PROTOCOL TITLE: Phase II Study of Pembrolizumab and Fractionated External Beam Radiotherapy in Patients with Relapsed and Refractory Non-Hodgkin Lymphoma

Protocol Number: 2017-0341

ClinicalTrials.gov Identifier: NCT03210662

Principal Investigator: Chelsea Pinnix

Version Number: 13

Date: 09/24/2021

CONFIDENTIALITY STATEMENT
This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator.

Phase II Study of Pembrolizumab and Fractionated External Beam Radiotherapy in Patients with Relapsed and Refractory Non-Hodgkin Lymphoma

Principal Investigator
Chelsea C. Pinnix MD, PhD
Associate Professor
Department of Radiation Oncology
Hematologic Malignancies Section
The University of Texas MD Anderson Cancer Center
1515 Holcolmbe Blvd.
Houston, TX 77030
USA

Table of Contents

1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab (MK-3475) and radiation for relapsed and refractory Non-Hodgkin Lymphoma
Trial Phase	II
Clinical Indication	Refractory Non-Hodgkin Lymphoma
Trial Type	Treatment (Interventional)
Type of control	Historical Control
Route of administration	Intravenous and external beam radiation
Trial Blinding	Unblinded, open label
Treatment Groups	MK-3475 200 mg every 21 days with concurrent External beam radiation therapy (EBRT)
Number of trial subjects	21
Estimated enrollment period	20 months
Estimated duration of trial	48 months
Duration of Participation	1.5 years
Estimated average length of treatment per patient	24 months

2.0 TRIAL DESIGN

2.1 Trial Design

This is a single center, open label, unblinded phase II trial to determine the efficacy of concurrent MK-3475 administered at a dose of 200 mg every 21 days with concurrent low to moderate dose external beam radiation therapy (EBRT) to 1-2 lesions in patients with relapsed and refractory Non-Hodgkin Lymphoma (NHL). Patients with NHL that have failed 2 or more lines of therapy (including autologous stem cell transplant) or are not candidates for additional cytotoxic chemotherapy are eligible if they have 1-2 lesions amenable to EBRT. This phase II trial will evaluate the efficacy and safety of systemic MK-3475 administered concurrently with low to moderate dose EBRT. Pembrolizumab will be given at a fixed dose of 200 mg to be administered intravenously every 21 days for up to 24 months (total of 35 infusions). Adverse events (AE) will be monitored throughout the trial and severity grading will be performed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Response to therapy will be assessed according to the Recommendation for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification [1].

Treatment with Pembrolizumab will continue until documented progression of disease, unacceptable AE(s), intercurrent illness that prevents continuation with therapy, withdrawal of consent by the patient or investigator, non-compliance with treatment requirements, administrative reasons or completion of all 35 infusions. Upon completion of therapy, each patient will be monitored for 30 days and 90 days for AE and serious

adverse events (SAEs), respectively. Subjects who discontinue therapy for reasons other than progression of disease, will have post therapy follow-up for disease status until disease progression, initiation of a non-study cancer therapy, withdrawal of consent or becoming lost to follow-up.

The primary trial objective is to determine the overall response rate (ORR) of non-irradiated lesion(s) to pembrolizumab with concurrent fractionated EBRT. Secondary objectives include determination of complete response rate (CRR), progression free survival (PFS), overall survival (OS), safety and the duration of response of irradiated and non-irradiated lesions to concurrent pembrolizumab and fractionated low to moderate dose EBRT in patients with relapsed and refractory NHL. Exploratory objectives include the identification of tumor and peripheral blood markers that are predictive of response to combination pembrolizumab and fractionated EBRT, evaluation of response to hypo-fractionated EBRT among patients who relapse or progress after pembrolizumab administered with standard fractionated EBRT.

The study will be conducted in conformance with Good Clinical Practices.

Phase II Trial

This phase II trial is an open label, unblinded study evaluating administration of MK-3475 at 200 mg every 21 days with concurrent EBRT. On Day 1 EBRT will be initiated to 1-2 lesions. Patients in cohort 1 will have at least one lesion that will remain out of the radiation field (unirradiated lesion). Patients in cohort 2 will have all sites of radiographic disease included in 1-2 radiation therapy fields. Patients will receive Pembrolizumab at a fixed dose of 200 mg beginning on Day 2 of cycle 1 and then Day 1 of subsequent cycles at 21 day intervals for a total of 24 months (total of 35 doses). In the planned efficacy evaluations, patients that develop progressive disease (PD) outside of the radiation therapy field can be treated with hypo-fractionated EBRT concurrent with the remaining cycles of MK-3475. In this second course of treatment, EBRT will be administered with a hypo-fractionated schedule with fraction sizes of at least 4 Gy regardless of disease histology.

2.2 Trial Diagram

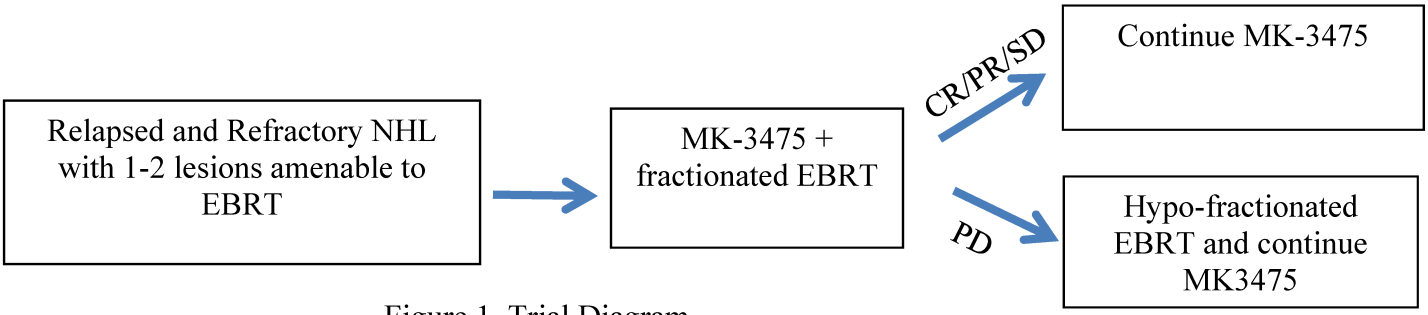

Figure 1. Trial Diagram

Aggressive NHL (40-50) in ≤ 3Gy fractions

Indolent NHL (20-24) in ≤ 3Gy fractions

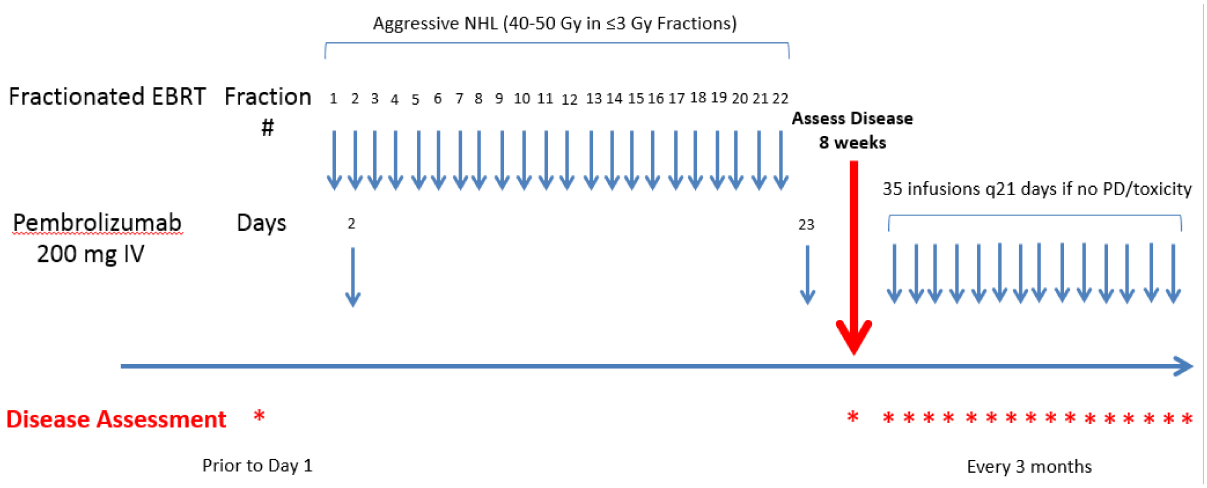

Figure 2. Clinical Trial Schema. Trial subjects will receive treatment with EBRT to a dose of 40-50 Gy in fraction sizes of 3 Gy or less on Day 1 (based on disease histology) and pembrolizumab at 200 mg intravenous infusion beginning on Day 2. Pembrolizumab will be given every 3 weeks at 200 mg IV if no progressive disease or toxicity is identified for a total of 35 infusions (24 months). The first efficacy evaluation is at 8 weeks (+/- 14 days) with subsequent disease assessments every 3 months (+/- 14 days).

3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objective & Hypothesis

1) **Primary Objective:** To determine the overall response rate (ORR) of pembrolizumab with concurrent fractionated EBRT among patients with relapsed and refractory NHL.

Hypothesis: Therapy with pembrolizumab concurrent with EBRT will result in an ORR of at least 35% in unirradiated lesions among patients with relapsed and refractory NHL and roughly 90% among patients with relapsed and refractory NHL treated comprehensively to all sites of radiographically apparent disease that can be encompassed in 1-2 radiation therapy fields.

3.2 Secondary Objectives & Hypotheses

1) **Objective:** To determine the safety of pembrolizumab with fractionated EBRT in patients with relapsed and refractory NHL.
2) **Objective**: To determine the overall response rate and complete response rate (CRR) of irradiated and non-irradiated lesions to treatment with concurrent Pembrolizumab and fractionated EBRT in patients with relapsed and refractory NHL.
3) **Objective**: To determine the Progression Free Survival (PFS) of pembrolizumab in combination with fractionated EBRT.
4) **Objective:** To determine the Overall Survival (OS) of pembrolizumab in combination with fractionated EBRT.
5) **Objective:** To determine the duration of response of irradiated and non-irradiated lesions after concurrent pembrolizumab and fractionated EBRT.

Hypotheses: Combination therapy with MK-3475 and EBRT will result in clinically meaningful CRR, PFS, and OS rates. Combination therapy with MK-3475 and EBRT is safe.

3.3 Exploratory Objectives and Hypotheses

1) **Objective**: To identify tumor and peripheral blood markers predictive of response to concurrent Pembrolizumab and low to moderate dose EBRT in the setting of relapsed and refractory NHL.
2) **Objective**: To determine if a course of hypo-fractionated EBRT can improve response after progressive disease among patients treated with fractionated EBRT and Pembrolizumab.

Hypotheses: Hypo-fractionated EBRT and MK-3475 will result in disease response when tumor progression occurs with Pembrolizumab and fractionated EBRT.

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Pharmaceutical and Therapeutic Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator brochure.

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. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in relapsed or refractory Non-Hodgkin Lymphoma. 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 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. Recently in March 2017, the Food and Drug Administration (FDA) granted accelerated approval for pembrolizumab for pediatric and adult patients with relapsed or refractory classical Hodgkin lymphoma (HL) who have progressive disease after 3 or more lines of therapy.

