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UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE
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SEATTLE CANCER CARE ALLIANCE

TITLE: Phase II Study of Anti-CD20 Antibody Therapy Plus Pembrolizumab (MK-3475) in Subjects with Relapsed Follicular and Diffuse Large B-Cell Lymphoma

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Table of Contents

TRIAL SUMMARY

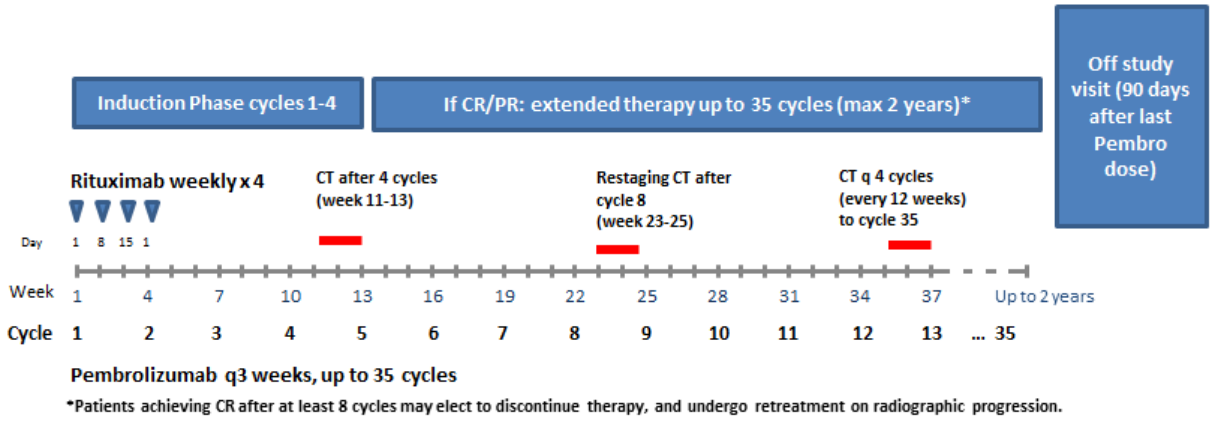
Abbreviated Title	Pembrolizumab and CD20-Directed Therapy in relapsed/refractory FL and DBLCL
Trial Phase	II
Clinical Indication	FL and DLBCL who have relapsed or refractory follicular or diffuse large B cell lymphoma
Trial Type	Nonrandomized, three-arm prospective clinical trial
Type of control	N/a
Route of administration	IV
Trial Blinding	N/a
Treatment Groups	A) Relapsed/refractory FL (pembrolizumab and rituximab), B) Relapsed/refractory DLBCL ineligible or declining autologous stem cell transplant (pembrolizumab and rituximab), C) Relapsed/refractory FL (pembrolizumab and obinutuzumab)
Number of trial subjects	Total 62 A) up to 20 patients, B) up to 17 patients, C) up to 25 patients
Estimated enrollment period	24 months
Estimated duration of trial	48 months
Duration of Participation	48 months
Estimated average length of treatment per patient	16 months

1.0 TRIAL DESIGN

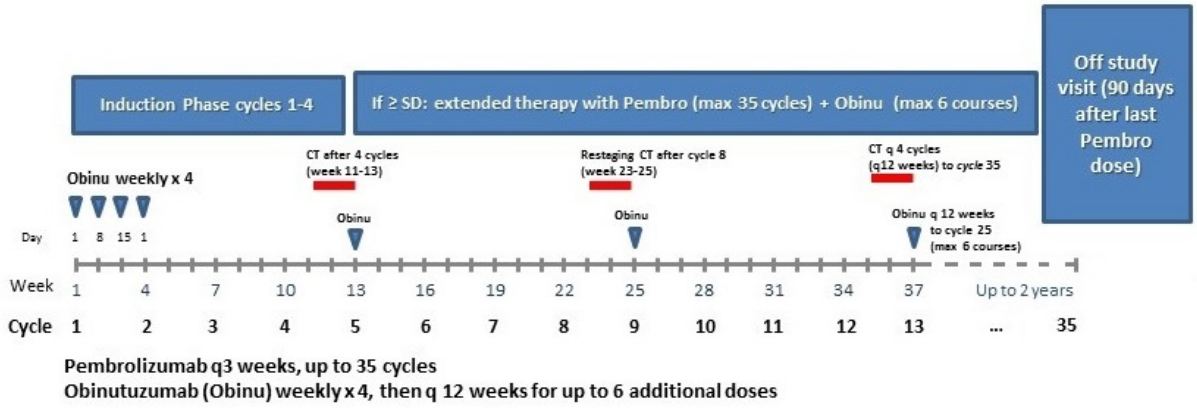
1.1 Trial Design:

The study is designed as a Phase II single center, open label, nonrandomized, three arm trial. Patients with relapsed/refractory follicular lymphoma (FL; Arm A) and diffuse large B cell lymphoma (DLBCL; Arm B) will receive pembrolizumab + rituximab for induction, and patients who achieve partial response (PR) or better may receive extended pembrolizumab therapy for up to 2 years (maximum, 35 doses). Patients with relapsed/refractory follicular lymphoma (FL, Arm C) will receive pembrolizumab + obinutuzumab induction, and patients with stable disease or better and clinical benefit may receive 6 additional obinutuzumab doses and extended pembrolizumab therapy for up to 2 years.

Trial Diagram: Arms A and B (Pembrolizumab + Rituximab)



Trial Diagram: Arm C (Pembrolizumiab + Obinutuzumab)



2.0 OBJECTIVES

2.1 Primary Objectives

(1) Overall response rate (ORR) of rituximab and pembrolizumab in relapsed/refractory FL.

(2) Overall response rate (ORR) of rituximab and pembrolizumab in relapsed/refractory DLBCL.

(3) Overall response rate (ORR) of obinutuzumab and pembrolizumab in relapsed/refractory FL

2.2 Secondary Objectives

(1) To evaluate the safety and tolerability of the combination of CD20-directed therapy and pembrolizumab

(2) To evaluate 2-year progression-free survival (PFS) and overall survival (OS) in each treatment group

2.3 Exploratory Objectives

(1) To explore correlates of response using peripheral blood flow cytometry.

(2) To evaluate the PDL1/PD1 axis and tumor microenvironment, using biopsies performed at baseline, between cycles 1 and 3, and at the time of persistent/progressive disease (optional).

