RADVAX™ FOR RELAPSED/REFRACTORY NON-HODGKIN LYMPHOMA: A PHASE II TRIAL OF PEMBROLIZUMAB + LOW DOSE RADIOTHERAPY

Principal Investigator: Michael J. LaRiviere, MD
Department of Radiation Oncology
3400 Civic Center Blvd. PCAM-4 West, Philadelphia, PA 19104
(215) 615-7239

Sub-Investigators: John P. Plastaras, MD, PhD

Jakub Svoboda, MD

Michael Farwell, MD

Stephen J. Schuster, MD

Sunita Nasta, MD

Daniel J. Landsburg, MD

Andrea Facciabene, PhD

Michele Kim, PhD

E. John Wherry, PhD

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Contents

1.0 LIST OF ABBREVIATIONS

ACC: American College of Cardiology

AE: Adverse event

DMC: Data Monitoring Committee

DM: Diabetes Mellitus

ECG: Electrocardiogram

PR: Partial Response

CR: Complete response

SD: Stable disease

2.0 TRIAL SUMMARY

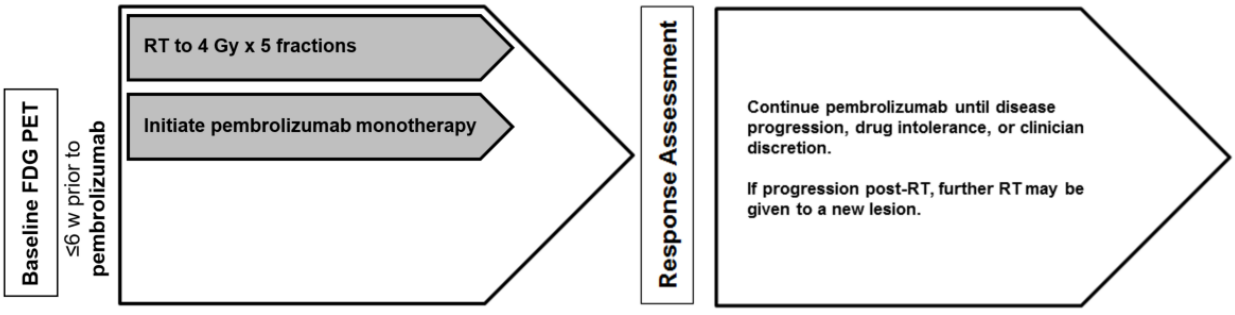
Abbreviated Title	Non-Hodgkin Lymphoma RadVax
Trial Phase	*II*
Clinical Indication	Relapsed/refractory non-Hodgkin lymphoma
Trial Type	Open-label, single center, single arm
Type of control	Historic controls
Route of administration	IV (pembrolizumab), external beam (radiation)
Trial Blinding	Non-blinded
Treatment Groups	Single arm
Number of trial participants	40
Estimated enrollment period	*2 years*
Estimated duration of trial	*4 years*
Duration of Participation	8-52 weeks (up to 104 weeks allowed)
Estimated average length of treatment per patient	8-52 weeks (up to 104 weeks allowed)

3.0 TRIAL DESIGN

3.1 Trial Design

This study is an open-label Phase II trial of non-Hodgkin lymphoma patients receiving initial treatment with low-dose (4 Gy x 5) involved-site radiotherapy plus the immunomodulatory agent, pembrolizumab. Eligible patients will have r/r disease with at least 2 sites of measurable disease (≥1.0 cm), and must be eligible for treatment with pembrolizumab. Biosamples (blood) will be collected as outlined below. Pembrolizumab will be continued after RT until disease progression, drug intolerance, or at the discretion of the treating medical oncologist.

3.2 Trial Diagram



Registration

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Pre-study

- Initial baseline FDG PET/CT (standard of care) </=6 weeks prior to RT administration.
- Collection of blood for correlative biomarkers.

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Study Phase – Pembrolizumab and Radiotherapy

- RT to 4 Gy x 5 fractions to target lesion(s)
- Pembrolizumab initiation to start after first fraction of RT, no later than 3 days following final fraction of RT.
- Administration of pembrolizumab and continued per standard of care and institutional practices.
- Blood sample collection for correlative biomarkers between RT and pembrolizumab initiation.
- Continue pembrolizumab per standard of care and institutional practices.
- Continue blood sample collection for correlative biomarkers at week 1.
- Continue blood sample collection for correlative biomarkers at weeks 6 and 8-12.

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Study Phase – Response Assessment

- Repeat PET/CT at 8-12 weeks (standard of care response assessment).
- CR, PR or SD continue on pembrolizumab until confirmed disease progression, drug intolerance, or at the discretion of the treating medical oncologist.
- If PD may repeat RT to 4 Gy x 5 fractions to additional, separate target(s). If an additional course of RT is administered, continue blood sample collection for correlative biomarkers at 1, 6, and 8-12 weeks post-re-RT.
- Repeat PET/CT (response assessment in non-target lesion) at 8-12 weeks post-re-RT.

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Study End

- Study will end at the time of disease progression, drug intolerance, or at the discretion of the treating medical oncologist. The duration of pembrolizumab must be limited to a maximum of 2 years.

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Primary Objective

- Determine the CR rate.

<u>See Section 7.0 Trial Flow Chart for full details</u>; an abbreviated flow chart is provided below:

	Pre-trial	Induction Assessment					Post-induction Assessment				
		Week					Week				
		0	1		6	8-12	0	1		6	8-12
Pembrolizumab		→									
RT		X					X[2]				
FDG PET/CT	X					X				X	
Correlative biomarkers[1]	X	X	X		X	X	X	X		X	X

[1]Collect times are approximate due to appointment scheduling.
[2]Repeat radiation to a different site if PD.

4.0 OBJECTIVE(S) & HYPOTHESIS(ES)

4.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective**: To determine the complete response (CR) rate for the study.

Hypothesis: The addition of radiation to pembrolizumab will increase CR compared to historic controls.

4.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: To determine the time to best response.

(2)**Objective**: To determine duration of best response.

