointestinal: Diarrhea, nausea, abdominal pain, decreased appetite, vomiting
Hematologic: Neutropenia, anemia, thrombocytopenia
Hepatic: increased AST/ALT, severe hepatotoxicity
Neuromuscular/skeletal: Weakness
Respiratory: Cough, pneumonia, dyspnea, upper respiratory tract infection
Miscellaneous: Fever

Common toxicities (≥ 1% and < 10%): Peripheral edema

Other toxicities: Anaphylaxis, hypersensitivity reaction, intestinal perforation, toxic epidermal necrolysis, severe and/or life threatening (grade 3 or higher) cutaneous reactions such as exfoliative dermatitis, rash (generalized, erythematous, macular-papular, pruritic, exfoliative)

15.28 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.29 Nursing Guidelines

15.291 Idelalisib can be taken with or without food and should be taken twice daily. Tablets must be swallowed whole. Doses should only be made up if less than 6 hours.

15.292 Gastrointestinal side effects are common, including diarrhea (including severe colitis), nausea, vomiting, etc. Treat symptomatically and monitor for effectiveness. Note that the diarrhea caused by this agent tends to respond poorly to antidiarrheal agents. Patients may need corticosteroids.

15.293 Serious and/or fatal hepatotoxicity can be seen. Monitor LFT's and instruct patients to report any abdominal pain, or jaundice to the study team.

15.294 Monitor CBC w/diff as neutropenia and thrombocytopenia is common. Instruct patients to report any signs or symptoms of infection and/or any unusual bruising or bleeding to the study team.

15.295 Rarely patients may experience pneumonitis. Instruct patients to report cough, shortness of breath, dyspnea, or chest pain to the study team.

15.296 Patients may experience pyrexia and/or chills. Rule out infection and treat symptomatically. Monitor for effectiveness.

15.297 Warn patients of potential fetal harm. Instruct women of child bearing potential to use appropriate and effective birth control while on agent.

15.3 Ibrutinib for Oral Administration (Imbruvica®)

15.31 **Background**: Ibrutinib is a potent and irreversible inhibitor of Bruton's tyrosine kinase (BTK), an integral component of the B-cell receptor (BCR) and cytokine receptor pathways. Constitutive activation of B-cell receptor signaling is important for survival of malignant B-cells; BTK inhibition results in decreased malignant B-cell proliferation and survival.

15.32 **Formulation**: Commercially available for oral administration as a capsule: 70 mg, 140mg (limited availability). Commercially available for oral administration as a tablet: 140 mg, 280 mg, 420 mg, and 560 mg..

15.33 **Preparation and storage**: Refer to package insert for complete dispensing instructions. Store capsules and tablets at room temperature between 20°C and 25°C (68°F and 77°F). Excursions are permitted between 15° and 30°C (59°F to 86°F). Keep in original container..

15.34 **Administration:** Refer to the treatment section for specific administration instructions. The manufacturer recommends Ibrutinib should be taken with water at the same time every day. Swallow capsules whole. Do not open, break, or chew the capsules. Do not cut, crush, or chew the tablets. Maintain adequate hydration during treatment. Hazardous agent; use appropriate precautions for handling and disposal.

15.35 Pharmacokinetic information:

Distribution: ~10,000 L
Bioavailability: Administration with food increased the maximum concentration by ~2 to 4-fold and the AUC 2-fold (compared with overnight fasting)

Protein binding: ~97%. Administration under fasting conditions resulted in exposure of ~60% compared to when administered either 30 minutes before or after a meal, or 2 hours after a high-fat meal.
Metabolism: Hepatic via CYP3A (major) and CYP2D6 (minor) to active metabolite PCI-45227
Half-life elimination: 4 to 6 hours
Time to peak: 1 to 2 hours
Excretion: Feces (80%; ~1% as unchanged drug); urine (<10%, as metabolites)

15.36 Potential Drug Interactions:

Metabolism Effects: Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A4/5. Avoid concomitant use of Ibrutinib with any of the following: CYP3A4 inducers (strong), CYP3A4 inhibitors (strong or moderate) and herbs that are CYP3A4 inducers or inhibitors. The levels of Ibrutinib may be increased by CYP3A4 inhibitors and decreased by CYP3A4 inducers (the active metabolite has inhibitory activity towards Bruton's tyrosine kinase that is approximately 15 times lower than that of Ibrutinib).

Transport Effects: Ibrutinib is a P-glycoprotein/ABCB1 inhibitor and may increase the serum concentrations of: afatinib, bosutinib, brentuximab, colchicine, active metabolites of dabigatran etexilate, doxorubicin, edoxaban, everolimus, ledipasvir, naloxegol, pazopanib, prucalopride, rifaximin, rivaroxaban, silodosin, topotecan and vincristine.

Ibrutinib may enhance the adverse/toxic effect of clozapine, leflunomide, natalizumab, pimecrolimus, tofacitinib, tacrolimus, and live vaccines. It may also enhance the adverse/toxic effect of anticoagulants and agents with antiplatelet properties. Dipyrone may enhance the adverse/toxic effect of Ibrutinib.

