UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE
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Protocol Title: MK-3475 in Combination with Standard RCHOP Therapy for Previously Untreated Diffuse Large B-Cell Lymphoma

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1.0 TRIAL SUMMARY

Abbreviated Title	MK-3475 (Pembrolizumab) +RCHOP in untreated DLBCL
Trial Phase	Pilot Study
Clinical Indication	Diffuse large B cell lymphoma patients who have not received prior systemic therapy
Trial Type	Nonrandomized, prospective trial
Type of control	N/a
Route of administration	IV
Trial Blinding	n/a
Treatment Groups	n/a
Number of trial subjects	30
Estimated duration of trial	36 months (enrollment)
Duration of Participation	48 months

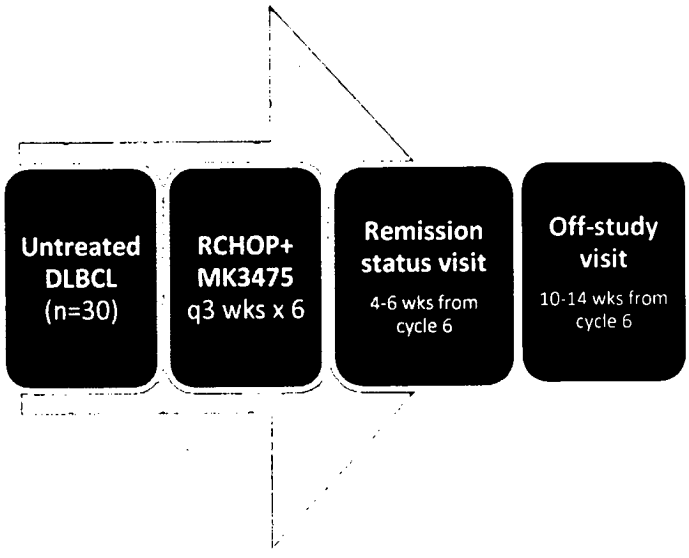
2.0 TRIAL DESIGN

2.1 Trial Design:

This is a nonrandomized, single-arm pilot study which will evaluate the safety and tolerability of MK-3475 (pembrolizumab) in combination with standard, full-course RCHOP chemoimmunotherapy in untreated DLBCL

Study duration: Subjects will be enrolled over 36 months. Last subject out (completing study follow-up) is projected to occur at 48 months. Subsequently, patients may be followed for outcomes for up to 5 years using standard-of-care assessments.

2.2 Trial Diagram



3.0 OBJECTIVES & HYPOTHESIS

3.1 Primary Objective

To measure the toxicity profile of MK-3475 (pembrolizumab) when co-administered with full-course RCHOP in subjects with previously untreated DLBCL.

Hypothesis: The addition of MK-3475 to 6 cycles of induction RCHOP for subjects with previously untreated DLBCL will not result in a significant increase in toxicity and treatment-related mortality beyond that which is expected using RCHOP alone.

Secondary Objective: To assess clinical outcomes including response rate, event-free survival, and overall survival after MK-3475 + RCHOP induction for subjects with previously untreated DLBCL.

3.2 Exploratory Objective:

To measure baseline expression of proteins in the programmed death-1 (PD-1) family on tumor cells and coexisting immune infiltrates, using archival tissue when

available, to measure peripheral blood T cell subsets before and after treatment using flow cytometry, and to measure baseline Vitamin D (25-hydroxy, total); and to explore relationships with these parameters and likelihood of response to therapy and outcomes.

4.0 BACKGROUND & RATIONALE

4.1 Background

Diffuse large B-cell lymphoma (DLBCL) is an aggressive lymphoid malignancy comprised of large, transformed B cells. DLBCL is the most common B-cell lymphoid neoplasm in the United States and Europe and accounts for approximately 28 percent of all mature B-cell lymphomas.[1] It most commonly presents in older adults, with a median age at diagnosis of 65 years, and exhibits an aggressive course with a variable prognosis. Standard therapy for DLBCL was defined in 1993 as the CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone).[2] Standard induction therapy subsequently evolved to include rituximab (RCHOP), after a prospective randomized trial found improved survival without significantly increased toxicity could be achieved with addition of rituximab immunotherapy.[3]

However, since the development of RCHOP, further efforts to improve upon the therapeutic index of modern therapy by adding chemotherapy agents, increasing dose density, or consolidating first-line therapy with high-dose chemotherapy and stem cell transplantation have shown limited success.[4-7] These therapies have failed to improve the therapeutic index of RCHOP overall, resulting in increased toxicity and modest or absent impact on efficacy. This suggests that increasing chemotherapy intensity—through either dose density or adding additional agents or high-dose consolidation with autologous stem cell rescue—is unlikely the best strategy for improving patient outcomes with DLBCL. Currently, 33-55% patients with high-risk clinical features are either refractory to initial induction RCHOP or relapse soon after therapy, typically within 2 years after its completion.[8-10]

Novel treatment approaches, with mechanisms of action and toxicity profiles distinct from those of cytotoxic chemotherapy, are clearly needed for DLBCL. In light of the high incidence of DLBCL, development of such therapies represents a global unmet medical need. Furthermore, since radiographic complete remission after induction is required for a high probability of disease control, novel therapies focused on the induction phase warrant the highest priority for further evaluation.