(3)**Objective**: To determine progression-free survival and overall survival.

(4)**Objective**: To evaluate safety and adverse events.

4.3 Exploratory Objective

(1) **Objective:** To evaluate baseline levels and post-treatment changes in biomarkers and determine whether biomarker changes are associated with clinical outcomes.

(2) **Objective:** To evaluate change from baseline in tumor FDG uptake on PET/CT after initiation of pembrolizumab.

(3) **Objective:** To evaluate association between change in tumor FDG uptake and progression-free and overall survival.

(4) **Objective:** To evaluate CRR in DLBCL patients who had previous CART therapy vs. those who did not.

5.0 BACKGROUND & RATIONALE

5.1 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.

A growing body of clinical and laboratory evidence support the promise of combining radiotherapy (RT) with immune checkpoint blockade. Irradiation of tumors can lead to an increase in the

production of tumor-associated antigens, potentially serving as a source of tumor-associated antigens to initiate downstream increased immune system anti-tumor activity. Very rarely, RT alone can trigger tumor regression in patients outside the radiation field. This so-called abscopal effect has been described and is felt to be the basis of RT-induced systemic immunity. However, in extensive preclinical experiments published in *Nature* in 2015, investigators at the Abramson Cancer Center have found that across multiple histologies, combining immune checkpoint blockade with RT can achieve major tumor regressions and complete responses in mice, without major toxicity.(Twyman-Saint Victor et al., 2015)

Immunotherapies have emerged as promising options for patients with relapsed/refractory (r/r) non-Hodgkin lymphoma (NHL). Activity of PD-1 inhibitors in r/r NHL has been documented.(Armand et al., 2013; Berger et al., 2008; Galanina, Kline, & Bishop, 2017; Lesokhin et al., 2016; Westin et al., 2014) Pembrolizumab utilizes the patient's own immune system to eliminate cancer cells. Despite promising activity, many patients fail to achieve complete remission (CR) and/or still ultimately progress on immune modulators, and T-cell exhaustion is potentially an important mechanism for immunotherapy failure. As in solid malignancies, it has been postulated that antigen presentation by radiotherapy (RT) is a potential tool to overcome this resistance. There are currently numerous trials using the combination of checkpoint blockade with high-dose RT (e.g. stereotactic body radiotherapy [SBRT]) in solid malignancies – i.e. the radiation vaccine or "RadVax" concept – yet lymphomas have not been formally studied with this approach. Lymphomas are unique in that very low-dose (2-4 Gy x 2-5) radiation can result in impressive response rates (30-80%), and this logistically convenient regimen is increasingly popular in an environment of otherwise declining RT use in the management of lymphomas.(Wright et al., 2021) Traditionally, lymphomas have been considered highly immune-sensitive cancers and have served as a model for development of immune based biological therapies over the past few decades. A companion study, UPCC 04418 was opened in April 2018 that uses a similar paradigm for r/r Hodgkin lymphoma. In this current study, we plan to study the combination of low dose radiation with pembrolizumab in patients with relapsed/refractory non-Hodgkin lymphoma.

5.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes 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 (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley et al., 2005; Hunder et al., 2008].

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 immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-

associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald et al., 2005; Okazaki et al., 2001].

The structure of murine PD-1 has been resolved [Zhang et al., 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail 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, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki et al., 2001; Chemnitz et al., 2004; Sheppard et al., 2004; and Riley, 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry et al., 2005; Francisco, 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in non-Hodgkin lymphoma.

5.1.2 Preclinical and Clinical Trial Data

Refer to the Investigator Brochure for Preclinical and Clinical data.

5.2 Rationale

5.2.1 Rationale for the Trial and Selected Population

PD-1 inhibitors are under clinical investigation for select patients with r/r NHL.(Lesokhin et al., 2016; Zinzani et al., 2017) Nivolumab was tested as single-agent monotherapy in a Phase Ib trial that included 54 r/r B- and T-NHL patients who progressed after multiple prior therapies, demonstrating 10% CR and 30% PR among 10 follicular lymphoma (FL) patients and 18% CR and 18% PR among 11 diffuse large B-cell lymphoma (DLBCL) patients.(Lesokhin et al., 2016) ORR was 17% among 23 T-cell lymphoma patients.(Lesokhin et al., 2016) More recently, a r/r primary mediastinal B-cell lymphoma (PMBCL) cohort from the KEYNOTE-013 Phase Ib trial saw 12% CR, 29% PR, and 35% SD among 17 patients treated with pembrolizumab.(Zinzani et al., 2017) However, patients who progress after nivolumab or pembrolizumab have limited additional options. Although CD19-targeted CAR T cell therapy was approved for r/r DLBCL in late 2017, this is not readily available to all patients and may be associated with significant toxicity. Of note, prior use of PD-1 inhibitors and/or radiation have not been exclusion criteria for the approved CART products. Furthermore, patients who progress after CAR T cell therapies have limited options.

Programmed Death-1 (PD-1) is an immunomodulatory receptor that has been targeted by several novel agents with exciting results in a variety of malignancies. PD-1 signaling involves binding to several discrete ligands, including PD-L1 and PD-L2. PD-L1 is often expressed within the tumor microenvironment by cancer cells and macrophages as well as on lymphoma cells to a lesser degree, whereas PD-L2 is expressed primarily on professional antigen presenting cells.(Pardoll,

2012) PD-1 negatively regulates the effector phase of the T cell response after ligation of PD-L1 to the receptor. Antibodies that block the PD-L1/PD-1 interaction prevent the downregulation of the anti-tumor immune response, hence augmenting the cytotoxic function of tumor-specific T cells. Although the RadVax concept was originally conceived in melanoma, the observation that RT can enhance immunomodulators has also been observed in lymphoma. A remarkable case report of a patient with r/r HL, who had progressed after about 1 year on pembrolizumab on a clinical study, showed that RT reversed resistance. (Michot et al., 2016) After this patient was treated with palliative RT to 30 Gy in 10 fractions, he responded not only within but also outside of the RT fields (see Figure in Appendix). Preclinical mouse models of lymphoma have shown the ability of RT to prime immune responses using other classes of immunomodulators, namely a TLR7 agonist and a CD40 inhibitor. (Systemic delivery of a TLR7 agonist in combination with radiation primes durable antitumor immune responses in mouse models of lymphoma.(Dovedi et al., 2013; Honeychurch, Glennie, Johnson, & Illidge, 2003) With both of these immunomodulators, it was shown that dendritic cells are key to generating long-term immunologic protection from the combination of immunotherapy and RT.(Dovedi et al., 2016) Taken together, lymphomas are a prime target for the RadVax concept, which can be integrated safely into clinical practice given the low RT doses required for lymphoma patients.