Grapefruit juice and Seville oranges moderately inhibit 3A4 and may increase Ibrutinib exposure.

15.37 **Known potential toxicities**: Consult the package insert for the most current and complete information.

Common known potential toxicities, >10%:
Cardiovascular: Peripheral edema, hypertension
Central nervous system: Fatigue, dizziness, headache, anxiety, chills
Dermatologic: Skin rash, skin infection, pruritis
Endocrine & metabolic: Increased uric acid, Hyperuricemia, hypoalbuminemia; hypokalemia, dehydration
Gastrointestinal: Diarrhea, nausea, constipation, abdominal pain, vomiting, decreased appetite, stomatitis, dyspepsia, gastroesophageal reflux disease, upper abdominal pain
Genitourinary: Urinary tract infection
Hematologic & oncologic: Decreased platelet count, bruise, neutropenia, decreased hemoglobin, hemorrhage, petechial, malignant neoplasm (secondary)
Infection: infection
Neuromuscular & skeletal: Musculoskeletal pain, arthralgia, muscle spasm, weakness, arthropathy
Ophthalmic: Dry eye syndrome, increased lacrimation, blurred vision, decreased visual acuity

Respiratory: Upper respiratory tract infection, dyspnea, sinusitis, cough, oropharyngeal pain, pneumonia, epistaxis, bronchitis
Miscellaneous: Fever, , falling

Less common known potential toxicities, 1% - 10%:
Cardiovascular: Atrial fibrillation, atrial flutter
Infection: Sepsis

Limited to important or life threatening:
Renal: Renal failure Increased serum creatinine

Limited to important or life threatening: Abnormal platelet aggregation, hepatic failure, hypersensitivity (includes anaphylactic shock, angioedema, urticaria), interstitial pulmonary disease, onychoclasis, pneumonia due to *Pneumocystis carinii*, pneumonitis, progressive multifocal leukoencephalopathy, reactivation of HBV, renal failure, Stevens-Johnson syndrome, tumor lysis syndrome

15.38 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.39 Nursing Guidelines

15.391 There are numerous drug to drug interactions. Record all of patient's medications including OTC, and herbal use. Avoid concomitant use with agents as listed in section 15.16.

15.392 Patients should be instructed to avoid eating grapefruit (including juice) and Seville oranges while on Ibrutinib.

15.393 Peripheral edema is common. Instruct patients to report this to the study team.

15.394 Gastrointestinal side effects are common (diarrhea, nausea, constipation, abdominal pain, vomiting, etc). Treat symptomatically and monitor for effectiveness of intervention.

15.395 Monitor CBC w/diff. Instruct patients in energy conserving lifestyle (anemia) and to report any unusual bruising or bleeding and/or signs or symptoms of infection to study team.

15.396 Arthralgias, Myalgias, and muscle spasm can be seen. Treat symptomatically and monitor for effectiveness.

15.397 Monitor renal function/uric acid levels, especially in patients who may be experiencing dehydration.

15.398 Respiratory symptoms may include, cough, SOB, and URI. Instruct patients to report these symptoms to the study team.

15.399a Rarely patients can experience secondary skin cancers. Instruct patients to report any new skin lesions to the study team.

15.399b Rash can be seen. Instruct patient to report to study team.

15.399c Cardiac arrhythmias have been seen with this agent including a-fib, atrial flutter and ventricular tachyarrhythmia's, some of which have led to

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

16.0 Statistical Considerations and Methodology

16.1 Overview: This Phase II study will utilize a one-stage binomial design in each arm independently (Arms A, B, and C) to assess the overall response rate associated with single-agent MK-3475 in patients with relapsed and progressive CLL/SLL, including CLL patients with Richter's transformation (RS) or Hodgkin's transformation (Arm A and Arm C) and other types of relapsed and progressive low grade B cell NHL including FL, WM and marginal zone lymphoma (Arm B).

16.11 Endpoint: The primary endpoint of this trial is the proportion of patients who achieve a confirmed response to single-agent MK-3475. A confirmed response is defined to be a PR, nPR, CCR, CRi or CR (Arms A and B) or CMR, PMR, PR, or CR (Arm C) noted as the objective status at any time while on single-agent MK-3475. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response, with the exception of patients determined to be a major violation.

16.12 Sample Size: This study is expected to require a maximum of 23 evaluable patients each in Arm A and Arm B. We anticipate accruing 1 additional patient in each arm to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, this study is expected to accrue between 46 - 48 patients in these two arms.

As of MCCC Addendum 3, due to promising response observed in CLL patients with Richter's transformation, an additional arm (Arm C) with 17 evaluable patients is added to the trial. We anticipate accruing 3 additional patients to account for ineligibility, cancellation, major treatment violation, or other reasons for a total of 20 patients on Arm C. These patients will be accrued to allow better evaluation of response and toxicity of single agent MK 3475 in patients with Richter's transformation. This study is now expected to accrue a maximum of 68 patients.

16.13 Accrual Rate and Study Duration: The anticipated accrual rate is approximately 2-4 patients per month. Therefore, the accrual period for this phase II study is expected to be approximately 2-3.0 years. The final analysis can begin as soon as the last patient has been observed for 6 months, or at approximately 3.0-3.5 years.