4.1.1 MK-3475 (Pembrolizumab): Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades.[11] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in

cancer tissue and favorable prognosis in various malignancies. [12-16] In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

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 unwanted or 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).[17, 18] The structure of murine PD-1 has been resolved.[19] 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.[17,20,21,22] 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.[23,24] 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. [25, 26] Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [17]. 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.[23,28,29,30] 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.[23] Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL).[31] 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.

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

4.2 Rationale for MK-3475 (Pembrolizumab) in Lymphoma

PDL1 is expressed by a subset of immune suppressor and tumor cells in non-Hodgkin lymphomas.[32] Tumor cell PD-L1 expression, which is proposed to cause T-cell exhaustion and defective immune surveillance, is associated with likelihood of clinical response to anti-PD-1 therapy in solid tumors, but such a relationship has not been defined in in lymphoma.[33] One clinical trial of anti-PD-1 blockade in DLBCL has been reported, using the monoclonal antibody pidilizumab as maintenance after autologous transplant for relapsed or refractory disease.[34] In that single-arm study, PD1 blockade was safe, with 19% experiencing grade 3-4 neutropenia (without symptoms or complications) the most notable high-grade toxicity; there was a 3% rate of drug-related SAE's. Notably, 70% of subjects with a positive post-salvage PET CT scan-- typically associated with a poor outcome after transplant[35]-- remained in remission 16 months after their first dose. Treatment with pidilizumab resulted in a significant increase in the absolute number of PDL1-bearing activated helper T cells in the peripheral blood, and changes in PD-1 bearing monocytes. In addition, an increase in the absolute number of circulating CD8 positive and central memory T cells, as well as CD4 positive central memory T cells, were observed. While exploratory and hypothesis generating, these findings supported an on-target and immunomodulatory effect of anti-PD-1 blockade in the setting of DLBCL.

A second trial of PD1 blockade in B-cell lymphomas, specifically relapsed or refractory follicular lymphoma, was subsequently reported.[36] In that study, pidilizumab was tested in conjunction with rituximab in treating 32 subjects. A median 10 pidilizumab treatments were given, and in conjunction with rituximab produced an overall response rate of 66%; median time to observed response was 88 days (range, 53–392). It was observed that naïve, effector memory, and central memory CD4+ T cells were increased post-treatment compared to baseline. In 2014, a study of nivolumab (a fully human anti-PD1 antibody) in relapsed lymphoma including a cohort with DLBCL was reported.[37] In that study, 36% (4/11) of patients with DLBCL responded to nivolumab as a single agent.

To date, no studies of PD1 blockade in treatment-naive lymphoma subjects have been reported, although this setting may represent a more opportune stage for immunomodulatory therapy. As opposed to the relapsed/refractory or post-transplant setting, in which prior cytotoxic therapy or absent and minimal tumor burden may present suboptimal conditions for generation of a robust immune

response, treatment-naive patients have relatively intact immunity, and tumor and immune infiltrate coexist in nodal tissue. In addition, certain therapies may enhance T cell antitumor immunity when combined with anti-PD-1 blockage. In the case of DLBCL, the standard RCHOP regimen contains cyclophosphamide, which has been shown to induce T lymphocyte homeostatic proliferation, and enhance antigen-driven proliferation of tumor-immune lymphocytes.[38] PD1 blockade concomitant with cyclophosphamide-containing chemotherapy may therefore result in additive augmentation of T cell antitumor immunity, although concomitant prednisone use may exert a suppressive effect. Further investigation of changes in T-cell subsets over time, and clinical outcomes when combining MK-3475 with chemotherapy, are underway in the solid tumor setting and proposed herein.

Given evidence of tolerability and immune activation in lymphoma patients receiving anti-PD-1 therapy to date, and in light of the high worldwide incidence of DLBCL and its incurability in particular subsets, anti-PD-1 blockade in conjunction with standard chemoimmunotherapy for DLBCL represents an important avenue for further research.
The selected subject population includes any patient with diffuse large B-cell lymphoma who are planned to receive 6 courses of R CHOP chemoimmunotherapy. The safety of co-administered PD1-blockade using MK-3475 and RCHOP chemoimmunotherapy is unknown. However, its unique and relatively favorable adverse effect profile to date suggest that such a combination may be feasible without expectation for significant additive toxicity.
Therefore, this study proposes to assess the safety, tolerability, and immune activation of MK-3475, when co-administered with rituximab CHOP during induction in subjects with previously untreated DLBCL.

4.2.1 Rationale for Dose Selection/Regimen/Modification

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 pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No maximum tolerated dose (MTD) has been identified.