While the best time to add RT to immunomodulatory therapy is still not well-defined in the nascent RadVax approach, careful preclinical sequencing experiments suggest that PD-1 inhibition combined with fractionated RT may be less effective when given either before RT is initiated, or at late time points following the completion of an RT course. (Dovedi et al., 2014; Wei et al., 2021) Multiple fractions of RT have been shown to more potently induce the RadVax effect than a single RT fraction in mouse models using a TLR7 agonist.(Dovedi et al., 2013) Our plan is to initiate RT (5 fractions of 4 Gy). At any time during the RT course after the first fraction is delivered, and within 3 days of the final fraction of RT, the first dose of pembrolizumab will be initiated. Another potential strategy would be to wait to radiate after disease progression on immunomodulatory therapy, but preclinical observations support the early use of RT to improve outcomes, with early immune stimulation by RT in the presence of immunomodulators leading to sustained memory T cells that can reject further challenge by tumor cells (Dovedi et al., 2013). Ultimately, as the timing of the addition of RT to a therapy with known efficacy comes down to clinical practicality, we have proposed a flexible schedule that ensures RT is initiated prior to pembrolizumab, but that pembrolizumab is started within approximately 1 week of the first fraction of RT.

Stimulated by our department's own anecdotal report of a patient having progressive disease on immunomodulatory therapy who had a dramatic abscopal response to radiotherapy, a Phase I/II trial was initiated at Penn to determine the safety of ipilimumab following hypofractionated radiotherapy in melanoma. Patients received either 2 or 3 fractions of radiotherapy, followed by 4 cycles of the anti-CTLA-4 agent, ipilimumab. By trial design, patients were required to have at least two discrete metastatic lesions from melanoma, only one of which was irradiated.

The primary goal of the trial was to assess safety. A single index lesion measuring 1-7 cm was irradiated with hypofractionated RT, delivered over two or three fractions, followed by ipilimumab (3 mg/kg), starting on average 4 days after the last dose of radiation. Ipilimumab was continued every three weeks for a total of four doses. Patients were stratified into two strata based on treatment site (lung or bone vs. liver or subcutaneous) and dose escalations of SBRT were

determined as follows: For lung/bone lesion, dose level 1 (DL1) was 8 Gy x 2; dose level 2 (DL2) was 8 Gy x 3; and for liver/subcutaneous lesion, DL1 was 6 Gy x 2; DL2 was 6 Gy x 3.

The details of the clinical trial are presented by Twyman-Saint Victor et al.(Twyman-Saint Victor et al., 2015) The impact of the therapy on the irradiated lesion and the non-irradiated lesion(s) was evaluated using two standard modalities: (i) 18F-2-deoxyfluoro-2-deoxyglucose (FDG) activity on positron emission tomography-computer tomography (PET-CT) as a measure of biological effects of therapy and (ii) CT imaging for Response Evaluation Criteria in Solid Tumors (RECIST 1.1) assessment.

Evaluation of the non-irradiated lesions (abscopal effect) by RECIST criteria demonstrated that 4 patients (18%) had a partial response (PR) as best response, 4 patients (18%) had stable disease (SD), and 14 patients (64%) had progressive disease (PD). Of 12 patients with available serial PET-CT, metabolic response in unirradiated lesions occurred in four patients that had a PR or SD by RECIST (2 complete metabolic responses and 2 partial metabolic responses), while the other 8 had progressive metabolic disease.

The median progression-free survival (PFS) for the 22 patients was 4.3 months (95% confidence limit is 3.1 - 7.9 months), and median overall survival (OS) was 10.7 months (95% lower confidence limit is 6.1 months; upper is undefined). By contrast, ipilimumab alone resulted in a response rate of 10.9%, as reported by Hodi et al.(Hodi et al., 2010).

Overall treatment was well tolerated with no deaths attributable to therapy and no grade 4 toxicities. The most common grade 3 toxicity was anemia. There were no dose-limiting toxicities (DLTs), which for this study was defined as any grade 4 or higher immune treatment-related toxicity or grade 3 or higher non-immune treatment (RT-related) toxicity. Fourteen patients completed the entire 4 cycles of ipilimumab (2 patients completed only 2 cycles and 2 patients only 3 cycles due to progressive disease; 2 patients received only 3 cycles due to the development of colitis). In summary, the combination of ipilimumab with hypofractionated radiotherapy was safe without DLTs. In other reports combining radiation and immune-modifying agents, ORR as high as 66% has been reported among melanoma and renal cell carcinoma patients treated with high-dose SBRT and IL-2(Seung et al., 2012).

Lymphomas are unique in that very low-dose (2-4 Gy x 2) radiation can result in impressive response rates (30-80%),(Russo et al., 2013) with recent data from our institution reporting an overall response rate of 72% and a complete response rate of 53% with a median 20 Gy total dose.(Wright et al., 2021) While the addition of radiotherapy to immunotherapy may increase toxicity, emerging data suggest that this is seen with higher radiation doses (36 Gy), larger target volumes (multiple vertebral bodies), and combination immunotherapy.(Arscott et al., 2017) By contrast, this study employs a lower radiation dose, smaller target volumes, and a single-agent PD-1 inhibitor.

5.2.2 Justification for Dose

The planned dose of pembrolizumab for this study is 400 mg every 6 weeks (Q6W).

Based on the totality of data generated in the Keytruda development program, 200 mg Q3W was initially the standard dose of pembrolizumab for adults across all indications and regardless of tumor type.