MCCC Addendum 3: In approximately 20 months, the study has accrued 41 patients. Based on current accrual rates, the total accrual period is now expected to be approximately 3.0 years. The final analysis can begin as soon as the last patient has been observed for 6 months, or approximately 3.5 years from trial opening.

16.2 Statistical Design:

16.21 Decision Rule for Arms A and B (to be evaluated in each arm independently):

MK-3475 monotherapy induces an ORR of 39% in patients with ipilimumab-naive melanoma by central independent RECIST review. The potential activity of this agent in relapsed CLL or low grade NHL has not been tested. Previous approved monoclonal antibodies, alemtuzumab or rituximab, have achieved ~20-30% ORR in CLL. We expect that CLL patients who develop resistance to novel CLL therapies will enroll into this clinical study. It is completely unknown how CLL patients will respond to any types of CLL therapy after they developed

Ibrutinib resistance. Therefore, it is logical to hypothesize that 30% ORR will be worthy of further testing in relapsed CLL and low grade NHL patients.

The largest success proportion where the proposed treatment strategy would be considered ineffective in this population is 10%. The smallest success proportion that would warrant subsequent studies with the proposed treatment strategy in this patient population is 30%. The following one-stage binomial design uses 23 evaluable patients to test the null hypothesis that the true success proportion in a given patient population is at most 10%.

16.211 Final Decision Rule: Enter 23 evaluable patients into the study. If 4 or fewer successes are observed in the first 23 evaluable patients, we will consider this regimen ineffective in this patient population. If 5 or more successes are observed in the first 23 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this population.

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

16.22 Assuming that the number of responses is binomially distributed, with a significance level of 7%, the probability of declaring that the regimen warrants further studies (i.e., statistical power) under various response proportions can be tabulated as a function of the true response proportion as shown in the table below.

If the true success proportion is…	0.10	0.15	0.20	0.25	0.30
Then the probability of declaring that the regimen is promising and warrants further study is…	0.07	0.26	0.50	0.72	0.86

16.23 Decision Rule for Arm C:

In the 9 Richter's transformation patients accrued to Arm A of this study, 4 patients were classified as a PET-CT or CT response by the Lugano 2014 response criteria. Due to the promising efficacy in selected patients with Richter's transformation, Arm C is being added to further test efficacy of this agent in this patient population. A confirmed response rate of 40% would be considered promising and would be of significant clinical interest. However, a response rate of 15% would be considered ineffective.

The largest success proportion where the proposed treatment strategy would be considered ineffective in this population is 15%. The smallest success proportion that would warrant subsequent studies with the proposed treatment strategy in this patient population is 40%. The following one-stage binomial design uses 17 evaluable patients to test the null hypothesis that the true success proportion in a given patient population is at most 15%.

16.231 Final Decision Rule: Enter 17 evaluable patients into the study. If 4 or fewer successes are observed in the first 17 evaluable patients, we will consider this regimen ineffective in this patient population. If 5 or more

successes are observed in the first 17 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this population.

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

16.24 Assuming that the number of responses is binomially distributed, with a significance level of 10%, the probability of declaring that the regimen warrants further studies (i.e., statistical power) under various response proportions can be tabulated as a function of the true response proportion as shown in the table below.

If the true success proportion is…	0.15	0.20	0.25	0.30	0.35	0.40
Then the probability of declaring that the regimen is promising and warrants further study is…	0.10	0.24	0.43	0.61	0.77	0.87

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

16.3 Analysis Plan (to be evaluated in each arm independently)

16.31 Primary Outcome Analyses:

16.311 Definition: The primary endpoint of this trial is the proportion of patients who achieve a confirmed response to single-agent MK-3475. A confirmed response is defined to be a PR, nPR, CCR, CRi or CR (Arms A and B) or PMR, CMR, PR or CR (Arm C) noted as the objective status at any time while on single-agent MK-3475. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response, with the exception of patients determined to be a major violation. For CLL patients with Richter's transformation, confirmed response is determined by response criteria defined for Richter's transformation.

16.312 Estimation: In each arm, the proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients in that arm. Exact binomial confidence intervals for the true success proportion will be calculated. In addition, the confirmed response rate for all Richter's transformation patients (9 patients from Arm A and all patients in Arm C) will be calculated.

16.32 Secondary Outcome Analyses (to be evaluated in each arm independently; Arm C analyses may include the 9 Richter's transformation patients from Arm A): (For all outcomes associated with combination therapy in Arms A and C, disease measurements obtained after the last cycle of single-agent therapy are set as the baseline measurements for combination therapy).

16.321 Progression-free survival (PFS) for single-agent MK-3475 is defined as

the time from registration to the earliest date of documentation of disease progression while on single-agent MK-3475 or death due to any cause. In Arm A and Arm C, patients who initiate combination therapy for stable disease after 3 months of single-agent MK-3475 will be censored on the date that combination therapy is initiated.

In Arm A and Arm C, PFS for the combination of MK-3475 and the signal inhibitor is defined as the time from intiation of treatment with the combination therapy to the earliest date of documentation of disease progression while on combination therapy or death due to any cause.