In KEYNOTE-001, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab 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 pembrolizumab 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.

Population PK analysis has been performed and has confirmed the expectation that intrinsic factors do not affect exposure to pembrolizumab 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.

4.2.2 Rationale for Endpoints:

The primary endpoint is estimation of clinically relevant toxicity and treatment-related mortality which result from the addition of MK-3475 to RCHOP chemoimmunotherapy (see section 8.0, Statistical Analysis Plan).

4.2.2.1 Exploratory Endpoints:

Overall response rate, event-free and overall survival. Event-free survival (EFS) is defined as time from diagnosis until relapse or progression, non-protocol re-treatment of lymphoma, or death as a result of any cause. Overall survival is defined as survival from date of diagnosis to death from any cause.

4.2.2.2 Biomarker Research:

Tissue-based assays for tumor and immune infiltrate will be conducted centrally when archival tissue is available.

In addition, we propose flow cytometric evaluation of CD3, CD4, CD8, CD14, PD-1, PD-L1, PD-L2 on peripheral blood mononuclear cells at several time points (see section 7.1.2.7). In previous studies of lymphoma patients treated with PD1 blockade, alterations in both PD L1 and PD 1 bearing monocytes have been observed in the peripheral blood. However neither of these studies were performed before or during first-line treatment. These analyses will seek to identify alterations in T cell subsets for comparison with these historical studies, and exploration of association with treatment outcomes achieved with study therapy.

5.0 METHODOLOGY

Entry Criteria: Previously untreated diffuse large B cell lymphoma or grade 3B follicular lymphoma (of any stage). Subjects must be planned to receive full course (6 cycles) of RCHOP chemoimmunotherapy as per clinical standard of care. Patients may have *de novo* DLBCL, and /or any of the following:-

- Composite lymphomas, which include both diffuse DLBCL and another histology (most commonly follicular lymphoma) in the same lymph node

- Transformed lymphoma with DLBCL histology, as long as the patient has not received prior therapy for lymphoma

- Discordant presentations, such as DLBCL in a lymph node and low-grade lymphoma such as follicular lymphoma in the bone marrow.

5.1.1 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.

3. Have measurable nodal disease, including at least 1 disease site measuring 1.5 cm in longest dimension on CT or FDG-PET
4. Have a performance status of 0 or 1 on the ECOG Performance Scale (PS)
5. Demonstrate adequate organ function as defined in Table 1 below:

Table 1: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL except in cases of marrow infiltration by lymphoma
Platelets	≥100,000 / mcL except in cases of marrow infiltration by lymphoma
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L except in cases of marrow infiltration by lymphoma
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants, or subject is shown to have an antiphospholipid antibody on workup
[a]Creatinine clearance should be calculated per institutional standard.	

6. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
7. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
8. Male subjects should agree to use an adequate method of barrier contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

5.1.2 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study drug or using an investigation device within 4 weeks of the first dose of treatment.
2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
3. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
4. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.
5. No active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment
6. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
7. Has an active infection requiring intravenous antibiotic therapy.
8. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
9. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

10. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
11. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
12. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
13. Has known active Hepatitis B (e.g., HBsAg reactive or HBV DNA detectable) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
14. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

5.2 Study Treatments

The experimental treatment MK-3475 is outlined below in Table 2. RCHOP is to be administered at standard doses which may be adjusted at clinician discretion at baseline and during treatment (rituximab 375 mg/m2 day 1, cyclophosphamide 750 mg/m2 day 1 , doxorubicin 50 mg/m2 day 1, vincristine 2 mg capped dose day 1 , prednisone 100 mg PO daily day 1-5).

Institutional guidelines and clinical judgment will be followed with regard to administration of RCHOP.

MK-3475 is to be administered on the same day or within 3 days of RCHOP for each cycle.

Table 2: Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
MK-3475	200 mg	Q3 wks induction*	IV infusion	Induction	Experimental

5.2.1 Dose Modification (Escalation/Titration/Other)

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below.

Table 3 Dose Modification Guidelines for Pembrolizumab-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	Recurrent grade 2, or grade 3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to Section 5.4: Infusion Treatment Guidelines for further management details.

[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Subjects who require delay in any RCHOP cycle for more than 14 days during the induction period (for any reason other than disease progression) will receive no further study therapy, and count toward the study stopping rule (see section 8.1) RCHOP administration may continue if pembrolizumab is held due to drug-related toxicity as per Dose Modification guidelines (Table 3) Subjects who discontinue study therapy will remain in follow-up as per protocol for improvement or stabilization of study drug-related toxicities.

5.2.2 Timing of Dose Administration

Trial treatment should be generally be administered on the day before (cycle 1) or concurrently (cycles 2-6) with RCHOP, every 3 weeks, after completion of baseline procedures/assessments Trial Flow Chart (Section 6.1). Note that MK-3475 may be administered within 3 days of RCHOP if indicated. Missed doses of MK-3475 will not be made up.