4.1.2 Preclinical and Clinical Trial Data

P001 is an open-label, Phase I, first-in-human (FIH) study of IV MK-3475 in subjects with progressive locally advanced or metastatic carcinomas, especially melanoma or NSCLC. Part

A of the study involved dose escalation that used a traditional 3+3 design. Cohorts of 3 to 6 subjects were enrolled sequentially at escalating doses of 1, 3, or 10 mg/kg administered Q2W. Once the dose escalation was completed, additional subjects were enrolled into Parts A1 and A2 to further characterize the PK and pharmacodynamics of pembrolizumab. In Parts B and D, subjects with metastatic melanoma were enrolled to assess the safety and antitumor activity of pembrolizumab. Additionally, Part B explored 3 different dose regimens in subjects with metastatic melanoma: 10 mg/kg Q2W, 10 mg/kg Q3W, and 2 mg/kg Q3W. In Part C, subjects with NSCLC (with prior systemic therapy) were enrolled at 10 mg/kg Q3W to assess the tolerability, safety, and antitumor activity of pembrolizumab in NSCLC. In Part F, subjects with NSCLC in Cohort F-1 (without prior systemic therapy) and Cohort F-2 (with prior systemic therapy), whose tumors expressed PD-L1, were enrolled at 10 mg/kg Q2W and 10 mg/kg Q3W to characterize the tolerability, safety, and antitumor activity of pembrolizumab. A small cohort of previously treated subjects with NSCLC and at least 2 lines of systemic therapy, whose tumors did not express PD-L1, were enrolled and treated at a dose of 10 mg/kg Q2W in Cohort F-2. In Cohort F-3, previously treated subjects with NSCLC whose tumors express PD-L1 were enrolled at 2 mg/kg Q3W to better characterize the efficacy, safety, and antitumor activity of pembrolizumab. Each of the 2 disease specific cohorts (melanoma and NSCLC) were enrolled to confirm tolerability and evaluate tumor response to pembrolizumab. The overall response rates for pembrolizumab treatment in P001 compared favorably to historical response rates for available treatments for melanoma, particularly in subjects who have progressed after multiple prior therapies (Investigator's Brochure, Version 10, August 31, 2015).

The primary efficacy endpoint of P001 is ORR. A secondary efficacy endpoint is disease control rate (DCR). The efficacy analysis was based upon the All Patients as Treated (APaT) population—all subjects who received at least 1 dose of study treatment and may or may not have had measurable disease at baseline per independent central review. For subjects without measurable disease at baseline, a partial response was not possible (even if there was a reduction in tumor burden) per RECIST 1.1, and non–complete response (CR)/non–progressive disease (PD) was equivalent to stable disease (SD) in subjects with measurable disease at baseline. The ORR and DCR analysis for 655 melanoma subjects who received pembrolizumab in Parts B1, B2, B3, and D, regardless of prior exposure to IPI and across all dose levels tested, is displayed in Table 30. Overall there were 44 complete responses and 159 partial responses. The ORR was 31% (95% CI: 28% to 35%). DCR was achieved in 51% of all subjects.

P002 is a partially blinded, randomized, Phase II pivotal study of pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W versus investigator-choice (standard-of-care) chemotherapy in a 1:1:1 ratio in subjects with IPI-refractory metastatic melanoma. There are 2 co-primary efficacy endpoints for this study: progression-free survival (PFS) and overall survival (OS). A secondary efficacy endpoint is ORR. The data cutoff date for efficacy events included in the efficacy analysis was 12-May-2014. The analysis was based upon the Intention-to-Treat (ITT) population – subjects were included in the treatment group to which they were randomized. A primary censoring rule, which censored at the last disease assessment without PD, when PD or death was documented after more than 1 missed disease assessment, was applied for the analysis. The hazard ratio was 0.57 and 0.50 in the pembrolizumab 2 mg/kg Q3W arm and 10 mg/kg Q3W arm over the control arm, respectively, favoring the pembrolizumab arms for PFS

(the one-sided p-value was <0.0001 in both comparisons). This met prespecified criteria for a positive study. The PFS rate at Month 6 was 34.3% (95% CI: 27.4 to 41.3%) and 37.7% (95% CI: 30.6% to 44.8%) for pembrolizumab 2 mg/kg and 10 mg/kg, respectively, versus 15.6% (95% CI: 10.5% to 21.5%) for the control arm. The median PFS was 2.9 months in both pembrolizumab arms and 2.7 months in the control arm. The PFS data show that administration of pembrolizumab (both dose regimens) resulted in a clinically meaningful improvement in PFS versus treatment with chemotherapy. The ORR per RECIST 1.1 by IRO is shown in Table 32: 21% in the pembrolizumab 2 mg/kg arm, 25% in the 10 mg/kg arm, and 4% in the chemotherapy arm (p<0.0001 for each pembrolizumab dose versus chemotherapy). A preliminary analysis of OS indicated that the hazard ratio was 0.88 in the pembrolizumab 2 mg/kg Q3W arm over the control arm and 0.78 in the pembrolizumab 10 mg/kg Q3W arm over the control arm. The one-sided p-value was 0.229 and 0.066 in 2 mg/kg Q3W and 10 mg/kg Q3W over the control arm, respectively, both favoring pembrolizumab. The pre-specified final analysis of OS will be performed after 370 deaths have occurred.

Efficacy data are available for a total of 655 P001 melanoma subjects treated with pembrolizumab and 540 P002 melanoma subjects treated with either pembrolizumab or chemotherapy. The data cutoff dates are 18-Apr-2014 for P001 melanoma subjects and 12-May-2014 for P002 subjects. For both clinical studies, assessment of overall response rate (ORR) was based on RECIST 1.1 and performed by blinded central reviewers.

The P001 overall response rate (ORR) demonstrated the antitumor activity of pembrolizumab in subjects with melanoma (ipilimumab-naïve and previously treated with ipilimumab). P002 demonstrated superior PFS for both pembrolizumab treatment arms compared to the chemotherapy control arm. Treatment with pembrolizumab lead to an ORR that was >4 fold higher than the response rate of the chemotherapy control arm. This difference was highly statistically significant, with a one sided p-value of <0.0001. The overall response rates for pembrolizumab treatment in P001 and P002 compared favorably to historical response rates for available treatments for melanoma, particularly in subjects who had progressed after multiple prior therapies. For example, the largest randomized clinical trial in previously treated advanced melanoma subjects, in which carboplatin and paclitaxel were used in the control arm, and sorafenib plus carboplatin and paclitaxel in the experimental arm, produced a response rate of 11% and 12%, respectively.

The approval for pembrolizumab among patients with relapsed and refractory HL was based on the KEYNOTE 087 trial, a nonrandomized, open-label study of 210 patients with refractory HL or relapsed disease after 3 or more prior lines of therapy. The ORR for pembrolizumab was 69% (95% CI 62-75) at a median follow up of 9.4 months. Of these overall responses, complete responses were reported among 22% of patients and partial responses on 47%. Among the 145 responding patients, the median duration of response was 11.1 months (range 0+ to 11.1). The median number of prior therapies was 4 (range of 1-12). Serious adverse side effects were reported in 16% of patients (most frequently pneumonia, Graft versus host disease (GVHD), herpes zoster, pyrexia, pneumonitis and dyspnea). Corticosteroids were required for adverse reactions in 15% of patients. Two patient deaths occurred that were unrelated to disease in a patient that died of septic shock and a patient that died of GVHD after undergoing subsequent allogeneic hematopoietic stem cell transplantation.

In regards to patients with non-Hodgkin lymphoma and other hematologic malignancies, there are two ongoing trials evaluating the safety and efficacy of pembrolizumab among patients with hematologic malignancies. The P013 trial is a Phase Ib, Multi-Cohort Trial of MK-3745 in patients with Hematologic Malignancies. P023 is a phase I dose escalation trial of Pembrolizumab, lenalinomide and dexamethasone in patients with multiple myeloma. In the P013 trial among 88 trial subjects, 73 (83.0%) experienced AEs of which 35 (39.8%) were considered drug related. Serious AEs were reported in 36.4% of subjects, and SAEs that were considered by Investigators to be drug related were reported in 4.5% of subjects overall. Three subjects (3.4%) died within 30 days of the last dose of pembrolizumab; none of the deaths were considered drug related. Deaths reported due to MedDRA preferred terms "Neoplasm Progression," "Malignant Neoplasm Progression," and "Disease Progression" not related to the drug are excluded from this count of subjects that died. Most subjects continued treatment despite AEs, with 9.1% discontinuing due to an AE. Only 4.5% of subjects discontinued study treatment due to an AE that was considered related to study treatment by Investigators.

Of the 10 subjects on the P023 trial, 8 (80.0%) experienced AEs of which 6 (60.0%) were considered drug related. Serious AEs were reported in 30.0% of subjects, and SAEs that were considered by Investigators to be drug related were reported in 20.0% of subjects overall. No subjects died within 30 days of the last dose of pembrolizumab and no subjects discontinued due to an AE. Due to the fact that this was a combination study, and also because of the small sample size, comparative evaluation of the AE profile of pembrolizumab combination therapy from this protocol to pembrolizumab monotherapy or to chemotherapy monotherapy in other studies cannot be made.

4.1.3 Radiation Therapy

Along with surgery and chemotherapy, radiation has long been regarded as one of the pillars of oncology. Radiation therapy is often utilized when local control is desired. In patients with solid tumors, radiation is often used before or after surgery to improve loco-regional control. In contrast, surgery has little role in the management of hematologic malignancies. The role of RT in the management of NHL has evolved over the course of history [2]. The initial curative approach for patients with Hodgkin's lymphoma and NHL was with RT. Long term disease control was achieved with radiation alone, especially for patients with limited stage I and II disease. In a study of 655 patients with stage I and stage II NHL treated in the 1970's, RT was found to be curative in a significant proportion of patients [3]. RT to moderate doses of 25-30 Gy in 10-25 fractions produced local control rates in excess of 90% for most patients with low grade NHL. Patients with diffuse large B cell lymphoma treated with radiation therapy for gross disease required higher doses to 40-50 Gy in 20-25 fractions to achieve local control greater than 75%. Prior to the widespread introduction of systemic therapy, extended field RT that included prophylactic radiation of all major lymph node regions above and below the diaphragm, afforded patients increased progression free survival and overall survival [4-7]. With the introduction of systemic therapy (mainly anthracycline containing regimens) in the 1980's as the primary treatment for patients with NHL, RT was used mainly as consolidation to improve local control and disease free survival [8].

Long term follow up of patients treated with extensive radiation fields with outdated techniques have demonstrated significant long term morbidity and in some cases, mortality. Radiation toxicity has been widely investigated and reported, especially among young Hodgkin lymphoma patients [9-11]. Through knowledge of this long term toxicity coupled with the recognition that prophylactic nodal radiation is unnecessary in patients that receive consolidative RT after a good response to chemotherapy, radiation fields have dramatically evolved. Extended field RT gave way to involved field RT (IFRT) introduced in 2002, where fewer prophylactic nodal basins were included in the radiation field [12]. Current "involved site" radiation therapy guidelines mandate that only sites of pre-chemotherapy disease involvement should be included in consolidative RT fields [13]. The reduced normal tissue exposure should result in lower treatment related morbidity as suggested by modeling studies [14,15].