The distribution of progression-free survival will be estimated using the method of Kaplan-Meier.

16.322 Treatment-free survial (TFS) for single-agent MK-3475 is defined as the time from registration to the date of initiation of subsequent treatment for CLL/SLL or lymphoma or death due to any cause. In Arm A and Arm C, the initiation of combination therapy with MK-3475 and the signal inhibitor will be considered subsequent treatment.

In Arm A and Arm C, TFS for the combination of MK-3475 and the signal inhibitor is defined as the time from initiation of combination therapy to the date of initiation of subsequent treatment for CLL/SLL or death due to any cause.

The distribution of treatment-free survival will be estimated using the method of Kaplan-Meier.

16.323 The time to next treatment (TNT) for single-agent MK-3475 is defined as the time from registration to the date of initiation of subsequent treatment for CLL/SLL or lymphoma. In Arm A and Arm C, the initiation of combination therapy with MK-3475 and the signal inhibitor will be considered subsequent treatment.

In Arm A and Arm C, TNT for the combination of MK-3475 and the signal inhibitor is defined as the time from initiation of combination therapy to the date of initiation of subsequent treatment for CLL/SLL.

The distribution of time to next treatment will be estimated using the method of Kaplan-Meier.

16.324 The complete response rate will be estimated by the number of patients who achieve a CRi or CR (Arms A and B) or CMR or CR (Arm C) divided by the total number of evaluable patients. Complete response rate will be evaluated for single-agent MK-3475 in each arm and also for the combination of MK-3475 and the signal inhibitor in Arm A and C. All evaluable patients will be used for this analysis. Exact binomial 95% confidence intervals for the true complete response rate will be calculated in each arm.

16.325 Duration of response (DR) is defined for all evaluable patients who have achieved a PR, nPR, CCR, CRi, or CR (Arms A and B) or PMR, CMR, PR or CR (Arm C) as the date at which the patient's objective status is first noted to be a PR, nPR, CCR, CRi, or CR (Arms A and B) or PMR, CMR, PR or CR (Arm C) to the earliest date relapse is documented. Duration of response will evaluated for single-agent MK-3475 in each

arm and also for the combination of MK-3475 and the signal inhibitor in Arm A and C. The distribution of duration of response will be estimated using the method of Kaplan-Meier.

16.326 Overall survival is defined as the time from registration to death due to any cause. The distribution of overall survival will be estimated using the method of Kaplan-Meier.

16.327 Arm A and Arm C: The overall response rate for the combination of MK-3475 and the signal inhibitor (targeted agents) will be estimated by the number of patients with an objective status of CR, CRi, nPR, CCR or PR (Arm A) or PMR, CMR, PR or CR (Arm C) while on the combination therapy divided by the total number of evaluable patients. All evaluable patients who receive the combination therapy will be used for this analysis. Exact binomial 95% confidence intervals for the true overall response rate to the combination will be calculated. In addition, the responders on this study will be further examined in an exploratory manner to determine if there are any patterns in prognostic factors or disease characteristics, including whether the patient had a Richter's transformation or Ibrutinib-resistant disease, for both single-agent MK-3475 and combination therapy responders.

16.328 Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration. Adverse events will be evaluated for single-agent MK-3475 in each arm and also for the combination of MK-3475 and the signal inhibitor in Arm A and Arm C.

16.33 Correlative Analyses:

16.331 PD-1, PD-L1 and PD-L2 will be measured for each patient at baseline and during treatment. Each measure will be summarized descriptively by median, min, max and interquartile range. Overall response and complete response will be correlated with each measure using Wilcoxon rank sum test. The relationship between each measure and time to event measures (DR, TNT, PFS) will be evaluated using Cox proportional hazard models.

16.332 Markers of immune modulation and immune profiles will be summarized descriptively by median, min, max, and interquartile range (continuous factors) or frequency distribution (categorical factors) at each time point. Patterns over time will be summarized by absolute difference or relative change. Changes across time will be assessed using paired analyses, including Wilcoxon signed rank tests for continuous measures and McNemar's tests for categorical measures. Overall response and complete response will be correlated with continuous factors using Wilcoxon rank sum tests. Jitplots will be used to visually examine differences between groups for continuous factors. Overall response and complete response will be correlated with categorical factors using Fisher's exact tests.

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

16.4 Safety Analysis Phase (Arm A and B only):

A safety analysis will be performed after the first 12 patients (6 each arm for Arm A and B) have been accrued to the study. Accrual will be temporarily halted while these patients are followed for one cycle to assess adverse events. If 2 or more of the first 6 patients in either arm experience a DLT as defined below, then accrual will continue to be temporarily suspended to the arm affected. All toxicity data will be reviewed by the study team and a decision will be made about whether the starting dose needs to be adjusted or the protocol should be continued.