MK-3475 and RCHOP may both be delayed for up to 14 days if clinically indicated. However, as noted in in section 5.2.1, , any subject who requires a delay in any RCHOP cycle for more than 14 days (e.g. 5 weeks from a prior dose on a planned 3 week cycle) requires discontinuation from therapy.

MK-3475 will be administered as a 30 minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. The Pharmacy Manual contains specific instructions for MK-3475 reconstitution, preparation of the infusion fluid, and administration.

5.2.3 Trial Blinding/Masking

This is an open-label, single arm prospective trial; therefore, the investigator and subject will know the treatment administered.

5.3 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 vaccination may be required. 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 and the subject.

5.3.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all

prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.
Use of filgrastim (GCSF, Neupogen) or peg-filgrastim (peg-GCSF, Neulasta) is permitted at the clinician's discretion.

Intrathecal methotrexate or cytarabine may be administered for central nervous system prophylaxis at the clinician's discretion.

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. Concomitant medications administered are to be recorded after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.3.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Induction Phase of this trial:

- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than MK-3475
- Radiation therapy (may be administered more than 30 days after last dose of study therapy if planned for consolidation)
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than as prescribed with the RCHOP regimen, or for management of rituximab or study-drug related infusion reactions, or if indicated to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids is permitted

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary. The Exclusion Criteria describes other medications which are prohibited in this trial.

5.4 Supportive Care

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

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to treat as below.Refer to Section 5.2.1 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- **Pneumonitis**:
  - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
  - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

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

  - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

    - For **T1DM** or **Grade 3-4** Hyperglycemia
        - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
        - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:

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

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

    - **Grade 2** hyperthyroidism events (and **Grade 3-4** hypothyroidism):
        - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
        - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
    - **Grade 3-4** hyperthyroidism
        - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hepatic**:
    - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
        - Treat with IV or oral corticosteroids
    - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
    - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
    -
- **Renal Failure or Nephritis**:

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

- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 2 business days of completion of infusion.

4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion), recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4:	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine	No subsequent dosing

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Life-threatening; pressor or ventilatory support indicated	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.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.4.1 Additional Events of Clinical Interest

An overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

5.5 Diet/Activity/Other Considerations

5.5.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.5.2 Contraception

MK-3475 may have adverse effects on a fetus in utero. Furthermore, it is not known if MK-3475 has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy. The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception

requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.5.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with MK-3475, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck without delay and within 2 business days of investigator knowledge if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Merck and followed as described above and in Section 7.2.2.

5.5.4 Use in Nursing Women

It is unknown whether MK-3475 is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.6 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be discontinued from the trial at the discretion of the investigator. In addition, a subject may be withdrawn by the investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Subjects who require cessation of study therapy but do not withdraw consent may remain in standard follow-up for up to 5 years.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed disease progression

  Note: A subject may be granted an exception to continue on treatment with radiographic progression if clinically stable or clinically improved, at clinician discretion
- A required dose delay of RCHOP of more than 14 days (past the typical 3 weekly cycle) during the Induction Period

- Adverse experiences deemed unacceptable by the investigator, including those described in Section 5.2 and Table 3
- Intercurrent illness that does not recover within 12 weeks, preventing further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

Subjects who discontinue for reasons other than progressive disease will complete off-study visit at 12 weeks after the last dose of MK3475 (+/- 14 days). However, all patients may have post-treatment follow-up for disease status up to 5 years at longest-- or until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up.

(For those with unacceptable adverse experiences grade 3 or higher, as described in section 5.2.1,follow-up on study until resolution or stabilization of toxicities is required up to a maximum of 1 year from occurrence of the toxicity.)

5.7 Subject Replacement Strategy

Subjects who fail to complete study therapy during induction will not be replaced.

5.8 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug
   In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Treatment Cycle/Title	Screening Period	Induction Treatment			Remission Status visit	Off-Study Visit[8]	Long term follow up
		C1 Day 1	C1 Day 2	Cycles 2-6[1]			

Scheduling Timing and Window	-42 to -1d	± 3d		± 3d	4-6 weeks after Cycle 6 ± 7d	12 weeks after cycle 6 ± 14d	
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Medical History	X						
Prior and Concomitant Medication Review	X	X		X	X	X	
Trial Treatment Administration		X	(RCHOP ONLY)	X			
Post-study anticancer therapy status							X
Survival Status							X
Review Adverse Events[3]	X	X		X	X	X[3]	
Physical Examination	X	X		X	X	X	
Vital Signs and Weight	X	X		X	X	X	
Height	X						
ECOG Performance Status	X	X		X	X	X	
Pregnancy Test – Urine or Serum β-HCG[2]	X						
PT/INR and aPTT	X						
CBC with Differential[10]	X	X		X	X	X	
Comprehensive Serum Chemistry Panel[10] and LDH	X	X		X	X	X	
HepB S Ag, Core Ab Hep C and HIV screen	X						
Urinalysis	X						
T3, FT4 and TSH	X			X	X	X	
Vitamin D level (25-hydroxy Vitamin D, total)	X						
Tumor Imaging[4]	X				X		
Bone Marrow Biopsy and Aspirate[5]	X				X		
Other Procedures (Optional)[6]	X						
Archival Tissue Collection, if Feasible[7]	X						
Correlative Studies Blood Collection[8]	X			X	X	X	