(3) Explore treatment outcomes in subsets of enrolled patients with rituximab-refractory follicular lymphoma

3.0 BACKGROUND & RATIONALE

3.1 Background

The Non-Hodgkin's Lymphomas (NHL) represent a heterogeneous group of lymphoproliferative malignancies. Follicular lymphoma (FL) is the most common low grade NHL accounting for approximately 35% of all NHL, but is incurable with standard therapy.[1] Diffuse large B cell lymphoma (DLBCL) is the most common lymphoma worldwide, and while remains curable for most patients, high-risk subsets defined by the National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI) face a 65-70% risk of relapse or death within 5 years from diagnosis.[1, 2] While a proportion of patients with relapsed/refractory DLBCL can be cured with second-line therapy, those who are ineligible for autologous transplant or fail this intensive approach face dismal outcomes.[3, 4] Both relapsed/refractory FL and DLBCL represent large-scale unmet needs for improved, less toxic therapies.

3.1.1 Relapsed/Refractory Follicular Lymphoma

Advanced stage FL, comprising most cases, is now associated with median survival over a decade, owing in part to the advent of monoclonal antibody therapy including rituximab. [5-7] Nonetheless, even with improvements in therapy, FL is incurable. Patients face an inexorable pattern of relapse, and sequential use of chemotherapy over years is associated with mounting myelotoxicity and progressively shorter remissions. Therefore, novel treatment approaches are needed to overcome chemoresistance and produce sustained remissions while minimizing toxicity.

Rituximab, administered for 4 weekly courses, produces response rates of about 50% in relapsed/refractory FL and affords disease control of about 1 year.[8-11] Retreatment for rituximab-exposed relapsed FL patients maintains reasonable efficacy, producing a response rate of 40%-61% and maintaining response durations of a year or more for patients with low tumor burden.[12, 13] Nonetheless, some FL will not respond to rituximab or progress within 6 months of treatment of a rituximab-containing regimen, denoted as rituximab resistance. Rituximab-resistant FL is present in up to 50% of previously untreated patients and develops with ongoing therapy, although the mechanisms are poorly understood.[14]

While various strategies have sought to reverse rituximab resistance, novel anti-CD20 antibodies have not shown promise except for obinutuzumab (GA101) which enhances potent antibody-dependent cell-mediated cytotoxicity (ADCC).[15, 16] When administered as induction therapy and an extended phase, (1600 mg day 1 and 8 of cycle 1, then 800 mg day 1 of cycles 2-8), obinutuzumab produced a response rate in 5/10 rituximab-refractory indolent NHL patients.[16] Obinutuzumab is approved in combination with chemotherapy for relapsed or refractory FL, in patients previously treated with rituximab. However, when administered with bendamustine induction followed by extended dosing, obinutuzumab is associated with a relatively high infectious risk and mortality rate of 6%.[30,31] Since obinutuzumab is a type II CD-20 antibody with enhanced ADCC, and preclinical models suggest enhancement of NK cell function with pembrolizumab, combination therapy using obinutuzumab with pembrolizumab represents a rational strategy.[32] The present trial will thus include one arm (Arm C) employing induction with pembrolizumab and obinutuzumab, and then up to 6 more courses of obinutuzumab every 3 months. The 3 month extended dosing interval for obinutuzumab has been previously studied and, extrapolating from observational data with rituximab, may result in lower toxicity than dosing every 2 months.[33,34] Overall, we hypothesize the present obinutuzumab/pembrolizumab combination arm (Arm C) as designed will afford a high rate of overall response, with less infectious risk than long-term, q 2-month obinutuzumab given after bendamustine chemotherapy.

3.1.2 Background: Relapsed/Refractory Diffuse Large B Cell Lymphoma

Patients with relapsed/refractory DLBCL ineligible for, or progressing after, autologous transplant lack a uniform recommended treatment approach. Standard therapy is largely palliative[3] and allogeneic transplant is associated with long-term survival in about 25% of patients, with non-relapse mortality occurring in 36-56% depending on conditioning regimen.[17] Novel therapies are needed for this high risk subgroup. Rituximab as a single agent showed a 37% overall response rate in relapsed, rituximab-naïve DLBCL and was well-tolerated with typical infusion reactions comprising most adverse events.[18] Rituximab efficacy in patients previously exposed to rituximab appears lower, based on data from its use as a component of salvage chemotherapy, particularly among patients who relapse within a year of diagnosis.[19, 20] Therefore, while rituximab is tolerable for relapsed DLBCL, its single agent activity modern cohorts who will have received first-line rituximab-containing chemoimmunotherapy is likely to be modest. Combination therapy with pembrolizumab may improve the efficacy of rituximab therapy for relapsed DLBCL patients failing or ineligible for transplant, while avoiding risk posed by chemotherapeutic regimens.

3.1.3 Pharmaceutical and Therapeutic Background

3.1.3.1 Pembrolizumab

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. 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). The structure of murine PD-1 has been resolved. 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. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. 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. 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. 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). 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.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

3.1.3.2 Rituximab

Rituximab is a recombinant chimeric murine/human monoclonal IgG1-k antibody. It binds specifically to the CD20 antigen; a transmembrane protein expressed on the surface of mature B cells, and produces complement-dependent cytotoxicity (CDC) and antibody-dependent, cell-mediated cytotoxicity (ADCC) and induces apoptosis in these cells.[21, 22] Rituximab was the first monoclonal antibody to be approved for use in the treatment of cancer in 1997, and is well established in the treatment of NHL.[21] Rituximab carries US FDA approvals for treatment of CD20-positive NHL in the follow settings: relapsed/refractory low-grade lymphoma or FL as a single agent, previously untreated FL in combination with chemotherapy, as maintenance therapy for FL in patients responding to chemotherapy induction, in non-progressing patients after CVP first-line for low-grade B-NHL, and in previously untreated DLBCL in combination with CHOP or similar regimens.