Toxicity will be measured per NCI-CTCAE version 4. DLT is defined as an adverse event possibly, probably, or definitely related to study treatment that meets one of the following:

- hepatic toxicity defined as AST or ALT > 5 - 10X ULN for > 4 weeks; Total bilirubin > 5X ULN for > 4 weeks ; Concurrent AST or ALT > 3X ULN and total bilirubin > 2X ULN (excluding liver involvement by CLL or lymphoma) for > 4 weeks (potential Hy's Law case)
- grade 4 non-hematological toxicity[except weight loss or fatigue or laboratory abnormalities not associated with clinical sequelae] lasting longer than 4 weeks despite of holding therapy and supportive treatments
- Any grade 5 AE

16.5 Data & Safety Monitoring:

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

16.52 Adverse Event Stopping Rules (to be evaluted in each arm independently for single-agent MK-3475 and separately for combination therapy): The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Single-agent MK-3475: Accrual will be temporarily suspended to the affected arm if at any time we observe events considered at least possibly related to study treatment during cycles with single-agent MK-3475 (i.e. an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy one of the following:

- If 4 out of the first 12 treated patients experience a DLT as defined in Section 16.4

- If after the first 12 patients have been treated, 30% of all patients experience a DLT as defined in Section 16.4.

Combination of MK-3475 and signal inhibitor (Ibrutinib or Idelalisib) in Arm A and Arm C: Initiation of treatment with the combination (addition of Ibrutinib or Idelalisib) will be halted in Arm A and Arm C if at any time we observe events considered at least possibly related to study treatment during cycles with the combination (i.e. an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy one of the following:

- If 2 out of the first 6 treated patients experience a DLT as defined in Section 16.4
- If after the first 6 patients have been treated, 30% of all patients experience a DLT as defined in Section 16.4.

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

16.6 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 3.5 years after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time all patients registered have achieved a response or have discontinued treatment before achieving a response.

16.7 Inclusion of Women and Minorities

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

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

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

Accrual Estimates by Gender/Ethnicity/Race

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	0	2	0	2
Not Hispanic or Latino	20	46	0	66
Ethnic Category: Total of all subjects*	20	48	0	68
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	0	0	0
Black or African American	0	2	0	2
Native Hawaiian or other Pacific Islander	0	0	0	0
White	20	46	0	66
Racial Category: Total of all subjects*	20	48	0	68

Ethnic Categories:
Hispanic or Latino – a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
Not Hispanic or Latino

Racial Categories:
American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."
Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens:

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

Pathology Review/ Correlative Study	Mandatory or Optional	Type of Tissue/ Slides to Collect	Block, Slides, Core, etc. (# of each to submit)	Visit 1: Baseline	Visit 2: At Progression	Specific details for the submission
Pathology review: Confirm diagnosis	Mandatory for non-mayo sites	H & E, stained slides	All H&E stained diagnostic slides,	X		17.2
Correlative Study:	Mandatory	Paraffin	Tissue block **(preferred)** or unstained slides (18 slides), 4-5 microns each	X	X	17.3

17.2 Diagnostic Slides from Original and /or Recurrent Tissue to confirm diagnosis

Central pathology review is not required as long as the tissue diagnosis of lymphoma was confirmed by a Mayo pathologist or other academic centers. If the tissue diagnosis is not confirmed by a Mayo pathologist/other academic centers, the slides will need to be reviewed to confirm the diagnosis. Completion of central pathology review is not required prior to registration; however materials for central review must be reviewed within 42 days after registration.

17.21 Central pathology review will be conducted as needed for confirmation of diagnosis by [redacted] and colleagues at Mayo Clinic Rochester if the initial tissue biopsy was not performed and evaluated at Mayo Clinic/other academic centers.

Required materials:

- Lymphoma Pathology Reporting Form (Complete Section I only)
- Tissue Submission Form
- Bone marrow biopsy report
- Tumor tissue pathology report
- Paraffin block containing tumor tissue from the most recent tumor tissue biopsy is preferred, not bone marrow or peripheral blood. If the institution is unwilling to release a block, 18 unstained, charged slides cut at 4μ should be submitted. Slides should be placed in appropriate slide container.
- All tumor tissue diagnostic H&E stained slides
- Tumor tissue immunochemistry or immunophenotyping by flow cytometry report (if available)
- FISH report if available

After central review is completed, the pathologist will return all diagnostic slides to the submitting outside institution. In addition, the pathologist will also forward the completed Lymphoma Pathology Reporting Form and accompanying reports to the study QAS for scanning and data entry purposes to the following:

[redacted]

17.3 Correlative Tissue Collection

17.31 Tissue Kits will not be provided for this protocol.

17.32 Paraffin Embedded Tissue (pre-treatment).

17.321 Paraffin embedded tissue block will be used to generate tumor derived genomic DNA for the correlative studies as described in section 17.4.

17.322 If tissue block is not available, then Ten (10) 4-5 micron paraffin embedded tissue slides will be collected for DNA isolation and sequencing.

17.323 Eight (8) 4-5 micro paraffin embedded tissue slides will be collected for staining cell specific markers for T cells, T cell subsets, tumors and PD-1, PD-L1, etc. other related co-stimulatory or inhibitory markers.

17.33 Shipping

Specimens need to be labeled with patient name and registration number, sex, age and specific diagnosis for the trial enrollment, as well as the arm of the study (A or B or C).