1. On Cycles 2-6, MK-3475 and RCHOP may be administered on the same day if scheduling/administrative factors permit. MK-3475 and RCHOP should be co-administered within 3 days. RCHOP+MK-3475 cycles may be delayed as clinically indicated.

2. For women of child-bearing potential only.

3. AE will be recorded from the time of a subject signing consent, up until 90 days after the last dose of MK-3475.

4. See Section 7.1.2.5: Tumor Imaging. Baseline and Remission Status imaging is mandatory. Other interim and surveillance scans are performed at clinician discretion. Baseline imaging must be performed within 8 weeks of initiating study drug therapy. Remission status imaging should be performed using FDG PET-CT,

5. Screening bone marrow biopsy and aspirate may be completed up to 12 weeks prior to study enrollment, and at time of CR. Bone marrow requirements may be waived at the discretion of the Sponsor-Investigator.

6. See Section 7.1.4. Other procedures during screening are at the discretion of the treating investigator and may include standard-of-care assessments of cardiac function, central venous access device placement, other laboratory studies, or other measures.

Treatment Cycle/Title	Screening Period	Induction Treatment			Remission Status visit	Off-Study Visit[8]	Long term follow up
		C1 Day 1	C1 Day 2	Cycles 2-6[1]			
Scheduling Timing and Window	-42 to -1d	± 3d		± 3d	4-6 weeks after Cycle 6 ± 7d	12 weeks after cycle 6 ± 14d	

7. The presence of archival tissue will be assessed during screening. When available this tissue will be provided for central biomarker analysis.

8. Baseline correlative blood draw may be done at any time prior to the C1D1 dose. Induction Treatment blood draw is completed only during C3D1, prior to study dosing. Off study blood draw should be done at time of disease progression or prior to start of second-line anticancer therapy, if possible, See Section 7.1.2.7. for discussion of correlative study blood draws.

9. The Off-Study visit is performed 12 weeks after the last dose of study drug, irrespective of the reason drug is stopped (completion of therapy, discontinuation for toxicity, other reason). It may be performed earlier in subjects who require additional antilymphoma therapy.

10. See Table 6 for details of these tests. Mid-cycle CBC with differential and CMP (without LDH) are to be performed as in section 7.1.3.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.1 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. Laboratory and imaging studies performed for standard of care purposes may be used to satisfy screening requirements, if they are performed within the appropriate timeframe noted in Section 6.1. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

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

7.1.1 Administrative and Study-Related Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level. The informed consent will adhere to IRB/ERC requirements, and applicable laws and regulations.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with MK-3475 exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE).
Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Physical Exam

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

7.1.2.3 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.4) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.5 Tumor Imaging and Assessment of Disease

Tumor imaging consists of standard of care imaging at baseline during the screening period, including either FDG-PET/CT or contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis.

FDG PET-CT scanning is preferred at baseline and required for determination of Remission Status visit. For measurement of response, 2014 criteria as described in "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification" will be used (see Appendix 14.3).[39]

- **Baseline imaging** must be performed within 8 weeks of initiating study drug therapy. Additional baseline imaging may be performed as indicated for standard of care and clinical purposes including MRI, or CT imaging of the neck.
- **Remission Status** tumor imaging performed 4-6 weeks, +/-7 days, after 6 cycles of induction therapy with MK-3475 + RCHOP is required.

Interim restaging using CT scan during R CHOP may be conducted as per standard of care but are not required.

All CT scans should be performed with IV contrast unless contraindicated, and abdominal and pelvis scans should be performed with oral contrast. When FDG PET/CT is performed, IV and oral contrast are not required and the scan used for PET attenuation correction is adequate.

All CT and FDG-PET/CT scans are to be interpreted locally; central review of radiology will not be performed.

7.1.2.6 Bone marrow aspirate and biopsy

A bone marrow aspirate and biopsy will be obtained up to 12 weeks before the first dose of study drug, and for confirmation of CR when indicated. FDG PET-CT may suffice for identification of bone marrow involvement[39] and bone marrow aspirate and biopsy requirements may be waived by the Sponsor-Investigator. These samples will be evaluated locally.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Assessment of available archival tumor tissue for correlative study analysis will be performed during the screening period. Any available pretreatment biopsy tissue will be provided for central correlative study analysis.