A 400-mg Q6W dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg Q3W, in all treatment settings where 200 mg Q3W pembrolizumab is currently approved. The proposed additional dosing regimen of 400 mg Q6W for pembrolizumab was selected using modeling and simulation analyses, primarily based on PK exposure matching with approved Q3W dosing regimens. Modeling and simulation predictions were corroborated by the observed PK profiles and exposures at 400 mg Q6W in KN555, Cohort **B.** Specifically, the dosing regimen of 400 mg Q6W is considered adequate, given the following rationale:

• PK simulations demonstrated that in terms of pembrolizumab exposures

- C_{avg} over the dosing interval or AUC at 400 mg Q6W are similar to those at the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.

- C_{min} at 400 mg Q6W is —12% lower at a mean level compared to that at the lowest clinically tested dose of 2 mg/kg Q3W, at steady state. In most (>99%) patients, however, C_{ain} at 400 mg Q6W is generally within the range of clinical experience of C_{rain} achieved with 2 mg/kg or 200 mg Q3W.

- C_{max} and concentrations over the entire PK profile at 400 mg Q6W are well below the Cmav and PK profile for the highest clinically tested dose of 10 mg/kg Q2W. Clinically, the observed safety profiles were similar among 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W dosing regimens in multiple tumor types based on randomized dose comparisons. Since the C_{ava},,, and C_{avg} through the dosing interval expected at 400 mg Q6W lies within the range of those achieved at these clinically tested doses, the safety profile is expected to be comparable to the established safety profile of pembrolizumab.

- The exposure-response relationship for pembrolizumab has been shown to be flat across multiple indications, in the dose/exposure range of 2 mg/kg Q3W or 200 mg Q3W to 10 mg/kg Q2W. Since the Cmin and Cav_g exposures over the dosing interval at 400 mg Q6W lie within the range of those achieved at the Q3W doses with established clinical efficacy, the dosing regimen of 400 mg Q6W is expected to be efficacious across indications where 200 mg (or 2 mg/kg) Q3W has demonstrated efficacy, given the generally similar PK and flat exposure-response relationship for pembrolizumab across tumor types.

The observed PK data from the interim analysis of Cohort **B** of KN555 in subjects treated with pembrolizumab at 400 mg Q6W demonstrated that in terms of pembrolizumab exposures through Cycle 1 (i.e., the first 6 weeks of treatment):

- The observed concentrations for 400 mg Q6W were well within the 90% prediction interval of simulated concentrations using the model.

- The geometric mean of the observed Gab, at Week 6 at 400 mg Q6W is —18% lower than the geometric mean of Cain, at Week 6 at 200 mg Q3W and —10% higher than the

geometric mean of Cmin at Week 6 at 2 mg/kg Q3W, i.e., the lowest clinically tested dose shown to be efficacious.

- The geometric mean of the observed C_{maa} at Week 6 at 400 mg Q6W is —38% lower than the geometric mean of Cm. at Week 6 at 10 mg/kg Q2W, i.e., the highest clinically tested dose shown to be safe.

Pembrolizumab has been studied in r/r NHL patients at a dose of 200 mg every 3 weeks.(Zinzani et al., 2017)

In the report of 54 r/r NHL patients treated with nivolumab, among all patients (additionally including 1 chronic myelogenous leukemia and 27 multiple myeloma patients), 22% experienced grade 3 or higher toxicities, including pneumonitis, anemia, and leukopenia in 4% each; other grade 3 or higher toxicities were reported in 1 patient each.(Lesokhin et al., 2016) Grade 4 toxicities included 1 patient with pustular rash and 1 with sepsis.(Lesokhin et al., 2016) One grade 5 pneumonitis/acute respiratory distress syndrome (ARDS) was reported.(Lesokhin et al., 2016) Among the 17 r/r PMBCL patients treated with pembrolizumab, 1 experienced grade 3 neutropenia and 1 developed grade 4 veno-occlusive liver disease after allogeneic stem cell transplant; the remaining toxicities were no worse than grade 2.(Zinzani et al., 2017) Broadly, for patients who ultimately undergo allogeneic hematopoietic stem cell transplantation, toxicity data are unclear, though there is a concern for increased severe acute graft versus host disease in the Hodgkin lymphoma literature.(Kasamon et al., 2017)

5.2.3 Rationale for Endpoints

CR, time to best response, duration of best response, PFS, OS, safety, and duration of immunotherapy use are clinically meaningful endpoints that allow for comparisons against reported historic controls.

5.2.3.1 Endpoints

Primary Study Endpoint:

- CR rate.

Secondary Study Endpoints:

- Time to best response.
- Duration of best response
- Progression-free survival (PFS)
- Overall survival (OS)
- Safety

- Duration of immunotherapy use for the pembrolizumab + RT induction CR cohort.

Primary, secondary, and exploratory study analyses will be further stratified by histology (e.g. DLBCL, PMBCL, FL, TCL, etc.).

5.2.3.2 Biomarker Research

Biosamples (blood) obtained from patients before and at serial time points during treatment will be analyzed. The primary goals for the basic studies with these human samples will be high dimensional (15-17 color) flow cytometry to analyze T cell subsets (including naïve, effector, memory (effector memory and central memory), effector memory RA, exhausted, Th1, Treg and Tfh), co-expression of sets of multiple inhibitory receptors by relevant T cell subsets, transcription factor expression, and T comprehensive functional analysis (expression of cytokines, chemokines, cytotoxic molecules, and degranulation). These studies will focus on sophisticated immune phenotyping and defining correlates of response.

- In addition, the following markers will be studied: CD3, CD4, CD8, CD25, CD39, CD73, CD127, FOXP3, CD122, CD212 (IL-12R), HLA-DR, CD14, CD19, CD56, CD69, FAS-L, Granzyme B, IL-2, IL-4, IL-10, IL-12, Rantes, IFN- γ, TGF-β, GM-CSF, sIL-2R.

- Circulating tumor material (e.g., circulating tumor cells, cell-free DNA, circulating tumor DNA, exosomes, etc.) will also be studied

Participants will additionally be screened for other companion biomarker studies.