3.1.3.4 Obinutuzumab

Obinutuzumab is a type II, CD20-directed monoclonal antibody that recognizes a unique CD20 epitope than rituximab, and was designed to have enhanced antibody-dependent, cell-mediated cytotoxicity.[33] Phase I data showed activity in relapsed NHL treated with a median of 4 prior regimens, and no unexpected AE's, when induction and maintenance every 3 months were administered.[33] In a subsequent randomized trial, directly comparing obinutuzumab with rituximab in patients with previously treated CD20+ indolent lymphoma, obinutuzumab produced a superior response rate (45% vs 33%) but no difference in progression-free survival.[35] More recently 2 trials showed superior results with obinutuzumab in previously untreated and relapsed indolent NHL leading to FDA approvals:

- In relapsed CD20+ NHL refractory to rituximab, obinutuzumab-bendamustine produced superior PFS than bendamustine alone, leading to approval of this combination in 2016. [31]

- In previously untreated FL: obinutuzumab-bendamustine produced superior PFS than rituximab-bendamustine, leading to approval in 2017 in the front-line setting. [30]

3.1.4 Clinical Trial Data

A combination trial of PD1 blockade and rituximab in relapsed or refractory follicular lymphoma has been fully reported. 24 In that study, pidilizumab was tested in combination 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). No deaths were observed for patients on this trial, and no autoimmune or therapy-related grade 3/4 toxicities were seen. It was observed that naïve, effector memory, and central memory CD4+ T cells were increased post-treatment compared to baseline.

An initial 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. [25] 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 transplant35-- 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.

The Keynote-13 trial, a phase Ib multi-cohort Trial of Pembrolizumab in subjects with hematologic malignancies, includes a cohort with primary mediastinal B-cell lymphoma (PMBCL), a DLBCL variant, with preliminary results presented in abstract form.[26] In that study, 19 patients with PMBCL were enrolled and 7/17 with evaluable disease responded. With a median follow-up of 11.3 months, the median duration of response had not been reached, and no patient discontinued therapy due to adverse events. 11 patients experienced treatment-related adverse events, mostly grade 1-2. This trial supports the ongoing study of pembrolizumab for DLBCL and its variants.

In 2016, a study of nivolumab (a fully human anti-PD1 antibody) in relapsed lymphoma including cohorts with relapsed/refractory FL and relapsed/refractory DLBCL was reported.[27] In that trial, 4/10 patients with FL, and 4/11 with DLBCL, responded to single-agent PD-1 blockade with nivolumab. Among the 81 patients enrolled in all cohorts, 15 patients experienced immune-related adverse events though only 5 discontinued nivolumab as a result. Fatal pneumonitis occurred in one patient, and 8 cases of pneumonitis were observed overall. Overall, 12 patients discontinued therapy due to drug-related adverse events (15%; includes immune-related and other adverse events).

Recently, preliminary results combining pembrolizumab and rituximab in relapsed FL were reported in abstract form.[29] In that study, 27 of planned 30 patients have initiated therapy; ORR was 80%, CR rate was 60%. Four immune-related adverse events, all grade 2, were reported and AE's were primarily grade 1-2 overall.

These data suggest a potential role for PD-1 blockade combinations in B-cell malignancies including relapsed/refractory FL and DLBCL, although biomarkers predicting response are incompletely defined.

3.1.5 Rationale for the Trial and Selected Subject Population

The selected subject population includes patients with relapsed/refractory follicular and diffuse large B cell lymphoma. Rituximab is thought to elicit its antitumor effect against B-cell malignancies primarily through CDC and ADCC, and by inducing apoptosis.[22] Pembrolizumab blockade of PD1 interactions leads to expansion of antitumor T-cells. This agent may promote additive or synergistic antitumor effects in lymphoma patients treated with rituximab. The favorable adverse effect profile to date of pembrolizumab and combination therapy using other agents (pidilizumab) suggests that the combination of pembrolizumab and rituximab is feasible without expectation for excess toxicity. A subgroup of rituximab-refractory FL patients will be

included to explore outcomes. Finally, Arm C will combine obinutuzumab with pembrolizumab, a combination not previously studied. Since a randomized study showed similar adverse events with obinutuzumab and rituximab, with the exception of infusion-related reactions (11% grade 3-4 with obinutuzumab vs. 5% with rituximab) and cough (all grade 1-2 events)[35] weexpect the safety profile of arms A (rituximab+ pembrolizumab) and C (obinutuzumab + pembrolizumab) to be similar. All study arms will have accrual suspended for excess deaths or serious adverse events and will be monitored in accordance with the Institutional Data Safety Monitoring plan (section 9.0).

Therefore, this study proposes to assess the safety, tolerability, and immune activation of pembrolizumab, when co-administered with rituximab or obinuzutumab, in subjects with relapsed/refractory FL and DLBCL.

3.1.6 Rationale for Dose Selection/Regimen/Modification

3.1.6.1 Pembrolizumab

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. Recent data from other clinical studies within the pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

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

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). 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 indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

3.1.6.2 Rituximab

This clinical trial will utilize the approved dose of rituximab for relapsed/refractory low-grade of follicular B-cell NHL, 375 mg/m2 weekly for 4 weeks.[23] Premedication for prophylaxis against hypersensitivity reactions will be administered per clinical standard of care on initial and subsequent infusions, with modifications permitted at investigator discretion.

3.1.6.3 Obinutuzumab

3.1.7 The third arm, Arm C, will combine obinutuzumab with pembrolizumab and will use obinutuzumab: 1000 mg weekly for 4 weeks then up to 6 additional doses (maximum 10 doses) at 1000 mg every 3 months, for patients achieving response (PR/CR) or SD with clinical benefit. Clinical benefit in the setting of stable disease per Lugano criteria will be assessed by the treating investigator. The obinutuzumab dose is identical to the approved dosing in relapsed follicular lymphoma (in combination with benadamustine[31]), although this study will employ a less frequent interval (q 3 months) and lower overall dose (maximum 6 doses extended therapy). Every 3-month dosing is supported by the initial phase I study

of obinutuzumab, and limiting the duration to a maximum of 6 additional doses may impart a more favorable risk/benefit ratio.[33]Rationale for Endpoints

3.1.7.1 Efficacy Endpoints

The primary endpoint is overall response rate assessed independently for each arm: relapsed/refractory FL (Arms A and C), and relapsed/refractory DLBCL (Arm B) . Overall response rate is defined as the rate of complete + partial responses using CT criteria (Lugano 2014).[28]

3.1.7.2 Biomarker Research

Tissue-based assays for tumor and immune infiltrate expression of PD1, PD-L1 will be performed by a third party laboratory to be designated by Merck, with tissue received from the most recent biopsy specimen when available.