Ship specimens via Priority Overnight service on **Monday – Thursday Preferred** (Friday only if you must) directly to:

[redacted]

Please email [redacted] to notify the laboratory when specimens are being shipped. The message should include the study name, sample type, Fed Ex air bill tracking number, contact name and telephone number.

Shipping costs will be covered by the study.

17.4 Background and Methodology

17.41 Background: accumulating evidence showed that the clinical response of checkpoint inhibitor is likely associated with tumor PD-L1 expression as well as tumor exomic mutation burden(Garon, Rizvi et al. 2015; Rizvi, Hellmann et al. 2015). Therefore, we plan to test the spectrum of tumor mutation using WES/targeted sequencing as well as tumor PD-L1 and other marker staining with immunohistochemistry analysis.

17.42 Sequencing: Genomic DNA will be extracted from formalin-fixed, paraffin-embedded tissue blocks. H&E-stained sections from each case will be reviewed by an expert hematopathologist and representative blocks with at least 30% tumor cells will be selected. 10 x 5-micron sections will be cut from blocks in the Mayo Clinic Pathology Research Core (based on tissue area of 25 mm^2). DNA will be extracted in the Mayo Clinic Biospecimens Accessioning and Processing Core using the Qiagen FFPE DNA extraction kit. DNA quantitation will be performed using a Qubit fluorometer prior to sequencing.

17.43 Expression of PD-L1 has been demonstrated to associate with clinical response of cancer patients treated with pembrolizumab. It is also established that CD8+ cytotoxic T cell response is critical to mediate anti-tumor immunity. Therefore, multiple markers including T cell, tumor cells, as well as related co-stimulatory and inhibitory markers will be stained to identify if there is any association of expression of these markers with clinical response. The RNA expression of immune markers can also be assessed using nanostring method in collaboration with Merck biomarker research team.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Initial Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)
On-Study	≤2 weeks after registration
Adverse Event – Baseline	
Measurement – Baseline [3]	
Immunophenotyping Reports including CD38, CD49d, and ZAP-70[1, 2] (CLL patients only)	
IGHV Mutation Analysis Report[1] (CLL patients only)	
Peripheral Smear Report[1] (CLL patients only)	
CLL FISH Report[1] (CLL patients only)	
Bone Marrow Biopsy Report[1]	
CT Scan Report[1]	
Pathology Report (NHL patients only)	
Pathology Reporting Lymphoma[4]	
Bone Marrow Biopsy – Baseline (CLL/SLL Patients Only)	
Research Blood Submission – Baseline	
Research Bone Marrow Aspirate Submission – Baseline	
Research Tissue Submission - Baseline	
FISH Results (CLL/SLL Patients Only)	
Other Laboratory Results	
End of Active Treatment/Cancel Notification	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy

1. Submit copy of the report, Attention: [redacted].
2. For patients who previously had full flow immunophenotyping performed and at pre-study workup had limited repeat flow immunophenotyping, submit a copy of both reports.
3. See Section 11.0 to determine which response criteria will be utilized.
4. See Section 17.0 if central pathology review is required based on requirements in Section 4.1.

Test Schedule Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation
Evaluation/Treatment	X[2]	X	
Evaluation/Treatment (Arms A and C – Continuation)	X[2]	X	
Evaluation/Observation			X[1]
Nadir/Adverse Event	X	X	X
Measurement [6]	X	X	X
Bone Marrow Biopsy Report[3]	X		
CT Scan Report[3]	X[4]		
FISH Results (CLL/SLL Patients Only)		X[5]	X[5]
Other Laboratory Results	X[4]		
Bone Marrow Biopsy (CLL/SLL Patients Only)	X[4]		
Research Blood Submission (see Section 14.0)	X	X[5]	X[5]
Research Bonne Marrow Aspirate Submission (see Section 14.0)	X		
End of Active Treatment/Cancel Notification		X	
ADR/AER	At each occurrence (see Section 10.0)		

1. Complete at each evaluation during Observation (see Section 4.0).
2. Complete at each evaluation during Active Treatment (see Section 4.0).
3. Submit copy of the report, Attention: [redacted]
4. Complete when required per the test schedule.
5. Complete at time of progression.
6. See Section 11.0 to determine which response criteria will be utilized.

Follow-up Material(s)

CRF	Event Monitoring Phase[1]				
	q. 6 months until PMD/PD or subsequent treatment	At PMD/PD or subsequent treatment	q. 12 mos. after PMD/PD or subsequent treatment	Death	New Primary
Event Monitoring	X[2]	X[2]	X	X	At each occurrence

1. If a patient is still alive 4 years after registration, no further follow-up is required.
2. Submit copy of documentation of response or progression to the MCCC Operations Office, Attention: [redacted].