Primary, secondary, and exploratory study analyses will be further stratified by histology (e.g. DLBCL, PMBCL, FL, TCL, etc.).

6.0 METHODOLOGY

6.1 Study Population

6.1.1 Participant Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male/female participants who are at least 18 years of age on the day of signing informed consent with histologically confirmed diagnosis of relapsed/refractory non-Hodgkin lymphoma (defined below) will be enrolled in this study.

Male participants:

2. 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 120 days after the last dose of study treatment and refrain from donating sperm during this period.

Female participants:

3. A female participant is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:

   a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 3 OR
   b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 120 days after the last dose of study treatment.

   Documentation of a discussion regarding the importance of contraception and patient's agreement is required.

4. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.

5. Have measurable disease based on RECIST 1.1. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

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.
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 start date of radiation.

8. Have adequate organ function as defined in the following table (Table 1). Specimens must be collected within 10 days prior to the start of study drug Pembrolizumab

Note: The patient can be considered eligible and started on RT prior to confirming adequate organ function is met provided they meet the rest of the eligibility criteria. Adequate organ function needs to be confirmed prior to starting the Pembrolizumab. If it is found that the patient does not have adequate organ function post starting RT and prior to administering Pembrolizumab they will be withdrawn from the study and considered as a screen failure.

9. Pathologically confirmed B-cell, T-cell, aggressive, or indolent non-Hodgkin lymphoma for whom pembrolizumab is clinically indicated per physician discretion as documented in a separate Medical Oncology note.

10. Relapsed/refractory disease treated with at least 2 lines of prior therapy.

    - Relapsed disease is defined as progression of disease after achieving a remission to the most recent therapy.
    - Refractory disease is defined as failure to achieve CR or PR.

- At least 2 lines of prior therapy are required, but, at physician and patient discretion with shared decision-making, not all FDA-approved treatments need be exhausted prior to enrollment.

11. For DLBCL and PMBCL:
    - Have relapsed after auto-SCT or have failed to achieve a CR or PR within 60 days of auto-SCT. Patients may have received intervening therapy after auto-SCT for relapsed or refractory disease, in which case they must have relapsed after or be refractory to their last treatment.
    - For patients who are ineligible for auto-SCT, have received at least ≥ 2 lines of prior therapy and have failed to respond to or relapsed after their last line of treatment. For patients who received consolidative local radiotherapy after systemic therapy, local radiotherapy will not be considered as a separate line of treatment.
12. Prior chimeric antigen receptor T-cell (CART) therapy is allowed but not required.
    - If the patient has received CART therapy, complete resolution of any active cytokine release syndrome is required
13. ≥2 sites of measurable disease (≥1.0 cm), at least one outside of intended RT fields.

Table 1 Adequate Organ Function Laboratory Values

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

Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal. [a]Growth factor and/or transfusion support is permissible to stabilize participant prior to study treatment if needed. [b]No lower limit if cytopenia is related to bone marrow involvement. [c]Creatinine clearance (CrCl) should be calculated per institutional-standard Cockcroft-Gault formula. Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.	

6.1.2 Participant Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. A WOCBP who has a positive urine pregnancy test within 72 hours prior to the first fraction of radiation (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.

   A patient may be considered eligible pending negative pregnancy test within 72 hours prior to the first fraction of radiation.

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

3. Has received prior systemic anti-cancer therapy including investigational agents within 2 weeks prior to the first fraction of radiation.

   Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.

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

4. Has received prior radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

5. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

6. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.

   Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

7. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

8. Has a known additional malignancy that is progressing or has required active treatment within the past 1 year. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, breast cancer, prostate cancer, or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

9. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

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

11. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

12. Has an active infection requiring systemic therapy.

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

14. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

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

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

17. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e. without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.

18. Has undergone allogeneic bone marrow transplantation within 5 years.

19. History of graft-versus-host-disease.

20. Has a known history of Human Immunodeficiency Virus (HIV).

    Note: No HIV testing is required unless mandated by local health authority.

21. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

    Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

6.1.3 Lifestyle Restrictions

6.1.3.1 Meals and Dietary Restrictions

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

6.1.3.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 3 for approved methods of contraception.

For this study, male participants 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).

6.1.4 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck within 2 working days if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to Merck and followed as described in Section 8.2.2.

6.1.5 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, participants who are breast-feeding are not eligible for enrollment.

6.2 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
External beam radiotherapy	4 Gy/ fraction	5 fractions total (1 fraction/ day)	External beam	Prior to start of pembrolizumab*	Experimental
Pembrolizumab	400 mg	Q6W	IV infusion	Day 1 (+/-7 days) of each 6 week cycle	Experimental

*The radiation schedule may be altered to accommodate planned pembrolizumab administration. The 5 fractions of radiation should be completed within a 2-week period. If PD at week 8-12 response assessment, repeat RT may be delivered on post-induction assessment day 1.

6.2.1 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 7.0). Trial treatment may be administered after the first fraction of RT, no later than 3 days following the final fraction of RT. As the 5 fractions of radiation should be completed within a 2-week period, this provides a 17-day window during which pembrolizumab may be initiated. Subsequent administrations may be delivered up to 7 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 400 mg will be administered as an IV infusion, every 6 weeks.

6.2.2 Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 3.

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 (CTCAEv5.0)**	**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 (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., 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
	Grade 4	Permanently discontinue		

				feasible, fluid and electrolytes should be substituted via IV infusion.
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 (e.g., 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 (e.g., levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
	Grade 2	Withhold		• Monitor changes of renal function

Nephritis and Renal dysfunction	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	
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).

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 4.

Table 4 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of _____ with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for interruption should be documented in the patient's study record.