Peripheral blood correlative study samples will be performed at the following time-points (see Section 6.1, Trial Flow Chart):

1. Baseline (collected any time prior to cycle 1 day 1 study drug dosing)
2. Cycle 3 day 1 prior to drug dosing
3. At the Response Assessment visit (4-6 weeks, +/-7 days, after cycle 6) for subjects who complete all 6 cycles of therapy
4. At the off-study visit, at the time of disease progression, or at time of initiation of second-line therapy (whichever occurs first).

Specimen Requirements: Submission for flow cytometry

- A 5-10 mL specimen of peripheral blood in a lavender- (EDTA) or green- (sodium heparin) tube is acceptable for each draw.
- Storage/Transport Temperature: Specimens can be transported with a cold pack or wet ice, but do not fix or freeze specimens.
- Unacceptable Conditions: Frozen specimens, specimens greater than 48 hours old, specimens fixed in formalin for flow cytometry
- Address for shipping specimens:
  Attn: Katy Dougherty, Hematopathology Lead
  Seattle Cancer Care Alliance
  Hematopathology Laboratory G7800
  825 Eastlake Ave E.
  Seattle, WA 98109

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below and in section 6.1 (Study Flow Chart). All chemistry and hematology studies required to start a new cycle may be performed within 3 days of dosing prior to day 1 of that cycle. In addition, a CBC with differential and chemistry panel (excluding LDH; see Table 6) will be performed between cycles. The recommended timing of this mid-cycle laboratory evaluation is between day 8-15 of each cycle.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 6 below.

HBV Surface Antigen (Hep B S Ag), HBV Core Antibody (Hep B Core Ab), HIV screening, Hep C Ab screening will be performed during the screening

period, and reviewed and managed at the study site as per clinical standard of care.

Table 6: Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
	(CO_2 or biocarbonate)	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		HBV Surface Antigen, HBV Core Ab, HIV screen, Hep C Ab screening
			Vitamin D (25-hydroxyvitamin D, total)
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

‡ If considered standard of care in your region.

After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.4 Other Procedures

Standard of care practices including baseline determination of cardiac ejection fraction, placement of a vascular access devices, mid-cycle analysis of laboratory parameters during therapy, any additional imaging, additional laboratory studies for evaluation or management tumor lysis, and any medications for management of rituximab infusion reactions may be undertaken as part of standard of care. Dose reductions of RCHOP may be performed at discretion of the treating clinician.

7.1.5 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, 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 7.2 - Assessing and Recording Adverse Events.

7.1.6 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.6.1 Screening Period

The screening period begins upon signing consent and includes evaluation of available tissue specimen for study-related, central review, any ancillary/staging/laboratory testing and standard-of-care evaluations (including "Other Procedures" as in Section 7.1.4) prior to Cycle 1 Day 1 of study therapy. The screening period may last up to 42 days.

7.1.6.2 Induction Treatment Period

The induction treatment period includes RCHOP + study drug therapy, administered every 3 weeks for 6 cycles. MK-3475 is to be administered on cycle 1 day 1, and RCHOP will be given on Cycle 1 day 2. On future cycles, both treatments will be administered on the same day when feasible. However, MK-3475 and RCHOP may be given up to 3 days apart if needed for scheduling or administrative reasons. Whenever RCHOP treatment is delayed, study drug administration will also be delayed so that MK-3475 and RCHOP are co-administered on the same day (or within 3 days). Interim restaging will be performed as clinically indicated (see Tumor Imaging 7.1.2.5).

7.1.6.3 Remission Status Visit

All subjects will undergo a visit for determination of remission status, 4-6 weeks (+/- 7 d) after completion of induction therapy.

This visit will include review of tumor imaging (FDG PET-CT)) as well as medical history, physical exam, and laboratory evaluations required for determination of remission status. Remission status is to be determined according to 2014 Criteria ("The Lugano Classification")[39] as in Appendix 14.3.

For patients with equivocal post-induction imaging or clinical findings, in whom remission status cannot be clearly ascertained, further workup as per clinical standard of care including tumor biopsy or repeat imaging should be undertaken to confirm remission status (PR or CR) prior to proceeding onto the Follow-Up Period

7.1.6.4 Off-Study Visit

12 weeks (+/- 14 d) after the last dose of MK-3475, irrespective of cause of cessation, an off-study visit should be performed. However, if a subject requires additional anti-lymphoma therapy, the off-study visit may occur earlier. The off-study visit is intended to coincide generally with the requirement that ECI be reported up to 90 days from last dose of MK-3475 except for subjects who require additional anticancer therapy.

The off-study visit will include laboratory studies (CBC diff, CMP, LDH), medical history, physical exam, remission status, concomitant medications, adverse events, and documentation of any ECI and subsequent management.
After the off-study visit, additional surveillance for DLBCL relapse will be conducted as per routine standard of care for up to 5 years unless other criteria for withdrawal are met (see Section 5.6).