Patients may undergo an optional tumor biopsy at baseline and up to one time between cycles 1 and 3. Patients may also undergo optional biopsies in the setting of persistent or relapsed disease. Correlative studies will evaluate the tumor microenvironment.

For all patients, baseline and serial evaluation of peripheral blood T cell populations by flow cytometry will be undertaken. In previous studies, alterations of both PD-L1 and PD1 bearing lymphocytes have been observed in peripheral blood. This study will analyze markers including (but not limited to) CD3, CD4, CD8, CD14, PD-1, PD-L1, and PDL-2 on peripheral blood mononuclear cells, and will explore whether alterations in T cell subsets occur with therapy and predict outcomes with treatment.

4.0 METHODOLOGY

4.1 Entry Criteria

4.1.1 Diagnosis/Condition for Entry into the Trial

Patients 18 years of age or older with relapsed/refractory FL, or relapsed/refractory DLBCL relapsing after, ineligible for, or declining autologous stem cell transplant, are eligible for this trial. Relapsed is defined as having achieved remission but then experienced progression of the malignancy. Refractory is defined as failing to attain a remission after therapy.

4.1.2 Subject Inclusion Criteria

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

1. Have relapsed/refractory DLBCL or relapsed/refractory FL.
    a. For DLBCL, patients must have relapsed after, declined, or considered ineligible for high-dose chemotherapy and autologous stem cell transplantation.

b. For FL, in addition to relapsed/refractory disease status, patients must have received therapy with CD20 antibody-directed therapy, and must have an indication for treatment. FL eligibility also requires patients have no standard options with curative potential, nor options with more favorable risk/benefit ratio in the judgment of the investigator.

c. For FL Arm C (obinutuzumab + pembrolizumab), patients must have relapsed/refractory disease after rituximab-containing therapy including:

   i. Rituximab in combination with chemotherapy (at 1 prior line) or

   ii. ≥ 2 prior lines of therapy

   iii. Patients may have no standard options with curative potential, nor options with more favorable risk/benefit ratio in the judgment of the investigator.

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

3. Be ≥ 18 years of age on day of signing informed consent.

4. Have measurable disease (1.5 cm or greater in the longest diameter of nodal or extranodal disease).

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

6. Demonstrate adequate organ function as defined in table 1 below, with screening labs to be performed within 28 days of cycle 1 day 1.

Table 1 Adequate Organ Function Laboratory Values

System	**Laboratory Value**
Hematological	
Absolute neutrophil count (ANC)	≥500/µL [a, b]
Platelets	≥25 000/µL [a, b]
Hemoglobin	≥8 g/dL [a, b]
Renal	
Creatinine OR Measured or calculated [c] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)

Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal. [a]Growth factor and/or transfusion support is permissible to stabilize participant prior to study treatment if needed. [b]No lower limit if cytopenia is related to bone marrow involvement. [c]Creatinine clearance (CrCl) should be calculated per institutional standard. Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.	

7. Female subjects of childbearing potential (Section 4.4.2) 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.

8. Female subjects of childbearing potential (Section 4.4.2) must be willing to use an adequate method of contraception as outlined in Section 4.4.2 – Contraception, for the course of the study until at least 12 months after the last dose of study therapy.

   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

9. Male subjects of childbearing potential (Section 4.4.2) must agree to use an adequate method of contraception as outlined in section 4.4.2 starting with the first dose of study therapy until at least 12 months after the last dose of study therapy.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

4.1.3 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 therapy or used an investigational 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, except for physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency which is permitted.

3. Has a known history of active TB (Bacillus Tuberculosis)

4. Hypersensitivity to pembrolizumab or any of its excipients.

5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

6. Prior allogeneic transplant, within the last 5 years.

7. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

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

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

8. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

9. Has known active central nervous system (CNS) metastases and/or lymphomatous meningitis. Subjects with previously treated brain metastases or lymphomatous meningitis 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.

10. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

11. Has known history of, or any evidence of active, non-infectious pneumonitis/interstitial lung disease.

12. Has an active infection requiring systemic therapy.

13. 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.

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

15. 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 until at least 12 months after the last dose of study treatment.

16. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

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

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

19. Has received a live vaccine or live-attenuated vaccine within 30 days of planned start of study therapy. Administration of killed vaccines is allowed.

    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

4.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle, up to 35 cycles	Experimental
Rituximab	375 mg/m^2	QW	IV infusion	Cycle 1 Day 1,8, 15; and Cycle 2 Day 1	Approved dosing regimen
Obintuzumab	1000 mg (flat dose)	QW x 4 doses, then Q3 months up to total 6 additional doses as extended therapy	IV infusion	Cycle 1 Day 1,8, 15; and Cycle 2 Day 1. If at least SD or better, proceed to extended therapy: day 1 of cycle 5, 9,13,17,21,25 if tolerated/nonprogressing	Approved dose, with attenuation of interval and total cumulative dose

4.2.1 Dose Selection/Modification

4.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 3.0 – Background and Rationale.

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

4.2.1.2 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. See Section 5.6 for supportive care guidelines, including use of corticosteroids. Table 3 lists dose modifications for pembrolizumab. Note that dose modification of rituximab, and management of rituximab-related infusion reactions, will follow institutional standard of care and investigator/sub-investigator discretion and is not specified in this protocol.

Table 3 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

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

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation	
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	
Myocarditis	1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	3 or 4	Permanently discontinue		
All Other immune-related AEs	Intolerable/ persistent Grade 2 [b]	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	3	Withhold or discontinue based on the event [c].		
	4 or recurrent Grade 3	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] 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.

[c] Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for interruption should be documented in the subject's study record.

4.2.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered first (on days when rituximab is also given) as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5

min/+10 min). Rituximab will be given as per institutional standard, after pembrolizumab when co-administered on the same day.

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

4.2.3 Trial Blinding/Masking

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

4.3 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 investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

4.3.1 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 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.

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

4.3.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy

- Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.

- 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, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

- Systemic glucocorticoids for any purpose other than management of rituximab-related hypersensitivity/infusion reactions; to modulate symptoms from an event of clinical interest of suspected immunologic etiology, or as physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency.

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.

4.3.3 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator, including medications for management of rituximab-related infusion reactions which may be administered per institutional standard of care.

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 does not need to follow the treatment guidance (as outlined below). Refer to Table 4 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.