6.2.3 Second Course *

All participants who stop study treatment with SD or better may be eligible for up to an additional 1 year of pembrolizumab treatment if they progress after stopping study treatment from the initial treatment phase. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the participant meets the following conditions:

Either

- Stopped initial treatment with study treatment after attaining an investigator-determined confirmed CR based on Lugano criteria, and
  - Was treated with at least 8 cycles of study treatment before discontinuing treatment, and
  - Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared

OR

- Had SD, PR, or CR and stopped study treatment after completion of 18 administrations (approximately 2 years) of study treatment for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined radiographic disease progression by Lugano criteria after stopping initial treatment, and
  - Upon unblinding at the time of centrally verified disease progression were found to have received pembrolizumab, and
  - No new anticancer treatment was administered after the last dose of study treatment, and
  - The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
  - The study is ongoing

An objective response or disease progression that occurs during the Second Course Phase for a participant will not be counted as an event for the primary analysis of either endpoint in this study.

**Note: patients must have measurable disease at the start of protocol treatment to be eligible for this provision.*

6.3 Treatment

This is a single-arm study; all patients will be allocated to receive pembrolizumab and up-front radiation. Patients with PD are eligible for continued pembrolizumab plus repeat radiation to a different site. See Section 7.0 Trial Flow Chart.

6.3.1 Pembrolizumab Administration

Pembrolizumab will be administered as an IV infusion on day 1 and continued per standard of care and institutional practices. Pembrolizumab will be given in the outpatient oncology units of the University of Pennsylvania Health System. Patients will be monitored in the clinic after the infusion and discharged when deemed stable by the clinical staff. Medications to treat hypersensitivity reactions should be immediately available, including epinephrine, diphenhydramine, methylprednisolone and nebulized albuterol.

For the purposes of scheduling and analysis, day 1 will refer to the date of pembrolizumab (not radiotherapy) initiation.

6.3.2 Radiotherapy Administration

Involved-site radiotherapy will be started, with at least the first fraction delivered prior to the initiation of pembrolizumab. All subjects will be immobilized as needed in a custom designed device in the appropriate position to isolate the index lesion(s) as needed. Radiotherapy treatment planning using CT or PET/CT scanning will be required to define the gross target volume (GTV) and clinical target volume (CTV). All tissues to be irradiated must be included in the CT scan. Planning CT scan will be done at 3 mm intervals from encompassing the region of interest with sufficient margin for treatment planning.

6.3.3 Target Contouring

Gross Tumor Volume (GTV) is defined as all known gross disease encompassing the selected index lesion(s). The GTV will consist of the index lesion(s) as visualized on CT and PET. A CTV (or ITV, internal target volume) will be defined using an involved site radiation therapy paradigm, and can include elective target volume at the discretion of the treating radiation oncologist. More than 1 lesion may be targeted, but volumes must be designed to allow for an additional measurable lesion to be excluded from the radiated volume (non-target lesion). Only extracranial lesions may be targeted.

Planning Target Volume (PTV) will be defined as per the convention for photon beam radiotherapy. A 3-dimensional margin will be created on the GTV or IGTV (if available) to allow for daily set-up variance.

6.3.4 Normal Structures

Organ at risk volume (OAR) is contoured as visualized on the planning CT scan depending on the location of the index lesion.

6.3.5 Dose Fractionation

All patients will be given 5 fractions of 4 Gy each over a period of 5-14 days, depending on the radiation oncology schedule, to the PTV as defined above. Treatment days do not have to be consecutive due to weekends or holidays.

6.3.6 External Beam Equipment and Beam Delivery

A radiation oncologist will check the first film on all fields. All set-up films will be permanently filed for all subjects.

6.3.7 Quality Assurance

All periodic and patient-based quality assurance for patient treatment will conform to established Penn Radiation Oncology Department standards and all treatment plans will be reviewed at weekly quality assurance meetings (chart rounds).

6.3.8 Preparation and Packaging

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

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.

6.4 Stratification

This is a single-arm study; no stratification will be performed.

6.5 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 final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician.

6.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant'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 in the Electronic Medical record (EMR) 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 in the EMR.

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 8.2.

6.5.2 Prohibited Concomitant Medications

Participants 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 study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

- 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.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue

the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

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

6.5.3 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.2.2, [Table 3]. Where appropriate, these guidelines include the use of oral or IV 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 of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to [Table 3] in Section 6.2.2 for guidelines regarding dose modification and supportive care.

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

6.6 Participant Withdrawal/Discontinuation Criteria

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 8.1.4 – Other Procedures.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Confirmed radiographic disease progression outlined in Section 8.1.2.6.3
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Unacceptable adverse experiences as described in Section 6.2.2.

- The participant has a medical condition or personal circumstance which, in the opinion of the investigator, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with study treatment or procedure requirements
- Recurrent Grade 2 pneumonitis
- Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 24 weeks, receiving at least 2 doses of pembrolizumab beyond the date when the initial CR was declared. These participants may be eligible for second course treatment described in Section 6.2.3.
- The participant is lost to follow-up
- Completion of 18 treatments (approximately 2 years) with pembrolizumab

Note: The number of treatments is calculated starting with the first dose. Participants who stop pembrolizumab after receiving 18 doses may be eligible for retreatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 6.2.3. Participants may be retreated in the Second Course Phase (Retreatment) for up to an additional 1 year.

Guidance on duration of pembrolizumab for hematologic malignances:

- For widespread, recurrent disease – 24 months of pembrolizumab
- When using pembrolizumab as consolidative therapy/ limited disease – 12 months.

- Administrative reasons

6.7 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 participants
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 participant treatment can be made.