19.0 Budget

19.1 Costs charged to patient: All routine clinical care. MK-3475 will be provided free of charge by Merck.

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

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

20.0 References

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Appendix I NYHA Classification

Class I: NO Symptoms with ordinary activity
Class II: Symptoms with ordinary activity
Class III: Symptoms with minimal activity
Class IV: Symptoms at rest

Appendix II Rai Classification

0	lymphocytosis (>5 x 10^9/L)
I	lymphocytosis and lymphadenopathy
II	lymphoctosis and splenomegaly +/- lymphadenopathy
III	anemia (Hgb < 11 g/dL)
IV	thrombocytopenia (platelets < 100 x 10^9/L)

Appendix III ECOG Performance Status Scale

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

Appendix IV Grading Scale for Hematologic Toxicity in CLL Studies[1]

Decrease from Pretreatment value (%)	Grade[2]	
	Platelets[3, 5]	Hemoglobin[4, 5]
No change - 10%	0	0
11-24%	1	1
25-49%	2	2
50-74%	3	3
≥ 75%	4	4

1. A decrease in circulating granulocytes is not being considered since it is not a reliable index in CLL.
2. Grades: 1–mild; 2–moderate; 3–severe; 4–life–threatening. Grade 5 (fatal) toxicity can potentially occur at any level of decrease from pretreatment values and will be recorded as such.
3. If, at any level of decrease the platelet count is < 20,000/μL, this will be considered grade 4, unless the initial platelet count was ≤ 20,000 μL in which case the patient is unevaluable for toxicity referable to platelet counts.
4. Baseline and subsequent hemoglobin determinations must be immediately prior to any given transfusions.
5. If, at any level of decrease from the baseline value the platelet and/or hemoglobin counts are within normal limits, this will be considered a grade 0.

* Hallek BD, et al.: Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer-Institute- Working Group 1996 guidelines: Blood 111:54465456, 2008.

Appendix V Specimen Checklist and Shipping Instructions

A Phase II Study of Anti-PD-1 Antibody (MK-3475) in Relapsed Chronic Lymphocytic Leukemia (CLL) and Other Low Grade B Cell Non-Hodgkin Lymphoma (NHL)

Blood Collection Kit Predolin Biobank

Specimen Checklist and Shipping Instructions

**** PLEASE AVOID DRAWING OR SENDING SPECIMENS ON FRIDAYS AND HOLIDAYS****

Kit Contents:

- Small Styrofoam box and cardboard mailing sleeve
- Patient Information Form
- FedEx Airbill with pre-printed return address
- One 6ml ACD (yellow) collection tube
- One10ml EDTA (purple) collection tube
- One10ml Red Top collection tube
- Six 10ml Sodium Heparin (green) collection tubes
- Absorbent tube holder
- Zip lock specimen bag

Packing and Shipping Instructions:

1. Collect the following specimens:
    1. Bone marrow – Draw:
        - Single Therapy - 6ml in one (1) ACD tube **(Baseline, 6 and 12 month visits only)**
        - Combination Therapy - 6ml in one (1) ACD tube **(6 and 12 month visits only)**
    2. Peripheral blood – Draw:
        - 10ml in one (1) EDTA tube
        - 10ml in one (1) Red top tube
        - 60ml in six (6) Sodium Heparin tubes
2. All specimens are to be clearly labeled with the protocol number MC1485, the patient's initials (last, first, middle), type of sample, date of collection and arm of the study (A or B or C).
3. Place the tubes in the absorbent holder and seal in the zip lock specimen bag.
4. Place the filled specimen bag in the Sytrofoam container.
5. Loosely pack with paper toweling.
6. Place the Styrofoam container and the Patient Information form within the cardboard mailing sleeve.
7. Prepare the package for shipping, applying packing tape as needed. Adhere the Fed Ex Airbill to the exterior of the box. Ship specimens via priority overnight delivery (next day delivery by 10am) the same day collected.
8. Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location.

    Please email [redacted] to notify the laboratory when samples are being shipped. Indicate the protocol number, the Fed Ex tracking number, patient initials (last, first, middle), type of samples, name and phone number of the contact person. The samples in prepared kits should be shipped to the following:

[redacted]

Patient Information Form

Specimen Date: / /

Patient Initials (last name, first name):

Protocol #: MC1485

Clinic Number:

Contact Person:

Institution:

Address:

City State Zip

Phone #:

FAX #:

Please indicate which sample time point is being shipped at this time:

1. Baseline
2. Prior to Cycle 2
3. Prior to Cycle 3
4. At 3 month visit
5. At 6 month visit
6. At 12 month visit
7. At Disease Progression

Please indicate which therapy the patient is on:

1. Single Inhibitor
2. Combination Therapy

Please indicate which arm of the study:

A. Relapsed CLL/SLL
B. Low grade B-NHL
C. CLL with Richter's transformation

Any questions concerning these samples or to obtain blood collection kits for the MC1485 study, please contact:

[redacted]

Affiliates who anticipate participating in this study should please call in advance for kits.

Appendix VI Ibrutinib/Idelalsib Medication Diary

CLL Arm only (Arm A or C)

Name _____ Mayo Clinic No_____

Patient Instructions

- Your study doctor will tell you which medication (Ibrutinib or Idelalisib) will be added to your treatment regimen.
- Please indicate on the calendar below *every* day that you take your medication by placing the dose taken on the line under the date.
- If you miss a dose, place a check "**0**" under the date, but remember to take your prescribed dose at the next regularly scheduled time.
- Bring ***all*** bottles and any unused study medication along with this diary when you return for your next appointment.
- If you are receiving Ibrutinib, you should avoid eating grapefruit (including juice) and Seville oranges while on Ibrutinib.