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to pembrolizumab alone, to rituximab alone, to obinutuzumab alone, or to the combination, for adverse events listed below, all interventions must be held according to the criteria below.

When study interventions are administered in combination, if the AE is considered immune-related, all interventions should be held according to recommended dose modifications.

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study.

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.

- If the toxicities do resolve and conditions are aligned with what is defined below, the combination of study therapies may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to rituximab or obinutuzumab alone, re-initiation of pembrolizumab as a monotherapy may be considered at the investigator's discretion.

- **Pneumonitis**:
    a. 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.
    b. For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    c. Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
    d. For recurrent grade 2 or grade 3-4 pneumonitis, permanently discontinue pembrolizumab.

- **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).

    a. 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.
    b. For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
    c. For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
    d. 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)**
    a. For **T1DM** or **Grade 3-4** Hyperglycemia

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

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

- **Hypophysitis**:
  a. 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.
  b. 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.

  a. **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
     i. In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
     ii. In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
  b. **Grade 3-4** hyperthyroidism
     i. 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**:
  a. For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
     i. Treat with IV or oral corticosteroids
  b. For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  c. 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.

- **Neurological Toxicities:** Ensure adequate evaluation to confirm etiology and/or exclude other causes.
  a. For **Grade 2** events, withhold pembrolizumab.
  b. For **Grade 3-4** events, permanently discontinue pembrolizumab.
  c. Administer corticosteroids based on severity of the AE.
- **Myocarditis:** Ensure adequate evaluation to confirm etiology or exclude other causes.
  a. For **Grade 1** events, withhold pembrolizumab.
  b. For **Grade 2-4** events, permanently discontinue pembrolizumab.
  c. Administer corticosteroids based on severity of the AE.
- **Exfoliative Dermatologic Conditions:** Ensure adequate evaluation to confirm etiology or exclude other causes.
  a. For **suspected** SJS (Stevens-Johnson syndrome), TEN (toxic epidermal necrolysis), or DRESS (Drug reaction with eosinophilia and systemic symptoms), withhold pembrolizumab.
  b. For **confirmed** SJS, TEN, or DRESS, permanently discontinue pembrolizumab.
  c. Administer corticosteroids based on severity of the AE.
- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

  Table 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (pembrolizumab). Management of rituximab or obinutuzumab infusion reactions will be performed according to institutional practice and investigator judgment.

Table 4 Pembrolizumab Infusion Reaction Dose Modification and 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 participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** 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 participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 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 participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of _____ with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug intervention.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

4.4 Diet/Activity/Other Considerations

4.4.1 Diet

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

4.4.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and until at least 12 months after the last dose of study therapy by complying with one of the following:

(1) practice abstinence[†] from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

- intrauterine device (IUD)

- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

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, subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period until at least 12 months after the last dose of study therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

4.4.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, 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 within 2 working days to Merck if the outcome is a serious adverse event (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The Sponsor-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.

4.4.4 Use in Nursing Women

It is unknown whether pembrolizumab 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.

4.5 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 should any untoward effect occur. 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. Specific details regarding discontinuation or withdrawal are provided in Section 6.1.3.1.

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

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

  Note: For unconfirmed radiographic disease progression, patients may remain on study until progression is confirmed by repeat imaging or biopsy.
- Unacceptable adverse experiences as described in Section 6.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed trial therapy, including Retreatment if applicable (see section 6.1.4.2, Treatment Period)
- Administrative reasons

Study visits are listed in Section 5 (Trial Flow Chart) and Section 6.1.4 (Visit Requirements). After the last cycle of pembrolizumab, each subject will be followed for 90 days for adverse event monitoring and will have an Off-Study visit at that time. Patients who discontinue for reasons other than progressive disease will have post-treatment follow-up as per standard of care, including disease status and survival.

4.5.1 Subject Replacement Strategy

Subjects who fail to complete study therapy before the first response assessment for reasons other than disease progression, death, SAE, or drug-related adverse events will be replaced, to allow response assessment in accordance with study stopping rules.

4.6 Clinical Criteria for Early Trial Termination

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

- Quality or quantity of data recording is inaccurate or incomplete
- Poor adherence to protocol and regulatory requirements
- Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
- 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.

5.0 TRIAL FLOW CHART

5.1 Study Flow Chart

Trial Period:	**Screening Phase**	**Treatment – Induction (cycles 1-4)**					**Treatment – Extended therapy (cycles 5, up to 35 max)**	**Off-Study Visit**
Treatment Cycle/Title:	Study Screening	Cycle 1 day 1	Cycle 1 day 8	Cycle 1 day 15	Cycle 2 day 1	Cycle 3-4 day 1	Cycles 5-35, day 1	90 days after last dose of pembrolizumab
Scheduling Window (Days):	-42 to -1	± 3	± 3	± 3	± 3	± 3	± 5	+/- 7
Administrative Procedures								
Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Medical History	X	X[1]			X	X	X	X
Prior and Concomitant Medication Review	X	X[1]			X	X	X	X
Arm A & B: Rituximab Administration		X	X	X	X			
Arm A, B & C: Pembrolizumab Administration		X			X	X	X	
Arm C: Obinutuzumab administration		X	X	X	X		(Cycles 5,9,13,17,21,25 only)	
Post-study anticancer therapy status								X

Survival Status								X
Clinical Procedures/Assessments								
Review Adverse Events	X (baseline AE)	X[1]			X	X	X	X
Full Physical Examination	X							X
Directed Physical Examination		X[1]			X	X	X	
Vital Signs and Weight (Height at Screening)	X	X[1]			X	X	X	X
ECOG Performance Status	X	X[1]			X	X	X	X
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory								
Pregnancy Test – Urine or Serum β-HCG	X[6]							
PT/INR and aPTT	X							
CBC with Differential	X	X[1]			X	X	X	X
Comprehensive Chemistry Panel, LDH	X	X[1]			X	X	X	X
Urinalysis	X							
T3, FT4 and TSH	X				X	X	X	X
HepB S Ag, Hep B Core Ab, Hep C Ab	X							
Efficacy Measurements								
Tumor Imaging	X[2]						X- within 2 weeks before starting Cycle 5 and Cycle 9, then q 4 cycles (q 3 mo)[2]	
Bone marrow aspirate	X[5]							
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood								
Archival or Newly Obtained	X[3]	X[3]	X[3]	X[3]	X[3]			