It is widely accepted that lymphoma cells are particularly sensitive to radiation therapy. In 1928 James Ewing recognized various degrees of radio-sensitivity and classified lymphoma as the most radiosensitive tumor[16]. Curative therapy with RT for patients with NHL requires low to moderate doses of radiation, from 20-50 Gy, as compared to 65-70 Gy required for definitive management of solid tumors.

In patients that are treated with radiation for consolidation after systemic therapy for aggressive NHL, a randomized trial conducted in the UK demonstrated that 30 Gy in 2 Gy fractions was equivalent to 40-45 Gy in similar fraction sizes, with no significant differences in local control, progression free survival or overall survival. Patients with gross, chemo-refractory aggressive NHL at the time of RT, however require increased final doses of RT. Studies suggest that doses greater than 40 Gy improve local control in the management of chemo-resistant intermediate to high grade NHL[17,18,40].

For patients with indolent NHL, curative RT is possible with lower doses of radiotherapy. A large, randomized trial established lower doses of 24 Gy in 12 fractions as standard of care for the definitive management of low grade NHL[19]. This treatment approach was associated with trends towards reduced toxicity as compared to the higher dose 40-45 Gy arm. Strategies with ultra-low dose RT, referred to as "boom" where 4 Gy administered in 2 fractions of 2 Gy per fraction over 2 consecutive days, offers an attractive palliative approach for patients with low grade NHL[20]. When 4 Gy was compared in a randomized fashion with 24 Gy however, local control and progression free survival was inferior in the low dose arm and 24 Gy was recommended for patients treated with curative intent.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Immune Checkpoint Therapy in Malignant Disease. Cancer immunotherapy has been investigated as a viable anti-tumor therapy for several decades but only recently has been accepted as a pillar of cancer therapy [21]. That the immune system is an effective treatment against hematologic malignancies is evidenced by the utilization of allogeneic stem cell transplantation, where graft versus lymphoma/leukemia effects result in valuable therapy. The

programmed death (PD-1) pathway is involved in potent inhibition of immune activation, especially through inhibition of effector T cell function. The PD-1 receptor is a transmembrane protein expressed on activated T cells and other immune cells. T cell exhaustion occurs when PD-1 ligands (PD-L1, PD-L2) activate their receptors, initiating an inhibitory signaling network that results in apoptosis of activated T cells. PD ligand expression is minimal in normal tissues, but markedly upregulated in acute inflammatory environments, implicating its role in peripheral tolerance. Recent pre-clinical and clinical studies suggest that the PD-1/PD-ligand pathway plays a pivotal role in tumor immune evasion, as PD-1 receptor and ligand expression is increased in several malignancies. Encouraging responses have been demonstrated in patients with advanced diseases treated with antibodies targeting PD-1 and PD-L1 leading to FDA approval of two antibodies against PD1 for the treatment of melanoma in 2014.

PD-1 blockade for lymphoma. Manipulation of the PD-1/PDL-1 pathway is of recent interest in patients with classical Hodgkin lymphoma (cHL) and several non-Hodgkin lymphomas (NHLs) including follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) [22]. Indeed in cHL, two distinct phase 1 clinical trials evaluating single agent PD-1 blockade with a monoclonal antibody demonstrated impressive overall response rates (ORR) of 87% and 53% among patients with refractory cHL, of whom the majority failed autologous stem cell transplantation as well as brentuximab[23,24]. Complete response (CR) rates were 17% and 20% in these studies. Data is also emerging regarding the clinical utility of immune checkpoint inhibition in NHL. We have recently demonstrated that in FL, PD-1 blockade in combination with anti-CD20 targeting agent rituximab was well tolerated and resulted in an ORR of 66% and CR in 52% of patients treated with this approach [25]. A recent publication in *Blood* revealed that among patients with DLBCL, tumor biopsy expression of PD-L1 negatively impacted overall survival suggesting a potential role for the PD-1/PD-L1 pathway in this patient population [26].

Preliminary data from an ongoing trial evaluating PD-1 blockade in NHLs, however suggests that the full potential of immune checkpoint blockage will not be reached with anti-PD-1 monotherapy [27,28]. In this study of 81 patients, including 31 and 23 patients with B-cell NHL and T-cell NHL respectively, the ORR was 26% among patients with B cell NHL and 17% among patients with T-cell NHL (Figure 3). The compete response rate was 10% among the B cell NHL subjects and 0% for those with T cell NHL. This suggests that effective cancer immunotherapy likely requires cooperation with other anti-tumor modalities for improved

efficacy. One potential combination strategy to augment response is external beam radiation therapy coupled with PD-1 blockade.

Tumor	OR, No. (%)	CR, No. (%)	PR, No. (%)	SD, No. (%)	Median PFS, Weeks (95% CI)
B-cell lymphoma (n = 31)	8 (26)	3 (10)	5 (16)	16 (52)	23 (7 to 44)
DLBCL (n = 11)	4 (36)	2 (18)	2 (18)	3 (27)	7 (6 to 29)
FL (n = 10)	4 (40)	1 (10)	3 (30)	6 (60)	NR (7 to NR)
Other B-cell lymphoma (n = 10)	0	0	0	7 (70)	11 (3 to 39)
T-cell lymphoma (n = 23)	4 (17)	0	4 (17)	10 (43)	10 (7 to 33)
MF (n = 13)	2 (15)	0	2 (15)	9 (69)	10 (7 to 35)
PTCL (n = 5)	2 (40)	0	2 (40)	0	14 (3 to NR)
Other CTCL (n = 3)	0	0	0	0	7 (6 to NR)
Other non-CTCL (n = 2)	0	0	0	1 (50)	10 (2 to 18)
Multiple myeloma (n = 27)	1 (4)	1 (4)*	0	17 (63)	10 (5 to 15)

Abbreviations: CR, complete response; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MF, mycosis fungoides; NR, not reported; OR, objective response; PFS, progression-free survival; PR, partial response; PTCL, peripheral T-cell lymphoma; SD, stable disease.

*CR was obtained after radiotherapy. SD was the best response to nivolumab.

Figure 3. Efficacy Results from a Phase I, open-label study or patients with relapsed or refractory B cell lymphoma, T-cell lymphoma and multiple myeloma treated with anti-PD 1 monocloncal antibody nivolumab. (From Lesokhin AM, Ansell SM, Armand P. et al, Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study. J Clin Oncol. 2016 Aug 10;34(23):2698-704).

Combination RT and immune checkpoint blockade. The primary mechanism of radiation induced cancer cell death is via DNA damage. However, several studies suggest that the immune system contributes to the anti-neoplastic effects of radiation and is required for the full therapeutic effects of RT to be realized. In 1979 Stone and colleagues recognized that increased doses of radiation were required to control fibrosarcomas in animals that were immunosuppressed, as compared to animals treated with a crude bacterial preparation aimed at immune system stimulation[29]. The abscopal effect describes a phenomenon where tumor regression occurs after RT within a non-irradiated tumor site. Pre-clinical work by Formenti and colleagues demonstrated that the ability of ionizing radiation to decrease tumor growth outside of the radiation field was immune mediated and T-cell dependent [30]. To increase dendritic cell number, growth factor Flt3-Ligand was given to mice harboring a syngeneic mammary carcinoma on both flanks, after local RT to one tumor. Growth of the non-irradiated tumor was reduced by the combination of RT and Flt3-Ligand; while Flt3-ligand alone did not produce this effect without radiation. These effects were not present in T cell deficient nude mice. Furthermore, growth of a non-irradiated lymphoma in the same mice that harbored a treated mammary tumor was not impaired. The potential for radiation to partner with the immune system to create an *in vivo* vaccine was proposed in 2005 by Formenti and colleagues and has gained momentum recently as evidence emerges supporting this hypothesis [31-33].

Recent clinical and pre-clinical data suggests that EBRT induces a tumor specific immune response in irradiated and non-irradiated tumors that is mediated by PD-1 blockade [34].

While stereotactic ablative radiation doses have been used primarily to this effect in patients with known radio-resistant tumor histologies such as melanoma, lower radiation doses may have similar efficacy in patients with hematologic malignancies given the inherent radiosensitivity of these tumors [35]. Utilization of lower doses also has the potential to decrease treatment related toxicity. Furthermore lower radiation doses may be more effective in preserving normal tissue and lymph nodes that are required for the most effective immune response. While there is ongoing controversy regarding the optimal dose and fractionation of RT required for anti-tumor immune responses, some preclinical data suggests that fractionated RT is more immunogenic and leads to increased immune mediated abscopal effects compared with large ablative doses of RT[36,37]. Indeed in the mammary model described above where treatment with Flt-3 Ligand and RT led to growth delay of both irradiated and non-irradiated tumors, single doses of 2 Gy and 6 Gy were evaluated for ability to induce an abscopal effect. The study investigators found that 2 Gy and 6 Gy both led to tumor growth impairment, however there was no significant difference in the level of growth delay of the irradiated or non-irradiated tumors based on these two doses. This prompted the authors to conclude that "a single clinically relevant RT dose is unlikely to trigger an abscopal effect without the addition of FLT3-Ligand" and that "a low RT dose may be as effective as a higher dose in inducing the abscopal effect". Indeed, in a phase I/II study evaluating *in situ* tumor vaccination with a Toll-like receptor 9 (TLR9) agonist and low dose fractionated radiation therapy in 2 Gy fractions in patients with low grade B-cell lymphoma, systemic clinical responses were detected [38]. Fifteen patients with relapsed low grade B cell lymphoma (13 with FL and 2 with MZL) were treated with an *in situ* vaccination approach with an intra-tumoral Toll-like receptor 9 (TLR9) ligand coupled with low dose RT at the same tumor site to a dose of 4 Gy in 2 fractions over two consecutive days. The overall response rate in this small study was 27%, with one patient experiencing a complete response, three patients with partial response and stable disease observed in 8 patients. Taken together, these data suggest that radiation with standard fractionation of 2 Gy and at lower total radiation doses can be immunogenic and sufficient to support immune mediated, radiation induced distant tumor death. Radiation at ablative doses administered on a hypo-fractionated schedule are likely not required for eliciting an abscopal effect in radiosensitive tumor types, such as lymphoma.

We propose a phase II open label, unblinded single arm trial to evaluate the potential for fractionated radiation therapy to augment responses with PD-1 inhibitor Pembrolizumab. Among patients with progressive disease outside of the radiation therapy field after concurrent fractionated EBRT and pembrolizumab, a second course of EBRT administered on a hypo-fractionated schedule of at least 4 Gy per fraction with pembrolizumab will be evaluated, This approach will afford the ability to 1) assess the potential added efficacy of fractionated EBRT (as opposed to stereotactic body radiation therapy) to PD-1 immunotherapy in this refractory patient population 2) assess the ability of hypo-fractioned EBRT to offer salvage therapy to patients with progression after initial therapy with pembrolizumab and fractionated EBRT and

3) identify tumor and peripheral blood markers that correlate with response and/or toxicity based on serial specimens collected over the course of the trial.