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including

placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.
Adverse events grade 3 and higher, as well as AEs requiring clinical intervention/dose modification, ECIs, and SAEs of any grade, will be recorded from the time the consent form is signed through 90 days following cessation of MK-3475 treatment on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to Merck

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for MK-3475 by 20% over the prescribed dose. No specific information is available on the treatment of overdose of MK-3475. In the event of overdose, MK-3475 should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. This reporting threshold will also be used for IRB reporting.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 2 business days of investigator knowledge to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.2 Reporting of Pregnancy and Lactation 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 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 2 business days of investigator knowledge to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.3 Reporting Requirements for Adverse Events/Adverse Reactions

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

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

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

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

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by a qualified investigator to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period

specified in the previous paragraph also must be reported immediately to Merck.

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

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) as defined below, and must be reported within 2 business days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

For the time period beginning when the consent form is signed through 90 days after the last dose of MK-3475, or until the initiation of new anticancer therapy (whichever is earlier), any ECI must be reported within 2 business days to Merck Global Safety.

Events of clinical interest for this trial include:
1. an overdose of Merck product, as defined in Section 7.2. Definition of an Overdose for This Protocol and Reporting of Overdose to Merck, that is not associated with clinical symptoms or abnormal laboratory results.

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

7.2.4 Evaluating Adverse Events

A qualified investigator will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness. Adverse events will be recorded, and SAE's reported, from the time of signed consent and for up to 90 days after the last treatment of MK-3475 is administered.

Table 7:Evaluating Adverse Events

A qualified investigator will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization**	

	(hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or
	Is a new **cancer;** (that is not a condition of the study) **or**
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within2 business days of investigator knowledge..
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units
Action taken	Did the adverse event cause the Merck product to be discontinued?
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):

	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE MERCK

		PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by a qualified investigator according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.		There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.
No, there is not a reasonable possibility Merck product relationship		Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

7.2.5 Sponsor-Investigator Responsibility for Reporting Adverse Events

The sponsor-investigator is required to report all problems, events and information that require prompt reporting to the IRB within ten (10) calendar days of learning of the problem.

Adverse events grade 3 and higher, as well as AEs requiring clinical intervention/dose modification, ECIs, and SAEs of any grade, will be reported from the time of signing of consent up until 90 days following the last dose of MK-3475.

If a problem, event or information is determined to be an unanticipated problem involving risks to participants or others, it will be reviewed by the convened

IRB, appropriate steps will be taken and it will be reported to appropriate institutional and governmental officials as provided under applicable law.

For the purposes of this protocol, the terms Adverse Event, Serious Adverse Event (Related, Possibly Related or Unexpected) and Unanticipated Problem are defined in accordance with Fred Hutchinson Cancer Research Center Institutional Review Board Policy 2.6, version 6.03.

Reporting Requirements

Expedited Reporting

With respect to each research study he or she is conducting, the principal investigator must ensure that the following problems, events, and information involving risks to research participants or others are reported to the IRB not later than ten (10) calendar days after he or she first becomes aware of the problem, event, or information.

Adverse Events Requiring Expedited Reporting

Adverse events require expedited reporting if they meet all three of the following criteria:
(1) unexpected, and
(2) related or possibly related to the research and
(3) serious or suggest that the research places research participants or others at a greater risk of physical or psychological harm than was previously known or recognized.

Unless otherwise specified in the Protocol, therapeutic oncology protocols are not required to specify monitoring parameters for Grade I or II toxicities as described in the Common Terminology Criteria for Adverse Events published by the National Cancer Institute. These adverse events are expected and occur routinely in the subject population being studied. They should be monitored and treated in the practice of routine clinical care.

8.0 STATISTICAL ANALYSIS PLAN: STUDY DESIGN AND STATISTICAL ANALYSIS PLAN

This is a single-arm pilot study which aims to estimate the toxicity of the addition of MK-3475 to RCHOP. Since MK-3475 possesses a novel mode of action, and a safety profile independent of dose and different than RCHOP, a phase I study is not planned. Rather, this is a pilot study of the addition of MK-3475 to standard RCHOP with a primary objective of measuring toxicity, with particular attention to Events of Clinical Interest (potential immune-mediated adverse events).

RCHOP administered every 21 (RCHOP-21) days is associated with significant toxicity, especially hematologic toxicity (grade 3-4 neutropenia in 60-80%), and is associated with a mortality rate of 5-10% depending on age; in addition, only 80-90% complete full-course

therapy. [3,5,6,40] Infusion reactions are common with rituximab on the first administration. [3,5,6,40] About 10-13% require reduction or elimination of a chemotherapy drug, even when white blood cell growth factors are routinely used, due to toxicity.[5,6,41] Studies of RCHOP-21 do not consistently parse out clinically relevant grade 3-4 toxicities from all high-grade toxicities, many of which are expected and relatively unimportant (asymptomatic grade 3-4 laboratory findings or alopecia). This poses a challenge to the rational design of studies seeking to identify the assess the clinically relevant, additive toxicity of a novel agent such as MK-3475 to standard RCHOP. One prospective study testing the addition of rituximab to CHOP or CHOEP (the MiNT trial) showed an overall grade 3-4 adverse event rate of 37% when grade 3 hematologic toxicity, and grade 4 hematologic toxicity without signs or symptoms, were excluded.[40]