Tissue Collection								
Correlative Studies Blood Collection	X[4]						X[4]	X[4]

1. Medical history, AE review, Prior/Concomitant medication review, weight, and ECOG, PE, height/weight, and lab studies do not need to be repeated if done within 7 days of start cycle 1 day 1 (e.g. at screening visit). VS should be recorded at screening and at each treatment visit.
2. See Section 6.1.2.5: Baseline CT imaging must be performed within 8 weeks of initiating study drug therapy. CT neck should be included for patients with palpable or known neck adenopathy. End of induction CT will be done before cycle 5 (week 11-13 of therapy). For patients on continued therapy, restaging CT will be performed before cycle 9 (week 23-25) and then every 3 months thereafter. Other imaging may be performed at clinician's discretion, including FDG PET/CT and/or MRI.
3. The presence of archival tissue will be assessed during screening. When available this tissue will be provided for central biomarker analysis including PD1/PDL1 expression on tumor cells. Patients may undergo optional lymph node biopsy at baseline and up to **one time** between cycles 1 and 3. Patients may also undergo optional biopsies in the setting of persistent or progressive disease, and tissue may be provided for correlative analysis at that time.
4. See section 6.1.2.6 for details on correlative study draws, which are drawn at baseline (any time prior to cycle 1 day 1 study drug dosing), cycle 5 day 1, and at the Off-Study visit (or at the time of disease progression/initiation of second-line therapy-- whichever occurs first).
5. Bone marrow aspirate (biopsy is not mandatory but is permitted) for routine analysis for lymphoma involvement will be performed at baseline for patients who have not undergone a marrow within 6 months prior to signing consent, and again to confirm complete response.
6. Negative Urine or serum pregnancy test is required within 72 hours prior to receiving the first dose of study medication.

6.0 TRIAL PROCEDURES

6.1 Trial Procedures

The Trial Flow Chart - Section 5.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor-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.

6.1.1 Administrative Procedures

6.1.1.1 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, applicable laws and regulations and Sponsor-Investigator requirements.

6.1.1.2 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.

6.1.1.3 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.

6.1.1.4 Prior and Concomitant Medications Review

6.1.1.4.1 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.

6.1.1.4.2 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 6.2.

6.1.1.5 Disease Details and Treatments

6.1.1.5.1 Disease Details

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

6.1.1.5.2 Prior Treatment Details

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

6.1.1.5.3 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. If a subject initiates a new anti-cancer therapy before the planned Off-Study Visit, that visit may be combined with a standard of care/previously scheduled visit, and tasks related to that visit completed before initiating additional therapy.

6.1.2 Clinical Procedures/Assessments

6.1.2.1 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 (Section 5.0) and more frequently if clinically indicated. Adverse events 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 6.2 for detailed information regarding the assessment and recording of AEs.

6.1.2.2 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 and at EOT. Otherwise, directed physical exams are permissible.

6.1.2.3 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 5.0). Vital signs should include temperature, pulse, respiratory rate, blood pressure. Weight is checked on day 1 of each cycle and at screening. Height will be measured at screening only.

6.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart (Section 5.0).

6.1.2.5 Tumor Imaging and Assessment of Disease

The primary mode of response assessment is contrast-enhanced CT imaging or noncontrast CT or MRI if CT contrast is contraindicated.

For measurement of response based on CT imaging, 2014 criteria will be used as described in "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification".[28] All CT and scans are to be interpreted locally.

- 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. CT neck should be performed for patients with known neck adenopathy.

- Restaging CT will be performed after 8 cycles (week 23-25) then every 3 months thereafter for patients on continued pembrolizumab therapy).

- FDG-PET/CT may be performed as clinically indicated but is not required. In particular, PET/CT is suggested to confirm metabolic CR for patients with residual CT abnormalities of unknown significance, or PR by CT criteria lasting 3 months or more.. A baseline bone marrow aspirate (biopsy optional) is required within 6 months prior to signing consent, if not available. Repeat bone marrow aspirate is required to confirm CR, only for patients with known BM involvement.

6.1.2.6 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. In addition, patients will undergo optional lymph node biopsy at baseline and up to one time between cycles 1 and 3, and at the time of persistent or progressive disease. Correlative studies will evaluate the tumor immunomicroenvironment.

Peripheral blood correlative study samples will be performed at the following time-points (see Section 5 Trial Flow Chart):

1. Baseline (collected any time prior to cycle 1 day 1 study drug dosing)

2. Cycle 5 day 1

3. At the Off-Study assessment visit; or 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 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 blood specimens for flow cytometry: Attn: Hematopathology Lead Seattle Cancer Care Alliance Hematopathology Laboratory G7800 825 Eastlake Ave E. Seattle, WA 98109

6.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis).

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Table 5 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)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		PK
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Potassium		
	Sodium		
	Magnesium		
	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.

6.1.3.1 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 6.2 - Assessing and Recording Adverse Events.

6.1.4 Visit Requirements

Visit requirements are outlined in Section 5.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 6.1 - Trial Procedures.

6.1.4.1 Screening

6.1.4.1.1 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 or other evaluations prior to Cycle 1 Day 1 of study therapy. The screening period may last up to 42 days (6 weeks).

Laboratory studies collected within the 42 days prior to study drug start, for standard of care purposes, may be used to satisfy screening requirements and do not need to be repeated at screening. In addition, if lab studies are done within 7 days of cycle 1 day 1, they do not need to be repeated for study purposes. Archival bone marrow aspirate /biopsy data is acceptable if performed within the 6 months prior to signing consent.

6.1.4.2 Treatment Period

The treatment period begins with the first administration of study treatment, and is designated as Cycle 1 Day 1.

6.1.5 Induction phase: The induction phase will consist of four cycles lasting 3 weeks: pembrolizumab 200 mg on day 1 every 3 weeks, and rituximab (Arms A and B) or obinutuzumab (Arm C) on day 1 (after pembrolizumab) x 4 doses (Cycle 1 day 1, 8, 15, and cycle 2 day 1).

6.1.6 Extended Therapy Phase: Patients with at least a partial response may continue on extended therapy: pembrolizumab 200 mg day 1 every 3 weeks for up to 2 years maximum of 35 infusions.) In addition, for arm C, patients with stable disease or better, who are experiencing clinical benefit in the judgment of the investigator, may receive up to 6 more doses of obinutuzumab every 3 months (cycles

5,9,13,17,21,and 25) in combination with pembrolizumab every 21 days, up to 35 cycles.