The effect of external beam radiation therapy fractionation on radiation induced augmentation of immune checkpoint therapy is unclear [39]. Most studies in solid tumors have utilized ablative stereotactic dose of RT. While we hypothesize that fractionated RT at 2 Gy per fraction will be effective for eliciting tumor responses (as supported by data stated above), it is plausible that hypo-fractionation is essential for synergy between checkpoint blockade immunotherapy and radiation. In an effort to identify the potential benefit of hypo-fractionation, among patients treated with standard fractionated EBRT and pembrolizumab that progress after combination therapy, we propose a second course of EBRT to be administered with a high dose per fraction, hypo-fractionated approach (of at least 4 Gy per fraction) , to be administered with continued pembrolizumab therapy.

It is likely that the timing of immune checkpoint blockade and EBRT influence the effectiveness of therapy. In a pre-clinical model of melanoma, breast and colorectal cancer, the anti-tumor activity of low dose fractionated RT was enhanced through the combination of a monoclonal antibody targeting PD-L1[35]. In this mouse model, treatment timing and scheduling was significantly affected treatment efficacy; with concurrent RT and PD-L1 therapy but not sequential therapy resulting in beneficial local control and survival. Based on these data we propose that pembrolizumab and fractionated RT should be administered concurrently.

The overall response rates of refractory NHL to single modality radiation therapy are relatively high but often not durable. In a retrospective study from the Dana-Farber Cancer Institute of 110 patients treated with a course of salvage radiation therapy for relapsed or refractory aggressive NHL, the overall response rate was 78% among refractory patients treated with curative intent and 81% for those refractory patients treated with palliative intent[40]. Among living patients the 5 year rate of progression free survival however was only 34%. Furthermore even among patients treated with doses greater than 40 Gy with curative intent the 2 year local control rate was only 61%. This highlights 1) the need for effective systemic therapies to pair with salvage radiation therapy and 2) the room for improvement in long term local control that for patients with refractory NHL that may be accomplished with concurrent systemic therapy.

Given this data this study will address the role of pembrolizumab and concurrent RT in two patient populations. The first eligible cohort will include patients with more disseminated disease where all disease will not be included in the radiation field and there will be an “unirradiated lesion”. The second cohort of eligible patients will be those with relapsed/refractory aggressive NHL where all sites of disease can be encompassed in 1-2 radiation therapy fields. We hypothesize that 1) the response rates of the unirradiated lesion will be higher than reported ORR among patients treated previously with PD-1 blockade monotherapy for relapsed and refractory NHL and 2) the response rates for patients treated

with pembrolizumab and RT fields encompassing all sites of disease will be also be improved over rates reported for salvage RT alone.

An open-label Phase I trial (Protocol 001) was conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 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 MK-3475 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. MK-3475 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 MK-3475 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 of 200 mg of pembrolizumab administered every 21 days (q3weeks) is planned for this study. Available PK results in patients with NSCLC, melanoma, classical HL and other solid tumor types support a lack of meaningful difference in PK exposures obtained at a given dose among tumor types. 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.

4.2.2 Rationale for Endpoints

The primary endpoint of this phase II trial is to determine the ORR fortreatment with pembrolizumab and concurrent EBRT. For patients in Cohort 1 with multiple sites of relapsed or refractory disease, the ORR of an unirradiated lesion to pembrolizumab with EBRT will be determined. For Cohort 2 eligible patients all sites of radiographic lymphoma will be included in 1-2 RT fields and the ORR will be determined. Secondary endpoints include the determination of CRR, PFS, OS and duration of response of irradiated and non-irradiated lesions among patients treated with pembrolizumab with fractionated EBRT.

Disease response will be according to standard response criteria for NHL that was revised in 2014 (Appendix 11.3) [1]. For patients with FDG-avid disease, the Deauville Criteria will be utilized for PET-CT scoring on a 5 point scale, in accordance with standard response criteria. The 5 point scale is as follows, with score of 1-3 considered negative and 4-5 considered positive:

1. No uptake
2. Uptake less than or equal to the mediastinum
3. Uptake greater than the mediastinum but less than or equal to the liver
4. Moderately increased compared with the liver
5. Markedly increased compared with the liver

X. New Areas of uptake unlikely to be related to lymphoma

While the immune related response criteria (irRC) are often utilized for immunotherapy trials, these criteria are best suited for assessing responses among patients with solid tumors and not in the setting of lymphoma. As we are interested in assessing the responses inside and outside of the irradiated field, in addition to determining overall response rates and overall complete response rates, we will also divide disease response into local (within the radiation field) and systemic (outside of the radiation field).

An ongoing challenge in assessing response to immunotherapy lies in the ability to distinguish true disease progression from immune induced inflammatory changes, i.e. pseudo-progression [41,42]. Given that disease response may only become apparent radiographically following a

period of initial disease stability or progression, early evidence of clinically asymptomatic disease progression or new lesions detected in less than 3 months will not be criteria for study removal. While the first efficacy evaluation will occur at 8 weeks, if the study investigators suspect radiographic pseudo-progression in the absence of definitive clinical proof of disease progression, a subject may be granted an exception to continue on treatment until progression is confirmed at least 4 weeks later, provided that the subject's clinical condition is stable as detailed in Section 7.1.2.6.4.

Efficacy Endpoints

Disease response will be assessed via revised Lugano classification for the response assessment of Hodgkin and non-Hodgkin lymphoma [1]. The end of treatment assessment is determined by positron emission tomography (PET)-computed tomography (CT) imaging for patients with fluoro-deoxyglucose (FDG) avid hematologic malignancies. Responses are designated, complete response (CR), partial response (PR) stable disease (SD) or progressive disease (PD). For disease histologies with low or variable FDG avidity, CT based response will be utilized. Disease response will be divided into local and systemic response and will be determined beginning at 3 months after treatment initiation.

4.2.2.1 Biomarker Research

Blood samples and tumor biopsies will be obtained from consenting patients at baseline and/or on treatment from subjects enrolled on the study at the indicated time points shown in the Trial Flow Chart under Section 6.0. The overall goal of the biomarker studies is to identify predictive, surrogate, mechanistic, and pharmacodynamic biomarkers of pembrolizumab and EBRT combination therapy. Peripheral blood mononuclear cells (PBMC) and serum will be isolated from blood samples and cryopreserved for batched analysis.

PBMC samples will be analyzed by up to 10-color multiparametric flow cytometry to determine alteration in effector and regulatory T cell subsets and to determine expression of various co-stimulatory and co-inhibitory receptors on T cells. Serum samples will be analyzed for alteration in various cytokines and chemokines. Tumor biopsies will be analyzed by whole genome gene expression profiling (GEP), immunohistochemistry (IHC), and/or flow cytometry. Immunohistochemical and flow cytometric analyses will be performed on baseline tumor biopsy specimens to evaluate for baseline levels of PD-L1, PD-1, CD4+ and CD8+ Tumor Infiltrating Lymphocytes (TILs) and regulatory T cells (Tregs) within the tumor. Gene expression profiling will also be performed on baseline tumor biopsy samples. We will also assess the predictive significance of the intra-tumoral effector T cell gene signature that was associated with clinical outcome in follicular lymphoma patients treated with rituximab plus pidilizumab therapy that was recently described by us [25]. The same analyses will be conducted on tumor biopsy samples obtained post-RT. Immunophenotyping via flow cytometry will be performed on peripheral blood mononuclear cells obtained from baseline and serial post-treatment samples to determine alteration in effector and regulatory T cell subsets and to determine expression of various co-stimulatory and co-inhibitory receptors on T cells.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male or female subjects with histologic evidence of aggressive Non-Hodgkin lymphoma (NHL) who have relapsed or progressive disease after 2 prior systemic therapies (including autologous stem cell transplant) or have relapsed/refractory disease and are no longer candidates for cytotoxic chemotherapy are eligible for this study.

5.1.2 Subject Inclusion Criteria

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

1. Have at least one site of lymphomatous disease amenable to external beam radiation therapy (EBRT)

2. Have pathologic confirmation of aggressive Non-Hodgkin Lymphoma (including diffuse large B cell lymphoma, transformed follicular lymphoma, transformed marginal zone lymphoma, primary mediastinal B-cell lymphoma, T cell lymphoma and NK T-cell lymphoma). Patients with indolent B cell lymphoma are excluded.

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

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

5. Have measurable disease (≥ 1.5 cm in the longest diameter for nodal or extranodal disease)

6. Have provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. *Newly obtained* biopsies are preferred to *archived* tissue. *Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen.* Note: If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from the date slides are cut.

7. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Evaluation of ECOG is to be performed within 7 days prior to the date of allocation/randomization.

8. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value

Hematological	
Absolute neutrophil count (ANC)	≥1,000 /mcL
Platelets	≥ 50,000/ mcL
Hemoglobin	≥ 8 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

9. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

10. Female subjects of childbearing potential (Section 5.7.2) must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, for the course of the study through 120 days, corresponding to time needed to eliminate any Merck study treatment(s) and/or any active comparator/combination, plus 30 days (a menstruation cycle) for study treatments with risk of genotoxicity after the last dose of study medication.

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

11. A male participant must agree to use a contraception as detailed in Appendix 3 of this protocol during the treatment period and for at least the entire period during which the male participant receives the study drug pembrolizumab, corresponding to time needed to eliminate any Merck study treatment(s) and/or any active comparator/combination, plus an additional 120 days (a spermatogenesis cycle) for study treatments with evidence of genotoxicity at any dose, after the last dose of study treatment and refrain from donating sperm during this period.

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

5.1.3 Subject Exclusion Criteria

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

1. Has had prior radiation therapy to the potential radiation target such that additional radiation therapy is considered unsafe by the treating radiation oncologist

2. Has a history of allogeneic stem cell transplantation.

3. Has a diagnosis of active scleroderma or lupus or any other autoimmune disease that by the opinion of the treating radiation oncologist would put the patient at unacceptable risk of toxicity.

4. 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.

5. 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.

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

7. Hypersensitivity to pembrolizumab or any of its excipients.

8. 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.

9. 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.

10. Has a known additional malignancy that is progressing or requires active treatment within the past 3 years. 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.

.

11. Has known active central nervous system (CNS) lymphoma or lymphomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.

12. 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 (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

13. Has history of (non-infectious) pneumonitis that required steroids, evidence of interstitial lung disease or active, non-infectious pneumonitis.

14. Has an active infection requiring systemic therapy.

15. 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.

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

17. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

18. A WOCBP who has a positive urine pregnancy test within 72 hours prior to receiving the first dose of study medication (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Note: in the event that 72 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for subject to start receiving study medication.

19. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

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

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

22. Has received a live vaccine within 30 days of planned start of study therapy.

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.