From this study and other available data with RCHOP-21, about 40% of patients receiving full-course therapy will experience at least one clinically relevant grade 3-5 toxicity – defined as grade 3-5 toxicity *excluding* alopecia, grade 3 hematologic toxicity, and grade 4 hematologic toxicity without and signs or symptoms. Amendment 4.0 expands the trial to 30 patients. This sample size will permit the estimation of a 40% incidence of grade 3-5 clinically relevant toxicity with a lower bound of 23% and upper bound of 57% (95% confidence interval). This expansion will also enhance the ability to detect uncommon events and relevant patterns, including immune-related adverse events.

Secondary endpoints include measurement of response rate, and event-free and overall survival. Event-free survival (EFS) is defined as time from diagnosis until relapse or progression, non-protocol re-treatment of lymphoma, or death as a result of any cause. Overall survival is defined as survival from date of diagnosis to death from any cause.

8.1 Stopping Rule

In conjunction with the amendment to expand the trial to 30 patients, if more than 3 patients fail to complete 6 cycles of RCHOP therapy (for any reason other than disease progression), or die during or within 90 days of the last dose of RCHOP (due to any cause other than disease progression or as a complication of subsequent, non-protocol therapy for DLBCL), enrollment will be stopped. Patients who require discontinuation of study therapy because they require a delay in administering RCHOP of more than 14 days (beyond scheduled administration, see section 5.2.1) will count toward the stopping threshold. Routine dose modifications, unless they result in RCHOP delay of more than 14 days or RCHOP discontinuation, will not count toward the stopping threshold.

Once enrollment is held, the nature of events to leading to stopping will be assessed by the Principal Investigator and reported to institutional regulatory authorities, in accordance with the institutional Data Safety Monitoring Plan. The institutional Data Safety Monitoring Committee will determine whether any further accrual may proceed.

Statistical analysis will entail descriptive statistics, and survival analysis including Kaplain-meier estimates, log-rank testing of univariate prognostic factors, cox

proportional hazards analysis, as well as T-testing and regression analysis for comparing continuous variables in correlative study data.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF INVESTIGATIONAL PRODUCT

9.1 Investigational Product

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

Table 8: Product Descriptions

Product Name & Potency	Dosage Form
MK-3475 100 mg/ 4mL	Solution for Injection

9.2 Packaging and Labeling Information

Investigational product will be labeled in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor-investigator and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Investigational product must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.
Investigational product may not be used for any purpose other than that stated in the protocol.

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the investigational product received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable

federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 DATA AND SAFETY MONITORING PLAN

Ongoing trial oversight is carried out by the Principal Investigator and study staff.. These individuals will communicate on a regular basis to review recently acquired data and adverse events. The data recorded within the research charts and protocol database is compared with the actual data that is available from the medical record and/or clinical histories. Data detailed in the research case report forms includes the nature and severity of all toxicities, which are also reported as described above.

Institutional support of trial monitoring will be in accordance with the FHCRC/UW Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support coordinates monitoring for data accuracy and compliance by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by a the Consortium Data Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

The IRB has the authority to suspend or terminate the study should it be deemed necessary.

11.0 RECORDS

Research staff under the supervision of the investigators will maintain case report forms and secured databases on the relevant clinical and laboratory data. Records maintained in investigators' offices will be secured with access limited to study personnel. Authorization for access to medical records will be obtained from all patients in accordance with provisions of the Health Insurance Portability and Accountability Act (HIPAA).

12.0 REGULATORY RESPONSIBILITIES OF SPONSOR-INVESTIGATOR

The Sponsor-Investigator will ensure that the study is conducted in accordance with all applicable institutional, state, and federal regulatory requirements, including, but not limited to: compliance with requirements for IRB and other regulatory approvals, monitoring responsibilities, reporting obligations, and compliance with standards for written informed consent from all patients entering the study. In addition, the IND sponsor will ensure oversight of the study via data and safety monitoring as described above.

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14.0 APPENDICES

14.1 ECOG Performance Status

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

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

14.2 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

14.3 Response Criteria: "The Lugano Classification" [38]

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	**Complete metabolic response**	Complete radiologic response (all of the following)
	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
Lymph nodes and extralymphatic sites	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	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial metabolic response**	**Partial remission (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	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 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 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 or biopsy or an interval scan	Not applicable
No response or stable disease	**No metabolic response**	**Stable disease**
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

Response and Site	PET-CT–Based Response	CT-Based Response
Bone marrow	No change from baseline	Not applicable
Progressive disease	**Progressive metabolic disease**	**Progressive disease requires at least 1 of the following**
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	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 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.