Medication(s)	Dose
Ibrutinib	MG
Idelalisib	MG

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

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

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

Date:_____Participants Signature_____

Appendix VII Inhibitors of CYP3A4/5

A strong inhibitor increase the plasma AUC values by > 5-fold or reduces clearance by > 80%. Moderate inhibitors increases plasma clearance by > 2-fold or decreases clearance 50-80%. A strong inducer may decrease the plasma AUC more than 80% while a moderate inducer may reduce the plasma AUC 50-80%. Sensitive substrates of CYP3A are designated as those with a > 5-fold increase in AUC when co-administered with a known CYP3A inhibitor. A CYP3A substrate with a narrow therapeutic index refers to medication whose exposure-response relationship in the presence of CYP3A inhibitors may lead to serious safety concerns.
The following lists are NOT to be considered as all inclusive. Providers should review the patient's home medications and consult package inserts prior to initiation of Ibrutinib or Idelalisib for complete and updated information of cytochrome P450 inhibitor and inducer status.

Strong Inhibitors of CYP3A4/5
Boceprevir (Victrelis®)
Clarithromycin (Biaxin®, Biaxin XL®)
Conivaptan (Vaprisol®)
Grapefruit juice
Indinavir (Crixivan®)
Itraconazole (Sporanox®)
Ketoconazole (Nizoral®)
Lopinavir/Ritonavir (Kaletra®)
Nefazodone (Serzone®)
Nelfinavir (Viracept®)
Posaconazole (Noxafil®)
Ritonavir (Novir®, Kaletra®)
Saquinivir (Fortovase®, Invirase®)
Telaprevir (Incivek®)
Telithromycin (Ketek®)
Voriconazole (Vfend®)

Moderate Inhibitors of CYP3A4/5
Aprepitant (Emend®)
Atazanavir (Reyataz®)
Ciprofloxacin (Cipro®)
Darunavir (Prezista®)
Delavirdine (Rescriptor®)
Diltiazem (Cardizem®, Cardizem CD®, Cardizem LA®, Cardizem SR®, Cartia XT™, Dilacor XR®, Diltia XT®, Taztia XT™, Tiazac®)
Erythromycin (Erythrocin®, E.E.S. ®, Ery-Tab®, Eryc®, EryPed®, PCE®
Fluconazole (Diflucan®)
Fosamprevnavir (Lexiva®)
Imatinib (Gleevec®)
Mifeprostone **(Korlym®, Mifeprex®)**
Verapamil (Calan®, Calan SR®, Covera-HS®, Isoptin SR®, Verelan®, Verelan PM®)

Strong Inducers of CYP3A4/5
Carbamazepine (Carbatrol®, Epitol®, Equetro™, Tegretol®, Tegretol-XR®)
Phenytoin (Dilantin®, Phenytek®)
Primidone (Mysoline®)

Rifampin (Rifadin®)
Rifapentine(Priftin®)
St. John's wort

Moderate Inducers of CYP3A4/5
Bosentan (Tracleer®)
Efavirenz (Sustiva®)
Etravirine (Intelence®)
Modafinil (Provigil®)
Nafcillin
Nevirapine (Viramune®)
Phenobarbital (Luminal®)
Rifabutin (Mycobutin®)

Sensitive CYP3A substrates

Alfentanil (Alfentanil®)
Aprepitant (Emend®)
Buspirone
Conivaptan (Vaprisol®)
Darifenacin (Enablex®)
Darunavir (Prezista®)
Dasatinib (Sprycel®)
Dronedarone (Multaq®)
Eletriptan (Relpax®)
Eplerenone (Inspra®)
Everolimus (Afinitor®, Zortress®)
Felodipine (Plendil®)
Indinavir (Crixivan)
Lopinavir/Ritonavir (Kaletra®)
Lovastatin (Altoprev®, Mevacor®)
Lurasidone (Latuda®)
Maraviroc (Selzentry®)
Midazolam (Versed®)
Nisoldipine (Sular®)
Quetiapine (Seroquel®, Seroquel XR®)
Saquinavir (Fortovase®, Invirase®)
Sildenafil (Revatio®, Viagra®)
Simvastatin (Zocor®)
Sirolimus (Rapamune®)
Tolvaptan (Samsca®)
Tipranavir (Incivek®)
Triazolam (Halcion ®)
Vardenafil (Levitra ®, Staxyn®)

CYP3A substrates with narrow therapeutic range
Cyclosporine (Gengraf®, Neoral®, SanIMMUNE®)
Dihydroergotamine (Migranal®)
Ergotamine (Ergomar®)
Fentanyl (Abstral®, Actiq®, Duragesic®, Fentora®, Ionsys®, Lazanda®, Onsolis®, Subsys®)
Pimozide (Orap®)
Quinidine

Sirolimus (Rapamune®)
Tacrolimus (Prograf®)