5.2 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	Q3Wa	IV infusion	Day 1 of each 3 week cycle	Experimental
External Beam Radiation Therapy	20-50 Gy in ≤ 3 Gy fractions	Daily	External Beam	5 days per week consecutively until treatment is complete (not including holidays and weekends)	Standard of Care
[b]The MK-3475 dosing interval may be modified secondary to toxicity as described in Section 5.2.1.2					

Trial treatment should begin on the day of randomization or as close as possible to the date on which treatment is allocated/assigned.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale. Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

Radiation will be given as per our instuitional standard for NHL. Fractionation schedules include 40-50 Gy in 3 Gy fractions or less, which are acceptable doses for salvage RT for patients with aggressive NHL. Hypofractionated radiation therapy when given to patients with progressive disease will be given at fraction sizes of at least 4 Gy per fractions. All radiation therapy will be administered daily (likely excluding weekends and holidays when applicable). All radiation therapy will be standard of care.

5.2.1.2 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 3 below. See Section 5.6 for supportive care guidelines, including use of corticosteroids.

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

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

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, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

5.2.2 Timing of Dose Administration

Trial treatment should be administered on Day 2 of the first cycle and Day 1 of cycles 2-25 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 due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 1 hour IV infusion every 3 weeks. Nurses 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).

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

Computed tomography (CT) based simulation for radiation treatment planning will generally occur one week prior to the initiation of EBRT. RT will be administered daily except for on weekends and holidays.

A subject with unconfirmed PD may continue trial treatment until PD is confirmed at the next scheduled assessment. Subjects may only receive study treatment while waiting for confirmation of PD of the following criteria are met:

1) Absence of signs and symptoms indicating disease progression (including worsening of laboratory values)

2) No decline in ECOG performance status

3) Absence of rapid PD

4) Absence of progressive tumor at a critical anatomical site (i.e. cord compression) requiring urgent alternative medical intervention.

5.2.3 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

This is an unblinded, non-randomized trial among patients with relapsed and refractory aggressive NHL. Trial enrollees will receive MK-3475 concurrent with fractionated EBRT. Patients will be stratified according to extent of disease included in the radiation therapy field (s)as follows:

1) Cohort 1: Relapsed/Refractory Aggressive B-cell lymphoma with disease excluded from the Radiation Therapy Field (n=20)

2) Cohort 2: Relapsed/Refractory Aggressive B-cell lymphoma with all sites of radiographically evident disease treated in 1-2 radiation therapy field(s).Disease (n=20)

5.4 Radiation Therapy

Radiation treatment will consist of definitive radiation therapy to a site of relapsed/refractory disease encompassed in one radiation therapy plan. Patients in Cohort 1 with relapsed or refractory lymphoma will be treated to one to two region(s) of disease with at least one distinct lesion excluded from the field and designated the "unirradiated lesion". Patients in Cohort 2 with relapsed or refractory lymphoma will be treated with one to two RT plan(s) encompassing all sites of evident active disease. All patients (in both cohorts) will receive EBRT to a dose of 40-50 Gy in fractions sizes of 3 Gy or less. Integrated boost technique is permitted. Treatment will be administered 5 days per week, excluding holidays and weekends. For patients that are eligible for salvage hypo-fractionated EBRT, fraction sizes of at least 4 Gy will be used with a conformal delivery approach.

Radiation Simulation
CT based simulation and RT planning is required for every patient. Simulation will be performed roughly one week prior to initiation of therapy. Custom immobilization should be used when appropriate. During simulation, patients will be evaluated for respiration induced motion of the target volume. Based on this evaluation, a 4D CT simulation or breath-hold may be used for motion management. The CT simulation images will be transferred over to the treatment planning system (Pinnacle or Eclipse) for radiation therapy planning.

Radiation Technique
The radiation technique utilized is at the discretion of the treating radiation oncologist and will be standard of care and institutional standards. Priority to sparing normal tissue should be maintained at all times. Potential treatment modalities include 3D conformal RT, Intensity Modulated Radiation Therapy (IMRT), Volumetric Arc Therapy (VMAT), Proton radiotherapy and Electron radiotherapy. Utilization of daily image guidance is at the discretion of the treating radiation oncologist with the goal of limiting set up uncertainty to less than 10 mm variation. Integrated boost technique is permitted at fractions of 3 Gy or less.

Radiation Target Volumes and Dosimetry
1) Gross tumor volume (GTV) is defined as the tumor bulk visible radiographically on the CT planning scan.

2) The Clinical Target Volume (CTV) and Planning Target Volume (PTV) will be 5 -15 mm based on the type of image guidance utilized and the planned radiation technique. The prescription isodose line should cover greater than 98% of the GTV. We recommend PTV coverage of >95% when possible.

For patients enrolled in Cohort 1, the lesion(s) designated as the non-index lesion(s) outside of the radiation field should be at least 5 cm away from the radiation field. This lesion should be identified and documented prior to initiation of protocol therapy. In cases where the lesion is within 5 cm of the field, the non-index lesion(s) should be contoured and should receive a dose no greater than 5 Gy over the course of the entire radiation treatment.

Dose Constraints

Dose constraints are according to QUANTEC as well as institutional dose constraint guidelines established by the Department of Radiation Oncology Hematologic Malignancy Section [43]. Important dose restraints include:

1) Spinal cord Max point dose <45 Gy
2) Lung: Mean lung dose (MLD) ≤13.5 Gy, V20 < 30%, V15<35%, V10 <40% and V55<55% [44].
3) Heart: Mean <15 Gy
4) Brachial Plexus: Maximum dose <66 Gy
5) Parotid gland: Mean <26 Gy
6) Submandibular gland: Mean <26 Gy
7) Small Bowel: 1cc <55 Gy [45]
8) Kidney: Mean <13 Gy, V20 < 33% for at least one kidney
9) Liver: Mean <28 Gy, V30 < 30% and V20 <50%
10) Bone marrow: pelvic bone marrow V10 <95% and V20 <76% [46]

5.5 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.

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject’s welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

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.

5.5.2 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
- 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 to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 5.2.1 for dose modification.

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

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
    - If grade 2 or higher pneumonitis occurs in patients receiving concurrent radiation therapy to the chest, radiation therapy will be suspended immediately.
- **Diarrhea/Colitis**:

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

    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - When grade 3 or higher diarrhea or colitis occurs in a patient receiving concurrent radiation therapy to the abdomen or pelvis and the bowel is receiving radiation, then the radiation therapy will be suspended immediately.
- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
    - For **T1DM** or **Grade 3-4** Hyperglycemia
        - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.

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

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

- **Hyperthyroidism or Hypothyroidism**:

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

    - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
        - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
        - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
    - **Grade 3-4** hyperthyroidism
        - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

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

- **Renal Failure or Nephritis**:
    - For **Grade 2** events, treat with corticosteroids.
    - For **Grade 3-4** events, treat with systemic corticosteroids.

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

- **Management of 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 3 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 3 Infusion Reaction Treatment Guidelines

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

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 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 for 120 days after the last dose of study drug 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 pill or 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 up to 120 days after the last dose of trial 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.

5.7.3 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 the Sponsor and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 7.2.2.

5.7.4 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.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor 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 7.1.4 – Other Procedures.

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, please see Section 5.2.2

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.1.2.7.1

- Unacceptable adverse experiences as described in Section 5.2.1.2

- 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 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.5

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab and at least 80% of the planned doses of EBRT beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator 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. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.5.5.

5.9 Subject Replacement Strategy

Additional subjects may be enrolled to ensure that the required number of evaluable subjects is achieved in the applicable analysis population.

5.10 Clinical Criteria for Early Trial Termination

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

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

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

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Screening Phase**		**Pembrolizumab Treatment Cycles[a]**								**End of Treatment**	**Post-Treatment**		
							To be repeated up to 16 cycles							
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
Scheduling Window (Days)[c]:		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 12 weeks post discon	Every 12 weeks
Administrative Procedures														
Pre-screening Consent	X													
Informed Consent[d]		X												
Inclusion/Exclusion Criteria		X												
Demographics and Medical History		X												
Prior and Concomitant Medication Review[e]		X	X	X	X	X	X	X	X	X	X	X	X	X
Pembrolizumab Administration			X	X	X	X	X	X	X	X				
EBRT Administration			X	X[f]										
Post-study anticancer therapy status												X	X	X
Survival Status				X							X	X		X
Clinical Procedures/Assessments														
Review Adverse Events[g]		X	X	X	X	X	X	X	X	X	X	X	X	X
Full Physical Examination		X												
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs and Weight[h]		X	X	X	X	X	X	X	X	X				
ECOG Performance Status		X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory														
Pregnancy Test – Urine or Serum β-HCG[i]		X												
PT/INR and aPTT[j]		X												

Trial Period:	**Screening Phase**		**Pembrolizumab Treatment Cycles[a]**								**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	3	4	To be repeated up to 16 cycles 5	6	7	8	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
Scheduling Window (Days)[c]:		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 12 weeks post discon	Every 12 weeks
HIV 1 and 2 antibody		X												
CBC with Differential[k]		X		X	X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel[k]		X		X	X	X	X	X	X	X	X	X	X	X
Urinalysis		X					X					X		
T3, FT4 and TSH		X			X		X		X			X[l]	X	
Quantitative immunoglobulins: IgG, IgA and IgM		X					X[m]					X	X	
Bone Marrow Biopsy and Aspirate		X[n]												
Efficacy Measurements														
Chest X Ray, PA and Lateral		X												
CT Neck, Chest, Abdomen and Pelvis[o]						X[p]							X	
PET-CT[o]		X				X[p]				X	X[q]			
Bio-Marker Studies														
Archival or Newly Obtained Tissue Collection (optional)[r]		X				X[r]								
Correlative Studies Blood Collection (optional)[r]		X	X	X		X								
*For patients treated with 22 fractions of EBRT, cycle#2 of pembrolizumab will occur during EBRT														

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21 days); however the treatment cycle interval may be increased due to toxicity according to the dose modification guidelines provided in Section 5.2.1.2. If the interval is increased, all procedures except for response assessment should be performed based on the new dosing schedule.

b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status as per the follow-up schedule until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.
c. In general, the window for each visit is ± 3 days unless otherwise noted.
d. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 28 days prior to the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.
e. Prior medications – Record all medications taken within 28 days of screening visit. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2.
f. For patients treated for aggressive NHL, cycle#2 of pembrolizumab will occur during EBRT
g. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, will also be evaluated for seriousness. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or the start of new anti-cancer treatment, whichever comes first. Afterwards, report only SAEs and ECIs that are related to trial treatment.
h. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at visit 1 only.
i. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
j. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
k. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests.

l. Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.
m. To be repeated every 4 cycles after Cycle 5.
n. Subjects will have bone marrow biopsy/aspirate performed at baseline at the discretion of the treating physician. Subsequent bone marrow assessments will only be performed in subjects who achieved a CR by imaging criteria and have had bone marrow involvement at baseline. Repeat marrow assessment is not required in subjects who do not achieve a CR by imaging criteria.
o. Disease response assessment is based upon Cheson 2014 lymphoma response criteria. "Diagnostic quality" PET-CT with oral contrast/water and IV contrast should be performed at Screening unless there is a contraindication. In general, follow-up assessments during therapy will be done by PET-CT scans for FDG avid disease. If PET-CT scans cannot be performed then contrasted CT scans will be obtained. PET-CT scan will be repeated to confirm complete remission and/or at treatment discontinuation. For lymphomas that are not FDG-avid at screening, PET does not need to be repeated in subsequent assessments. Response assessments should occur at Screening (within 42 days prior to first dose of trial treatment), after Wk 8 (+/- 14 days), and every 3 months (+/- 14 days) during therapy and for one year after treatment discontinuation and then every 6 months (+/- 14 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies. For subjects who discontinue for reasons other than PD, assessments should continue until the subject has documented PD. The first assessment may be performed earlier than 8 weeks if in the opinion of the investigator the patient is clinically progressing.
p. At the Week 8 assessment (prior to cycle #4) disease can be assessed by contrasted PET-CT scan *or* CT imaging of the neck, chest, abdomen and pelvis. Subjects who have progressive disease at the Wk 8 assessment should have a confirmation assessment performed at least 28 days (+/- 14 days) later (after Wk 9) (+/- 14 days). If subjects have stable disease, partial response, or complete response a confirmation assessment is not required, they should continue on the assessment schedule.
q. In subjects who discontinue study therapy without confirmed disease progression, a radiological assessment should be performed at the time of treatment discontinuation (i.e. date of discontinuation ± 4 week window). If previous scan was obtained within 4 weeks prior to the date of discontinuation, then a repeat scan at treatment discontinuation isn't mandatory.
r. Blood and tumor sample collection for biomarker studies is optional. In consenting subjects, 40 ml of blood sample [one red top tube (10 ml) and 3 heparin containing green top tubes (30 ml)] will be collected within 28 days prior to the first infusion of pembrolizumab, at day 9 (+/- 3 days) (during the course of EBRT) prior to the 2nd infusion of pembrolizumab on Day 23 (+/- 3 days) and prior to fourth infusion of pembrolizumab on Day 64 (+/- 3 days). These samples will be transported within 6 hours of collection to Dr. Neelapu's laboratory for processing at the South Campus Research Building I, Room 4.3206, at M. D. Anderson Cancer Center (MDACC). In consenting patients, core needle biopsies and fine needle aspirates (FNA) will be obtained by Interventional Radiology from accessible lymph node under ultrasound or CT-scan guidance within 28 days prior to the first infusion of pembrolizumab. A second set of optional core needle biopsies will be obtained with the same process of a non-irradiated lesion around the time of the fourth infusion of pembrolizumab on Day 64 (+/- 4 days).

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 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 and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial. The informed consent will adhere to IRB requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.1 General Informed Consent

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 requirements.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Medical History

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

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

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

7.1.1.4.2 Concomitant Medications

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

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

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

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

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

7.1.1.6 Assignment of Screening Number

All patients will be assigned a screening number prior to trial initiation during the main study screening visit.

7.1.1.7 Assignment of Randomization Number

All patients that will enroll in the Phase II component of the trial will be assigned a randomization number prior to therapy initiation during the screening visit.

7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)

Patients will be monitored for systemic and radiation treatment compliance in addition to general compliance with clinic visits, concomitant medications and prohibited activities. If a patient is unwilling or unable to maintain compliance, then the patient may be removed from the study based on the discretion of the trial investigators and/or treating physician.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Appendix Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam

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

7.1.2.3 Directed Physical Exam

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

7.1.2.4 Vital Signs

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

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 11.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

Tumor response will be assessed radiographically according to the revised Lugano classification for response assessment of HL and NHL[1]. In patients with FDG avid disease contrasted PET-CT will be utilized for baseline imaging as well as for determination of tumor response according to the standard of care. For patients with non-FDG avid or FDG-variable disease, CT imaging will be utilized for baseline radiographic examination as well as for assessment of tumor response.

7.1.2.6.1. Measurable Disease Prior to Therapy

Initial disease assessment or tumor imaging must be performed within 42 days prior to the first dose of trial therapy. PET-CT fusion imaging scans with oral contrast/water and IV contrast will be used for the initial disease assessment unless there is a contraindication. Disease assessments or scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 42 days prior to the first dose of trial treatment. A unilateral bone marrow aspiration and biopsy will be performed within 42 days prior to the first dose of trial treatment at the discretion of the treating physician.

7.1.2.6.1 End of Treatment and Follow-up Tumor Imaging

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory.

In participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment to monitor disease status until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.2.6.3. Guidelines for Evaluation of Measurable Disease

The initial disease response will occur at 8 weeks (+/- 14 days) after initiation of therapy. Subsequent disease response assessments will occur every 12 weeks (+/- 14 days) during therapy and for the first year after discontinuation of therapy, and then every 6 months thereafter. There is a ±14-day window for all imaging assessments. Disease response assessments will be performed by CT scans or PET-CT scan at q3 month intervals.

In subjects achieving a complete remission by CT scan criteria, PET-CT scan will be repeated once to confirm response. In addition, unilateral bone marrow aspiration and biopsy will be repeated once in such patients if the bone marrow was involved with lymphoma at baseline.

Disease assessments or scans should not be delayed for delays in cycle starts or extension of pembrolizumab cycle intervals. Disease assessments and imaging should continue to be performed until documented disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. Subjects who have unconfirmed disease progression may continue on treatment until progression is confirmed by imaging provided they have met the conditions detailed in Section 7.1.2.6.4. For lymphomas that are not FDG-avid at screening, PET-CT does not need to be repeated in follow-up assessments

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses, which may be functionally anergic. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard response assessment criteria may not provide a complete response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, in the setting where a subject's assessment shows PD at the first disease response assessment at Week 8, a subject may be granted an exception to continue on treatment until progression is confirmed at least 4 weeks later, provided that the subject's clinical condition is stable as detailed in Section 7.1.2.6.4.

7.1.2.6.4 Confirmation Assessments

A subject with progression of disease documented at the Week 8 (+/- 7) assessment may continue trial treatment at the discretion of the investigator until confirmation of progression of disease is documented per the response evaluation criteria at least 28 days (+/- 7) later (after Week 9) (+/- 7 days). When feasible, subjects should not be discontinued until repeat disease

response assessment is performed at least 28 days later. Subjects may only receive treatment while waiting for confirmation of PD if the following criteria are met:

• Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression

• No decline in ECOG performance status

• Absence of rapid progression of disease (defined as: rapidly growing mass that is greater than 5 cm in the long axis, weight loss, drenching night sweats, marked fatigue, or fever in the absence of an infection) based on the clinical judgment of the investigator.

• Absence of progressive tumor at critical anatomical sites (e.g. cord compression) requiring urgent alternative medical intervention

Subjects that are deemed clinically unstable after first disease response assessment.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Blood and tumor sample collection for biomarker studies is optional. In consenting subjects, 40 ml of blood sample [one red top tube (10 ml) and 3 heparin containing green top tubes (30 ml)] will be collected within 28 days prior to the first infusion of pembrolizumab, at day 9 (+/- 3 days) (during the course of EBRT), prior to the 2nd infusion of pembrolizumab Day 23 (+/- 3 days) and prior to third infusion of pembrolizumab Day 43 (+/- 3 days). These samples will be transported within 6 hours of collection to Dr. Neelapu's laboratory for processing at the South Campus Research Building I, Room 4.3206, at M. D. Anderson Cancer Center (MDACC). Blood from red top and green top tubes will be processed for isolation of serum and PBMC, respectively using standard laboratory protocols. The isolation of serum and PBMC may also be performed at the Clinical and Translational Research Center (CTRC) Laboratory at MDACC using standard laboratory protocols.

In consenting patients, core needle biopsies and fine needle aspirates (FNA) will be obtained by Interventional Radiology from accessible nodal or extranodal location under ultrasound or CT-scan guidance within 28 days prior to the first infusion of pembrolizumab. Whenever feasible, up to 3 cores will be obtained using 18 or 20 gauge needles as deemed appropriate by an Interventional Radiologist. The three cores will be processed as follows: i) the first core biopsy specimen will be preserved in RNAlater for microarray studies; ii) second core will be formalin-fixed and paraffin-embedded for IHC; and iii) third core will be snap frozen for DNA, RNA, or protein isolation. FNA sample will be analyzed by flow cytometry. These samples will be transported in RNAlater (core # i)/formalin (core # ii)/normal saline (cores # iii and FNA) within 6 hours of collection on ice to Dr. Neelapu's laboratory for processing at the South Campus Research Building I, Room 4.3206, at MDACC. If fresh biopsies are not feasible, archival tissue from prior tumor biopsy may be used for biomarker studies. A second

set of optional core needle biopsies will be obtained with the same process of a non-irradiated lesion prior to third infusion of pembrolizumab Day 43 (+/- 3 days).

Samples will be maintained until the study has been terminated.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below in the Laboratory Safety Evaluations Section (Hematology, Chemistry and Urinalysis). Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Laboratory tests for screening or entry into the trial should be performed within 28 days prior to the first dose of treatment. CBC with differential and serum chemistry panel will need to be repeated if screening tests were performed more than 7 days prior to the first dose of pembrolizumab as detailed under Trial Flow Chart. After Cycle 1 of pembrolizumab, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

The schedule for laboratory assessments is provided under the Trial Flow Chart. CBC with differential should include total white count, absolute neutrophil count, absolute lymphocyte count, hemoglobin, and platelet count. Comprehensive serum chemistry panel should include sodium (Na), potassium (K), chloride (Cl), glucose, bicarbonate (CO2), blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), magnesium (Mg), phosphorus, total protein, albumin, alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, uric acid, and lactate dehydrogenase (LDH). Direct bilirubin should be obtained if total bilirubin is above the upper limit of normal. Urinalysis should include blood, glucose, protein, and specific gravity. If blood, glucose, and protein are abnormal on urinalysis, a urine microscopic exam should be performed. Total triiodothyronine (T3) will be performed if TSH is abnormal.

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 thyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	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.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3.1 Pharmacokinetic/Pharmacodynamic Evaluations

7.1.3.1.1 Blood Collection for Serum Pembrolizumab

Sample collection, storage and shipment instructions for serum samples will be provided in the Laboratory Manual.

The time points for PK blood sampling are described in Section 6 – Trial Flow Chart.

7.1.3.1.2 Blood Collection for Anti-Pembrolizumab Antibodies

Sample collection, storage and shipment instructions for blood samples will be provided in the Laboratory Manual.

Other Procedures

7.1.3.2 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.5. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.1.3.3 Blinding/Unblinding

N/A

7.1.4 Visit Requirements

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

7.1.4.1 Screening

7.1.4.1.1 Screening Period

Approximately 28 days prior to enrollment, potential trial subjects will be evaluated to determine if they fulfill the entry requirements as set forth in Section 5.1. Visit requirements are outlined in Section 6.0- Trial Flow Chart.

Written consent for the main study must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

• Laboratory tests are to be performed within 7 days prior to the first dose of trial treatment.

• For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met.

7.1.4.2 Treatment Period

7.1.4.2.1 Salvage Hypo-Fractionated Radiation Therapy

Patients that receive initial therapy with MK-3475 and fractionated EBRT that develop progressive disease (PD) in any of the follow up evaluations may be considered for salvage EBRT. Patients will be scheduled for simulation and will initiate salvage radiation therapy as soon as possible (usually within 1 week). EBRT will be given concurrently with remaining cycles of MK-3475 with a fraction size of at least 4 Gy (hypo-fractionated approach). The final dose will be determined by the treating radiation oncologist according based on disease histology.