6.1.6.1 Discontinuation of Study Therapy after CR: Patients may elect to stop therapy during the extended therapy phase, if in CR after at least 8 cycles (24 weeks) of pembrolizumab therapy. CR may be defined by CT, PET-CT, either in conjunction with biopsy when applicable (including marrow assessment). These patients are eligible for the Second Course period as in section 6.1.6.2 if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Ninety days after receiving the last dose of pembrolizumab, subjects in CR who are potential retreatment candidates may convert to standard of care surveillance visits, while remainingeligible for the Second Course period as in 6.1.6.2.

6.1.6.2 Second Course (retreatment) Period:

Subjects who elect to stop study therapy for proven CR are eligible for up to one year of additional pembrolizumab therapy, and for Arm C patients q12 week obinutuzumab (maximum of 6 courses q 3 months, and 10 total doses, including all prior doses) if they progress after stopping study treatment.

This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- Stopped therapy after receiving at least 8 cycles (24 weeks), and attaining an investigator-determined CR (CT, PET-CT, and/or biopsy-proven CR).

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab

- Did not receive any anti-cancer treatment since the last dose of pembrolizumab

- Has a performance status of 0 or 1 on the ECOG Performance Scale

- Demonstrates adequate organ function as per Inclusion Criteria

- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.

- Female subject 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 until at least 12 months after the last dose of study therapy (Reference Section 4.4.2). Subjects

of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.

- Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy until at least 12 months after the last dose of study therapy.

- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might 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.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received study therapy with pembrolizumab and obinutuzumab. Treatment will be administered for up to one additional year, with CT restaging performed every 3 months.

6.1.6.3 Off-Study Visit

The mandatory Off-Study Visit should be conducted approximately 90 days (+/- 7days) after the last dose of pembrolizumab irrespective of reason it was stopped, but may be done earlier for patients embarking on additional anti-lymphoma therapy. All AEs that occur prior to the Off-Study Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until stabilization or resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

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 will be conducted as per routine standard of care. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or end of study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Patients who initiated retreatment require a second off-study visit, to be performed as above 90 days after their last dose of pembrolizumab (+/-7 days).

6.2 Assessing and Recording Adverse Events

Adverse events will be recorded, and ECI and SAE's reported, from the time of signed consent and for up to 90 days after the last dose of pembrolizumab is administered.

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 product, is also an adverse event. Progression of the cancer under study is not considered an adverse event.

Laboratory abnormalities will only be recorded if grade 3 or higher, possibly related to study therapy, and clinically significant in the judgment of the investigator. 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.

All adverse events will be recorded from the time the consent form is signed through 90 days following cessation of MK-3475 treatment and at each examination on the Adverse Event worksheets.

6.3 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.

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 Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-993-1220)

6.4 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 12 months 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)

6.5 Reporting Requirements for Adverse Events/Adverse Reactions

6.6 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

Exceptions to Serious Adverse Event Reporting include events related to progression of the cancer under study, including hospitalization or death. These events are not to be reported as serious adverse events. Hospitalization related to convenience (e.g. transportation issues, etc.) will not be considered an SAE. 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.

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

6.7 Reporting of 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 until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 2 business days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new

anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, 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 6.3 - 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.

6.8 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 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 6 Evaluating Adverse Events

An investigator, who is a qualified physician, 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 for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); 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) **(**although not serious per ICH definition, is reportable to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported to Merck within 2 working days.	

	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 Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that 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 Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to 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 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 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 investigational product; or (3) the trial is a single-dose drug trial); or (4) investigational product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to 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) investigational 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 MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR-INVESTIGATORAS 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 Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the worksheets by an investigator who is a qualified physician 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 Merck product relationship).**	
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.	

No, there is not a reasonable possibility of Merck product relationship	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a subject with overdose without an associated AE.)

6.8.1 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 will be reported from the time of signing of consent up until 90 days following the last dose of MK-3475.

Laboratory abnormalities will be recorded as adverse events only if they meet the following criteria: the abnormality is symptomatic, warrants a change to study drug dosing, is designated clinically significant by the investigator, or reaches severity of grade 3 or higher (asymptomatic lab values < grade 3 will not be recorded as AEs).

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.

7.0 STATISTICAL ANALYSIS PLAN

This study administers therapy to two groups of patients, relapsed/refractory FL and relapsed/refractory DLBCL.

Subjects who fail to complete study therapy or withdraw consent before the first response assessment for reasons other than disease progression, death, SAE, or drug-related adverse events will be replaced, to allow response assessment in accordance with study stopping rules. The first group (Arm A) includes patients with relapsed or refractory follicular lymphoma, and will include at least 9 patients with rituximab-refractory disease.

The second group (Arm B) consists of patients with relapsed/refractory diffuse large B-cell lymphoma ineligible for, or failing to respond to or progressing, after autologous stem cell transplantation**.**

These groups will employ independent rules, using Simon's two-stage design, and accrual will be suspended for review if futility thresholds are met. Two-stage designs which limit the maximum sample size will be considered. Once enrollment is suspended, 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. Categorical variables will be summarized by number and percentage, and continuous variables will be summarized by min/median/max/mean/sd, respectively. Overall response rate, and response quality, will be evaluated according to CT criteria and PET/CT in relevant patients, as per the 2014 Lugano criteria.[28] PFS/OS distribution will be estimated and Kaplan-Meier curves will be presented. Log-rank testing and Cox proportional hazard regression models might be applied to evaluate the association between survival endpoints and prognostic factors. To compare continuous variable in the correlative studies, student's t-test and regression analysis might be applied if deemed appropriate.

Subjects who fail to complete study therapy before the first response assessment for reasons other than disease progression, death, SAE, or drug-related adverse events will be replaced, to allow response assessment in accordance with study stopping rules.

7.1. Study Stopping Rules: Efficacy

7.1.1. Arm A: Relapsed/refractory FL

The following assumptions will underlie the two-stage design for Arm A: At the end of induction response rate will be 60% with this combination, against a null hypothesis of 30%. With this 2-stage design, 7 patients will be enrolled in the first stage. If 2 or fewer respond among these 7 patients, enrollment to this study arm will be stopped. Otherwise, 13 additional patients will be accrued in the second stage for a total of 20. The null hypothesis will be rejected if 10 or more responses are observed in 20 patients. This design yields a type I error rate of .05 and a power of 0.82 when the true response is 60%.