7.1.4.3 Post-Treatment Visits

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the 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. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 7.1.5.5) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

7.1.4.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 3 months (+/- 14 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 6 months (± 14 days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1.5.5. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7.1.5.5 will move from the follow-up phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.2 – Trial Flow Chart for Retreatment.

7.1.4.4.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.4.5 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab with SD or better may be eligible for up to one year of additional pembrolizumab therapy 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:

- **Either**
    - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR and
        - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
        - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

OR

- Had SD, PR or CR and stopped pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability

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 detailed in Section 5.1.2
- 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 through 120 days after the last dose of study medication (Reference Section 5.7.2). 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 through 120 days 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 pembrolizumab. Treatment will be administered for up to one additional year.

Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example),

symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

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 as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

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

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided

if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an 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 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.1 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.2 Immediate Reporting of Adverse Events to the Sponsor and to Merck

7.2.2.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;

- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is another important medical event

- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
    - Is a new cancer (that is not a condition of the study);
    - Is associated with an overdose.

Refer to Table 6 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, 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 (reference Section 7.2.3.3 for additional details) that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/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 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 (reference Section 7.2.3.3 for additional details), whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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 following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck Global Safety.

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

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.

7.2.2.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor and within 2 working 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 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/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 24 hours to the Sponsor and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

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

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.*

> *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.2.2.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 7.2.3.- Immediate Reporting of Adverse Events to the Sponsor and to Merck, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety as a SAE within 2 working days of determination that the event is not progression of the cancer under study

Hospitalization related to convenience (e.g. transportation issues etc.) will not be considered a SAE.

7.2.3 Evaluating Adverse Events

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

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

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 the Sponsor within 24 hours and 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 within 24 hours to the Sponsor and 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 Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's 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) Sponsor's 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 AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /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.)

7.2.4 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This is an investigator initiated, open label, phase II clinical trial to evaluate the efficacy of the combination therapy of Pembrolizumab and fractionated external beam radiotherapy (EBRT) in patients with relapsed and refractory aggressive Non-Hodgkin lymphoma (NHL). The maximum number of patients that will be recruited for the study is 40.

The primary objective of the trial is to determine the overall response rate of Pembrolizumab and fractionated EBRT in patients with relapsed and refractory NHL. The secondary objectives are to evaluate the safety, CRR, PFS, OS and duration of response of pembrolizumab with concurrent fractionated EBRT. Patients will receive 200 mg IV of Pembrolizumab with concurrent EBRT at standard of care doses of 40-50 Gy of EBRT in fractions of ≤3 Gy.. The trial enrollment will be stratified according to the extent of relapsed/refractory disease included in the RT field(s) with 2 cohorts of patients enrolled based on the treated RT field. For Cohort 1, patients with aggressive NHL, will receive RT to 1-2 region(s) of disease and the ORR will be determined for a designated "unirradiated" lesion (Cohort 1). For patients with relapsed/refractory aggressive NHL in Cohort 2, RT will be administered to encompass all sites of radiographically evident disease in 1-2 RT plan(s), the ORR will be based on the disease treated within the RT field. The maximum number of patients in each cohort is 20 with a total anticipated trial enrollment of 40 patients..

Overall response rates to PD-1 blockade monotherapy among patients with hematologic malignancies is based on published data[27]. For cohort 1, we assume that concurrent external beam radiation therapy with concurrent pembrolizumab will improve ORR (of the non-irradiated lesion[s]) over the reported rates of PD-1 blockade which are roughly 26% for B cell lymphoma and 17% for T cell lymphoma.

While the ORR for definitive RT for patients with de novo aggressive NHL approach 100%, overall response rate to salvage RT for patients with refractory aggressive NHL treated with curative intent has been reported to be 78%, with a 5 year progression free survival rate of 34%[40]. We assume that concurrent EBRT and pembrolizumab will improve the ORR when all sites of known disease are radiated.

8.2 Statistical Analysis Plan

Phase II design:

The overall response (OR: complete response + partial response) of non-irradiated lesion(s) at three months and dose limiting toxicity (DLT) at one cycles (3 weeks) will be monitored simultaneously using the Bayesian stopping boundaries calculated based on beta-binomial distributions. Independence is assumed between OR and DLT.

DLT is defined as the following toxicities observed during cycle one of the treatment that are considered by the investigator to be related to therapy:

1. Grade 4 neutropenia (ANC < 500/mm3) lasting more than 7 consecutive days.

2. Grade 3 neutropenia with fever and/or infection, where fever is defined as an oral Temperature ≥ 38.5°C.

3. Grade 4 thrombocytopenia (platelets < 25,000/mm3) lasting more than 7 consecutive Days.

4. Grade 3 thrombocytopenia with clinically significant bleeding.

5. A platelet count < 10,000/mm3 at any time.

6. Grade 3 or greater nausea and/or emesis despite the use of optimal anti-emetic Prophylaxis. Optimal anti-emetic prophylaxis is defined as an anti-emetic regimen that employs a 5-HT3 antagonist given in standard doses and according to standard schedules.

7. Grade 3 or greater diarrhea that occurs despite maximal supportive therapy.

8. Any other Grade 3 or greater non-hematologic toxicity with the following exceptions: Grade 3 arthralgia/myalgia or brief (< 1 week) Grade 3 fatigue.

9. A delay of more than 2 weeks in the initiation of Cycle 2 of treatment because of a lack of adequate recovery of therapy related hematological or non-hematologic toxicities.

In cohort 1 for the patients with multiple sites of aggressive NHL, we will consider that the regimen is promising if the OR rate of the non-irradiated lesion (s) at 3 months is at least 35% and the DLT rate at cycle one is below 30%. A sample size of 20 ensures that, if the trial is not terminated early, a posterior 90% credibility interval for OR rate at 3 months will have width of 0.335 at most, when 7 responses are observed out of the 20 patients, under the assumption of 35% OR rate. The prior probability of OR and DLT for the regimen are modeled by beta distribution (*Beta*(0.35, 0.65) and *Beta*(0.3, 0.7), respectively). Denoting the probability of OR and DLT by $\{\theta_{OR}, \theta_{DLT}\}$, and they are compared to fixed targets of OR and DLT rates. The following decision criteria will be applied:

1) Stop if Prob$\{ \theta_{OR} < 0.35 \mid \text{data}\} > 0.95$, and

2) Stop if Prob$\{ \theta_{DLT} > 0.30 \mid \text{data}\} > 0.95$

Patients will be monitored by a cohort size of 10 according to the following stopping boundaries for OR at 3 months and DLT at cycle one. If the number of responses required for moving the trial to next stage has not been achieved, the patient enrollment will be halted until enough responses observed.

Number of patients evaluated	Stop if <= OR observed	Stop if >= DLT observed
10	0-1	6-10
20	Always stop with this many patients	

The operating characteristics are summarized in the following table (based on simulations from 10,000 trials).

True DLT Rate	True OR Rate	Prob (stop the trial early)	Average number of patients treated
0.1	0.15	0.5444	14.56
	0.25	0.2441	17.56
	0.35	0.0861	19.14
	0.45	0.0234	19.77
	0.55	0.0046	19.95
0.2	0.15	0.5472	14.53
	0.25	0.2488	17.51
	0.35	0.0918	19.08
	0.45	0.0295	19.71
	0.55	0.0108	19.89
0.3	0.15	0.5659	14.34
	0.25	0.2798	17.20
	0.35	0.1292	18.71

	0.45	0.0695	19.31
	0.55	0.0516	19.48
0.4	0.15	0.6201	13.80
	0.25	0.3697	16.30
	0.35	0.2379	17.62
	0.45	0.1856	18.14
	0.55	0.1700	18.30
0.5	0.15	0.7161	12.84
	0.25	0.5290	14.71
	0.35	0.4305	15.69
	0.45	0.3914	16.09
	0.55	0.3798	16.20

In cohort 2 patients will be treated to all sites of relapsed or refractory NHL that can be completely included in 1-2 RT field(s), we will consider that the regimen is promising if the OR rate of the radiated disease at 3 months is at least 90% and the DLT rate at cycle one is below 30%. A sample size of 20 ensures that, if the trial is not terminated early, a posterior 90% credibility interval for OR rate at 3 months will have width of 0.203 at most, when 18 responses are observed out of the 20 patients, under the assumption of 90% OR rate. The prior probability of OR and DLT for the regimen are modeled by beta distribution (*Beta*(0.9,0.1) and *Beta*(0.3,0.7), respectively). Denoting the probability of OR and DLT by $\{\theta_{OR}, \theta_{DLT}\}$, and they are compared to fixed targets of OR and DLT rates. The following decision criteria will be applied:

1) Stop if Prob$\{ \theta_{OR} < 0.90 \mid \text{data}\} > 0.95$, and
2) Stop if Prob$\{ \theta_{DLT} > 0.30 \mid \text{data}\} > 0.95$

Patients will be monitored by a cohort size of 10 according to the following stopping boundaries for OR at 3 months and DLT at cycle one. If the number of responses required for

moving the trial to next stage has not been achieved, the patient enrollment will be halted until enough responses observed.

Number of patients evaluated	Stop if <= OR observed	Stop if >= DLT observed
10	0-6	6-10
20	Always stop with this many patients	

The operating characteristics are summarized in the following table (based on simulations from 10,000 trials).

True DLT Rate	True OR Rate	Prob (stop the trial early)	Average number of patients treated
0.1	0.6	0.6178	13.82
	0.7	0.3505	16.50
	0.8	0.1210	18.79
	0.9	0.0129	19.87
	0.95	0.0012	19.99
0.2	0.6	0.6202	13.80
	0.7	0.3545	16.45
	0.8	0.1265	18.74
	0.9	0.0191	19.81
	0.95	0.0074	19.93
0.3	0.6	0.6358	13.64
	0.7	0.3811	16.19
	0.8	0.1625	18.38
	0.9	0.0595	19.40
	0.95	0.0483	19.52

0.4	0.6	0.6813	13.19
	0.7	0.4584	15.42
	0.8	0.2670	17.33
	0.9	0.1769	18.23
	0.95	0.1671	18.33
0.5	0.6	0.7618	12.38
	0.7	0.5953	14.05
	0.8	0.4523	15.48
	0.9	0.3849	16.15
	0.95	0.3776	16.22

The above stopping boundaries and operating characteristics are calculated using MultcLean (v.2.1.0) design software downloaded from http://biostatistics.mdanderson.org/SoftwareDownload.

ANALYSIS PLANS

For each patient cohort, summary statistics will be provided for continuous variables such as age. Frequency tables will be used to summarize categorical variables such as gender, histology, response, toxicity type and severity. Response rate and its 95% confidence interval will be estimated for each patient cohort separately. The distribution of time-to-event endpoints, such as time to progression and overall survival, will be estimated using the method of Kaplan and Meier. Comparison of time-to-event endpoints by important patient characteristics will be made using the log-rank test.

Time-to-event outcomes, including PFS and OS will be estimated using the Kaplan-Meier method, with analysis beginning at the receipt of the first dose of MK-3475. The log-rank test will be performed to test the difference in time-to-event distributions between patient groups. Cox proportional hazards model may be used to include multiple covariates in the time-to-event analysis.

Assuming an accrual rate of 2 patients per month, we anticipate an accrual period of roughly 20 months. Data from all subjects who receive any study drug will be included in the safety

analyses. Subjects who entered the study and did not take any of the study drug and had this confirmed, will not be evaluated for safety.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

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

Table 7. Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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.

9.5 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.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

Confidentiality will be maintained throughout this study in accordance without the Health Insurance Portability and Accountability Act. This study will be presented and approved by the Internal Review Board at MD Anderson Cancer Center.

10.2 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 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.

10.3 Quality Management System

10.3.1 IND Safety Report

The investigator will be notified by Merck via an IND Safety Report of the following: 1) serious and/or unexpected adverse events associated with pembrolizumab n this study or other studies or 2) any findings from studies in lab animals suggesting a significant risk for human patients including reports of carcinogenicity or teratogenicity. The Investigator will notify the IRB promptly of new unexpected and/or serious adverse event(s) or potential serious risks to patients. The investigator will keep copies of all adverse event information on file.

10.4 Data Confidentiality Plan

All information, including but not limited to patient data/information, biomarker research data, and information related to the conduct of the study will be kept confidential. Blood and tissue samples will be identified by coded numbers. Data will be stored in password-protected

databases, protected by an institutional firewall. All data collected for this project, including all clinical information, will be kept confidential by limiting access only to the investigators and collaborators involved in the study. In order to maintain confidentiality, the investigator will maintain a personal patient identification list (coded numbers for blood and tissue samples corresponding with patient identifiers) to enable records to be identified and verified as authentic. This list will be maintained at the study site with other study records under adequate security and restricted access.

11.0 APPENDICES

11.1 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.	

11.2 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)

11.3 Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification

The Lugano Classification will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, for FDG avid tumors, PET-CT is the preferred imaging technique in this study.

Table 3. Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Table 3. Revised Criteria for Response Assessment (continued)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

* As published in the Journal of Clinical Oncology: Bruce D. Cheson, Richard I. Fisher, Sally F. Barrington, Franco Cavalli, Lawrence H. Schwartz, Emanuele Zucca, and T. Andrew Lister. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin. Oncol. 2014 Sept; Volume 32, Number 27.

References:

1. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014;32(27):3059-3068.
2. Specht L. The history of radiation therapy of lymphomas and description of early trials. . In: Armitage JO CB, Dalla-Favera R, Harris N, Mauch PM, ed. *Non-Hodgkin's Lymphomas*. 2nd ed. Baltimore: Lippincott Williams & Wilkins; 2009:12-24.
3. Bush RS, Gospodarowicz M, Sturgeon J, Alison R. Radiation therapy of localized non-Hodgkin's lymphoma. *Cancer Treat Rep.* 1977;61(6):1129-1136.
4. Hellman S, Chaffey JT, Rosenthal DS, Moloney WC, Canellos GP, Skarin AT. The place of radiation therapy in the treatment of non-Hodgkin's lymphomas. *Cancer.* 1977;39(2 Suppl):843-851.
5. Musshoff K, Schmidt-Vollmer H. Prognostic significance of primary site after radiotherapy in non-Hodgkin's lymphomata. *Br J Cancer Suppl.* 1975;2:425-434.
6. Peters MV, Middlemiss KC. A study of Hodgkin's disease treated by irradiation. *Am J Roentgenol Radium Ther Nucl Med.* 1958;79(1):114-121.
7. Rosenberg SA, Dorfman RF, Kaplan HS. A summary of the results of a review of 405 patients with non-Hodgkin's lymphoma at Stanford University. *Br J Cancer Suppl.* 1975;2:168-173.
8. Yahalom J, Varsos G, Fuks Z, Myers J, Clarkson BD, Straus DJ. Adjuvant cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy after radiation therapy in stage I low-grade and intermediate-grade non-Hodgkin lymphoma. Results of a prospective randomized study. *Cancer.* 1993;71(7):2342-2350.
9. Dores GM, Metayer C, Curtis RE, et al. Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. *J Clin Oncol.* 2002;20(16):3484-3494.
10. Travis LB, Curtis RE, Glimelius B, et al. Second cancers among long-term survivors of non-Hodgkin's lymphoma. *J Natl Cancer Inst.* 1993;85(23):1932-1937.
11. Travis LB, Ng AK, Allan JM, et al. Second malignant neoplasms and cardiovascular disease following radiotherapy. *J Natl Cancer Inst.* 2012;104(5):357-370.
12. Yahalom J, Mauch P. The involved field is back: issues in delineating the radiation field in Hodgkin's disease. *Ann Oncol.* 2002;13 Suppl 1:79-83.
13. Specht L, Yahalom J. The concept and evolution of involved site radiation therapy for lymphoma. *Int J Clin Oncol.* 2015;20(5):849-854.
14. Koh ES, Tran TH, Heydarian M, et al. A comparison of mantle versus involved-field radiotherapy for Hodgkin's lymphoma: reduction in normal tissue dose and second cancer risk. *Radiat Oncol.* 2007;2:13.
15. Kriz J, Spickermann M, Lehrich P, et al. Breath-hold technique in conventional APPA or intensity-modulated radiotherapy for Hodgkin's lymphoma: Comparison of ILROG IS-RT and the GHSG IF-RT. *Strahlenther Onkol.* 2015;191(9):717-725.
16. Ewing J. Radiosensitivity. *Radiology.* 1929;13(313).

17. Aref A, Narayan S, Tekyi-Mensah S, et al. Value of radiation therapy in the management of chemoresistant intermediate grade non-Hodgkin's lymphoma. *Radiation oncology investigations.* 1999;7(3):186-191.
18. Martens C, Hodgson DC, Wells WA, et al. Outcome of hyperfractionated radiotherapy in chemotherapy-resistant non-Hodgkin's lymphoma. *Int J Radiat Oncol Biol Phys.* 2006;64(4):1183-1187.
19. Lowry L, Smith P, Qian W, et al. Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: a randomised phase III trial. *Radiother Oncol.* 2011;100(1):86-92.
20. Haas RL, Poortmans P, de Jong D, et al. High response rates and lasting remissions after low-dose involved field radiotherapy in indolent lymphomas. *J Clin Oncol.* 2003;21(13):2474-2480.
21. Sharma P, Allison JP. The future of immune checkpoint therapy. *Science.* 2015;348(6230):56-61.
22. Nastoupil LJ, Neelapu SS. Novel immunologic approaches in lymphoma: unleashing the brakes on the immune system. *Curr Oncol Rep.* 2015;17(7):30.
23. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med.* 2015;372(4):311-319.
24. Moskowitz CH RV, Michot J-M et al. PD-1 Blockade with the monoclonal antibody pempbrolizumab (MK-3475) in patients with classical Hodgkin lymphoma after brentuximab vedotin failure: preliminary results from a phase 1b study (KEYNOTE-013). *Blood.* 2014;21(124):Abstact 290.
25. Westin JR, Chu F, Zhang M, et al. Safety and activity of PD1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: a single group, open-label, phase 2 trial. *The Lancet Oncology.* 2014;15(1):69-77.
26. Kiyasu J, Miyoshi H, Hirata A, et al. Expression of programmed cell death ligand 1 is associated with poor overall survival in patients with diffuse large B-cell lymphoma. *Blood.* 2015.
27. Lesokhin AM AS, Armand P. Preliminary results of a phase I study of nivolumab (BMS-936558) in patients with relapsed or refractory lymphoid malignancies. *Blood.* 2014;21(124):Abstract 291.
28. Lesokhin AM, Ansell SM, Armand P, et al. Nivolumab in Patients With Relapsed or Refractory Hematologic Malignancy: Preliminary Results of a Phase Ib Study. *J Clin Oncol.* 2016;34(23):2698-2704.
29. Stone HB, Peters LJ, Milas L. Effect of Host Immune Capability on Radio-Curability and Subsequent Transplantability of a Murine Fibro-Sarcoma. *J Natl Cancer I.* 1979;63(5):1229-1235.
30. Demaria S, Ng B, Devitt ML, et al. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. *Int J Radiat Oncol Biol Phys.* 2004;58(3):862-870.
31. Demaria S, Bhardwaj N, McBride WH, Formenti SC. Combining radiotherapy and immunotherapy: a revived partnership. *Int J Radiat Oncol Biol Phys.* 2005;63(3):655-666.
32. Hiniker SM, Chen DS, Reddy S, et al. A systemic complete response of metastatic melanoma to local radiation and immunotherapy. *Transl Oncol.* 2012;5(6):404-407.

33. Postow MA, Callahan MK, Barker CA, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. *N Engl J Med.* 2012;366(10):925-931.
34. Park SS, Dong H, Liu X, et al. PD-1 Restrains Radiotherapy-Induced Abscopal Effect. *Cancer Immunol Res.* 2015;3(6):610-619.
35. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. *Cancer Res.* 2014;74(19):5458-5468.
36. Dewan MZ, Galloway AE, Kawashima N, et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. *Clin Cancer Res.* 2009;15(17):5379-5388.
37. Dovedi SJ, Melis MH, Wilkinson RW, et al. Systemic delivery of a TLR7 agonist in combination with radiation primes durable antitumor immune responses in mouse models of lymphoma. *Blood.* 2013;121(2):251-259.
38. Brody JD, Ai WZ, Czerwinski DK, et al. In situ vaccination with a TLR9 agonist induces systemic lymphoma regression: a phase I/II study. *J Clin Oncol.* 2010;28(28):4324-4332.
39. Sharabi AB, Lim M, DeWeese TL, Drake CG. Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy. *The Lancet Oncology.* 2015;16(13):e498-509.
40. Tseng YD, Chen YH, Catalano PJ, Ng A. Rates and durability of response to salvage radiation therapy among patients with refractory or relapsed aggressive non-Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys.* 2015;91(1):223-231.
41. Hoos A, Eggermont AM, Janetzki S, et al. Improved endpoints for cancer immunotherapy trials. *J Natl Cancer Inst.* 2010;102(18):1388-1397.
42. Cohen JV, Alomari AK, Vortmeyer AO, et al. Melanoma Brain Metastasis Pseudoprogression after Pembrolizumab Treatment. *Cancer Immunol Res.* 2016;4(3):179-182.
43. Marks LB, Ten Haken RK, Martel MK. Guest editor's introduction to QUANTEC: a users guide. *Int J Radiat Oncol Biol Phys.* 2010;76(3 Suppl):S1-2.
44. Pinnix CC, Smith GL, Milgrom S, et al. Predictors of radiation pneumonitis in patients receiving intensity modulated radiation therapy for Hodgkin and non-Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys.* 2015;92(1):175-182.
45. Kelly P, Das P, Pinnix CC, et al. Duodenal toxicity after fractionated chemoradiation for unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys.* 2013;85(3):e143-149.
46. Rose BS, Aydogan B, Liang Y, et al. Normal tissue complication probability modeling of acute hematologic toxicity in cervical cancer patients treated with chemoradiotherapy. *Int J Radiat Oncol Biol Phys.* 2011;79(3):800-807.