A goal of 9 rituximab-refractory FL patients will be included in this arm. The proposed response rate is hypothesized to be no different among these patients (60%). Enrollment will be adjusted to permit enrollment of these patients without over-accruing to the study. The 95% confidence interval for the proposed 60% response rate in 9 rituximab-refractory FL patients is 28-92%. Thus, by enrolling 9 rituximab-refractory patients, this study will reasonably exclude a response rate of <30% in this subgroup.

7.1.2. Arm B: Relapsed/refractory DLBCL

The following assumptions will underlie the two-stage design for Arm B: At the end of induction response rate will be 50% with this combination, against a null hypothesis of 20%. With this 2-stage design, 9 patients will be enrolled in the first stage. If 2 or fewer respond among these 9 patients, accrual to this study arm will be stopped. Otherwise, 8 additional patients will be accrued in the second stage for a total of 17. The null hypothesis will be rejected if 7 or more responses are observed in 17 patients. This design yields a type I error rate of .05 and a power of .8 when the true response is 50%.

7.1.3 Arm C: Relapsed FL, Obinutuzumab +_Pembrolizumab

Arm C includes patients exposed to prior alkylating agent (including bendamustine) and rituximab therapy. The following assumptions will underlie the two-stage design for this arm: At the end of induction response rate will be 70% with this combination (similar to that observed with obinutuzumab and chemotherapy[31], against a null hypothesis of 45% (as observed with single-agent obinutuzumab[35]. With this 2-stage design, 12 patients will be enrolled in the first stage. If 5 or fewer respond among these 12 patients, enrollment to this study arm will be stopped. Otherwise, 13 additional patients will be accrued in the second stage for a total of 25. The null hypothesis will be rejected if 16 or more responses are observed in 25 patients. This design yields a type I error rate of .04 and a power of 0.80 when the true response is 70%.Patients with stable disease and clinical benefit, as determined by the treating investigator, or response qualifying as PR or CR, will be permitted to proceed to the extended dosing phase in Arm C.

7.2. Study Stopping Rules

7.2.1. Arms A and B

We plan to enroll a total of up to 37 patients on Arms A and B of this study. The study will be suspended and referred to the institutional Data Safety Monitoring Committee (DSMC) for consideration of results and appropriate modification or termination of the study if there is sufficient evidence that the probability of death (due to any cause other than disease progression) exceeds 10%, or if more than 50% of patients experience a serious adverse event (SAE).

This will be deemed to occur if the lower level of a one-sided 80% confidence interval for death proportion exceeds 10% or SAE proportion exceeds 50% at any time. Operationally, the study will be suspended in the following circumstances:

- If 2 out of the first 8 or fewer patients, 4 out of the first 16 or fewer, 5 out of the first 24 or fewer, 6 out of the first 32 or fewer, or 7 out of the 37 or fewer patients experience death for any reason other than disease progression, or

- If 6 out of the first 8 or fewer, 11 out of the first 16 or fewer, 16 out of the first 24 or fewer, 20 out of the first 32 or fewer, or 23 out of the 37 or fewer patients experience serious adverse events.

In summary, the following will lead to suspension of accrual:

- Non-disease-progression death rate > 10% (2/8, 4/16, 5/24, 6/32, 7/37).

- SAE occurring in >50% of patients (6/8, 11/16, 16/24, 20/32, 23/37)

If the true probability of death due to causes other than the underlying disease is 5%, then the probability of suspending the trial due to excess death after 16, 24, and 32 patients is approximately 0.01, < 0.01, < 0.01, respectively. If the true probability of death is 25%, the probability of suspension due to excess death is approximately 0.73, 0.84, and 0.90, respectively.

If the true probability of grades III-IV AE is 30%, the probability of suspending the trial due to excess AEs after 16, 24, and 32 patients is approximately 0.01, 0.01, and <0.01, respectively. If the true probability of AE is 70%, the probability of suspension due to excess AE is approximately 0.73, 0.82, and 0.91, respectively. (Probabilities of suspension estimated from 5,000 simulations).

Accrual after suspension may continue after DSMC review, and if the DSMC permits a protocol revision to allow further accrual that may permit the study to address its objectives while maintaining a favorable safety profile.

7.2.2 Arm C

We plan to accrue at most 25 patients to Arm C, testing the combination of obinutuzumab and pembrolizumab. As with arms A and B, accrual to this arm will be suspended and referred to the institutional Data Safety Monitoring Committee (DSMC) for consideration of results and appropriate modification or termination of the study if there is sufficient evidence that the probability of death (due to any cause other than disease progression) exceeds 10%, or if more than 50% of patients experience a serious adverse event (SAE).

For Arm C the following will lead to suspension of accrual:

- Non-disease-progression death rate > 10% (2/8, 3/15, 4/23).
    i. If the true probability is 5%, the probability of suspension is approximately 3.9% (probabilities estimated from 5,000 simulations).
    ii. If the true probability is 35%, the probability of suspension is approximately 91.7% (probabilities estimated from 5,000 simulations).

- SAE occurring in > 50% of patients (3/3, 4/5, 5/6, 6/8, 7/10, 8/12, 9/13, 10/15, 11/17, 12/19, 13/21, 14/22, 15/24)

8.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

8.1 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.

Clinical Supplies will be provided by Merck as summarized in Table 7.

Table 7 Product Descriptions

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

8.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

8.3 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.

8.4 Storage and Handling Requirements

Clinical supplies 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.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

8.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies 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.

9.0 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 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 by a FHCRC Scientific Review Committee (SRC) and the FHCRC/Cancer Consortium Institutional Review Board (IRB). The review committee evaluates accrual, adverse events, stopping rules, and adherence to the 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 both committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by the regulatory committees of the FHCRC (SRC and IRB) and other institutional, state and federal guidelines.

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

10.0 RECORDS

Research staff under the supervision of the investigators will maintain 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).

11.0 REGULATORY RESPONSIBILITIES OF SPONSOR-INVESTIGATOR

The Principal 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.

12.0 COMPLIANCE WITH TRIAL REGISTRATION AND RESULTS POSTING REQUIREMENTS

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

12.0 APPENDICES

12.1 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.	

12.2 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)

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