7.0 TRIAL FLOW CHART

7.1 Trial Flow Chart

Trial Period:	**Screening Phase**			**Treatment Cycles[a]**									**End of Treatment**	**Post-Treatment**		
														Active Follow-up	Long-term Follow-up	
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	RT[1]	1[1]	2	+/- RT[2]	3	4	To be repeated beyond 8 cycles: 5	6	7	8	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
Scheduling Window (Days):		-42 to -1			± 7		± 7	± 7	± 7	± 7	± 7	± 7	At time of Discon	30 days post discon	Std-of-care Sched	Std-of-care Sched
Administrative Procedures																
Pre-screening Consent	X or X															
Informed Consent	X or X															
Inclusion/Exclusion Criteria	X or X															
Demographics and Medical History		X		X	X		X	X	X	X	X	X		X	X	X
Prior and Concomitant Medication Review		X		X	X		X	X	X	X	X	X		X	X	X
Trial Treatment Administration				X	X		X	X	X	X	X	X				
Post-study anticancer therapy status														X	X	X
Survival Status				X	X		X	X	X	X	X	X	X	X	X	X
Clinical Procedures/Assessments																
Review Adverse Events					X		X	X	X	X	X	X	X	X	X	X
Full Physical Examination		X					X			X				X		
Directed Physical Examination				X	X			X	X		X	X			X	X
Vital Signs and Weight		X		X	X		X	X	X	X	X	X		X	X	X
ECOG Performance Status		X		X	X		X	X	X	X	X	X		X	X	X
Radiotherapy			X[1]			X[2]										
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory																

Trial Period:	**Screening Phase**			**Treatment Cycles[a]**									**End of Treatment**	**Post-Treatment**		
														Active Follow-up	Long-term Follow-up	
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	RT[1]	1[1]	2	+/- RT[2]	3	4	To be repeated beyond 8 cycles: 5	6	7	8	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
Scheduling Window (Days):		-42 to -1			± 7		± 7	± 7	± 7	± 7	± 7	± 7	At time of Discon	30 days post discon	Std-of-care Sched	Std-of-care Sched
Pregnancy Test – Urine or Serum β-HCG[4]		X					X									
Standard-of-care Labs (Table 6)		X[9]		X	X		X	X	X	X	X	X		X[3]	X[3]	X[3]
Efficacy Measurements																
Tumor Imaging		X				X[10]				X			X		X[3]	X[3]
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood																
Archival or Newly Obtained Tissue Collection		X														
Correlative Studies Blood Collection		X	X[8]	X[5]	X		X	X[6]	X[6,7]				X			

Trial Period:	Screening Phase			Treatment Cycles[a]									End of Treatment	Post-Treatment		
														Active Follow-up	Long-term Follow-up	
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	RT[1]	1[1]	2	+/- RT[2]	3	4	To be repeated beyond 8 cycles				Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
									5	6	7	8				
Scheduling Window (Days):		-42 to -1			± 7		± 7	± 7	± 7	± 7	± 7	± 7	At time of Discon	30 days post discon	Std-of-care Sched	Std-of-care Sched

[1]Radiotherapy is initiated prior to the first cycle of pembrolizumab. The 5 fractions of radiation should be completed within a 2-week period. Pembrolizumab is administered after the first fraction of RT, no later than 3 days following the final fraction of RT. This provides a 17-day window during which pembrolizumab may be initiated.

[2] If PD at week 8-12 response assessment, repeat RT may be delivered on post-induction assessment day 1.

[3]As indicated clinically

[4]Pregnancy test is required only for women of childbearing potential within 72 hours prior to the first fraction of radiation. Pregnancy test only required at cycle 3 if re-RT will be given 72 hours prior to CT simulation or 72 hours prior to initiation of re-RT.

[5]1-week post-treatment initiation

[6]If re-RT

[7]Not to be repeated beyond 8 cycles

[8]After the start of RT and before Pembrolizumab initiation

[9]Within 10 days prior to Pembrolizumab initiation

[10] To be done within 8-12 weeks post first Pembrolizumab infusion

[a]The duration of pembrolizumab must be limited to a maximum of 2 years

8.0 TRIAL PROCEDURES

8.1 Trial Procedures

The Trial Flow Chart - Section 7.0 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.

8.1.1 Administrative Procedures

8.1.1.1 Informed Consent

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

Consent must be documented by the participant's dated signature or by the participant'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 participant before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB/ERC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant'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 participant's dated signature or by the participant's legally acceptable representative's dated signature.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

8.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator to ensure that the participant qualifies for the trial.

8.1.1.2.1 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 participant 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 participant will move into survival follow-up.

8.1.1.3 Assignment of Screening Number

Each subject will be assigned a screening number by the clinical research coordinator.

8.1.2 Clinical Procedures/Assessments

8.1.2.1 Procedures Prior to Protocol Therapy

The following tests must be performed within 6 weeks of enrollment and prior to starting pembrolizumab.

Baseline standard of care procedures that include:

- Standard-of-care history, physical examination, and laboratory tests as clinically indicated
- Pregnancy test is required only for women of childbearing potential within 72 hours prior to the first fraction of radiation. A serum or urine test can be performed.
-
- FDG-PET/CT
- Correlative biomarkers

8.1.2.2 Procedures During Radiation

As per standard of care, patients will be seen by a physician once while receiving radiation treatment and a toxicity assessment will be performed. Patient records will be reviewed by the clinical research coordinator in conjunction with the investigator to determine toxicities, including the grade and attribution to radiation.

Prior to initiation of radiation, a blood sample will be collected for correlative biomarkers.

8.1.2.3 Procedures During Pembrolizumab Administration

As per standard of care, patients will be seen by a physician, advanced practice provider, or registered nurse prior to pembrolizumab infusion and a toxicity assessment will be performed. The following laboratories will be performed prior to infusion every 6 weeks, depending on the pembrolizumab dosing regimen used:

- Standard-of-care laboratory tests appropriate for pembrolizumab

Patient records will be reviewed by the study coordinator in conjunction with the investigator to determine toxicities, including the grade and attribution to pembrolizumab.

8.1.2.4 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated.

The Medical Monitor will be Dr. Edgar Ben-Josef, a physician who is not directly involved in the trial and is not part of the Lymphoma Oncology Group at Penn. Because of Dr. Ben-Josef's background and experience in radiation oncology, he is an appropriate Medical Monitor (MM) for this study. In the role, he will review all AEs including grading, toxicity assignments, dose modifications, and all other safety data and activity data observed in the ongoing clinical trial along with discussing relevant animal and toxicology studies and similar investigational agents. The MM may recommend reporting of adverse events and relevant safety data not previously reported and may recommend suspension or termination of the trial. The investigator will meet with the MM every 6 months +/- 1 month (or more frequently as needed). Serious and unexpected issues will be handled on an ad hoc basis through calls or e-mail. Documentation of MM activity will be maintained in the study specific Regulatory Binder. Copies of an MM report requiring action on the part of the PI to protect subject safety or study integrity must be submitted to the DSMC within 10 business days.

Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0 (see Appendix 2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 8.2 for detailed information regarding the assessment and recording of AEs.

8.1.2.5 Tumor Imaging and Assessment of Disease

8.1.2.5.1 FDG PET/CT Imaging Visits

The following procedures will be done at each imaging session, as per routine clinical practice for FDG PET/CT imaging.

A total of at least 2 FDG PET/CT exams will be performed as follows:

- Baseline: A clinical baseline FDG PET/CT will be obtained no more than 6 weeks prior to initiation of pembrolizumab to assess baseline, pre-therapy tumor glycolytic activity. This exam is clinical standard of care for staging of disease prior to initiation of a new line of therapy and would be performed even if the patient was not enrolled in the study. This exam may occur prior to consent and enrollment in this study.
- Response assessment: At weeks 8-12 after the start of pembrolizumab, FDG PET/CT will be obtained for response assessment. For patients undergoing retreatment with radiotherapy, an additional FDG PET/ Subsequent FDG PET/CT(s) will be obtained as clinically indicated in follow-up. CT will be obtained at weeks 8-12 after the delivery of radiation.

  Per the revised Lugano Classification, FDG PET-determined Deauville score will be incorporated into the determination of CR (Deauville 1-3: FDG uptake no greater than liver uptake), PR (reduced FDG uptake vs. baseline but Deauville 4-5: FDG uptake

greater than liver uptake), and PD (increased/new sites of uptake vs. baseline and Deauville 4-5: FDG uptake greater than liver uptake).(Cheson et al., 2016)

For any planned PET/CT noted throughout this protocol: if PET/CT cannot be obtained for any patient- or insurance-related factors, CT may be performed as an alternative. Revised Lugano Classification lymphoma response criteria using CT-based definitions will be used for these patients (see Section 8.1.2.6.6).

8.1.2.6 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 6 weeks prior to the first fraction of radiation. The participant must have measurable disease as defined below.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 6 weeks prior to the first fraction of radiation and can be assessed by the central imaging vendor.

Brain imaging, if performed to document the stability of existing metastases, should be by MRI if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

8.1.2.6.1 Definitions of Measurable and Non-Measurable Disease

Measurable disease is defined as at least one lesion whose longest diameter can be accurately measured as ≥1.0 cm with spiral CT. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

In the absence of definite FDG avidity, nodes with a short axis of ≥1.0 cm by CT are considered measurable and assessable as target lesions. Only the short axis measurement should be included in the sum of lesions in calculation of tumor response. Nodes that shrink to ≥1.0 cm short axis are considered normal.

All other lesions (or sites of disease), including PET-silent small lesions (<1.0 cm with spiral CT) are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

8.1.2.6.2 Guidelines for Evaluation of Measurable Disease

Measurement Methods: The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use spiral CT imaging for both pre- and post-treatment tumor assessments. Imaging-based evaluation is

preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

8.1.2.6.3 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 8-12 weeks (56-84 days ±7 days]) from the first date of pembrolizumab. Subsequent tumor imaging should be performed every 8-12 weeks (56-84 days ±7 days) or more frequently if clinically indicated. After 24 weeks (168 days ±7 days), participants who remain on treatment will have imaging performed every 8-12 weeks (56-84 days ±7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator.

Per the Lugano criteria (Section 8.1.2.6.6), disease progression should be confirmed within 8 weeks after first radiologic evidence of PD in clinically stable participants. If the PET FDG/ tumor imaging done as a response assessment 8-12 weeks after starting pembrolizumab or as a standard of care procedure, shows disease progression then it should be reported as PD within 8 weeks from the date of the scan.

Participants who have unconfirmed disease progression may continue on treatment at the discretion of the Investigator until progression is confirmed provided they have met the conditions detailed in Section 8.1.2.5. Participants who have confirmed disease progression by the Lugano criteria, as assessed by the physician, may receive additional radiotherapy. Exceptions are detailed in Section 8.1.2.5.

8.1.2.6.4 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 due to documented disease progression and the Investigator elects not to implement the Lugano criteria, this is the final required tumor imaging.

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 (at the discretion of the treating Medical Oncologist) 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.

8.1.2.6.5 Second Course (Retreatment) Tumor Imaging

Tumor imaging must be performed within 6 weeks prior to treating with additional radiotherapy. Local reading (Investigator assessment with site radiology reading) will be used to determine eligibility.

The first on-study imaging assessment should be performed at 8-12 weeks (56-84 days ±7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 8-12 weeks (56-84 days ±7 days) or more frequently, if clinically indicated.

Imaging should continue to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. Disease progression may be confirmed by the Investigator using Lugano criteria, in clinically stable participants within 8 weeks from the date of the scan that raised concern for PD.

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 due to documented disease progression, this is the final required tumor imaging.

In participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging at the discretion of the treating Medical Oncologist until either the start of a new anticancer treatment, disease progression, pregnancy, death, or the end of the study, whichever occurs first.

8.1.2.6.6 Assessment of Disease Response

8.1.2.6.6.1 Cutaneous Assessment of Disease Response

For Mycosis Fungoides, response and progression can be assessed using the mSWAT criteria based on skin evaluation proposed by Olsen EA (Olsen EA et all, 2011) United States Cutaneous Lymphoma Consortium.

Response	**Definition**
Complete response	100% clearance of skin lesions[*]
Partial response	50%-99% clearance of skin disease from baseline without new tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease
Stable disease	< 25% increase to < 50% clearance in skin disease from baseline without new tumors (T_3) in patients with T_1, T_2, or T_4 only skin disease
Progressive disease[†]	≥ 25% increase in skin disease from baseline or
	New tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease or

Response	Definition
	Loss of response: in those with complete or partial response, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse	Any disease recurrence in those with complete response

NOTE. Based on modified Severity Weighted Assessment Tool score.

*A biopsy of normal appearing skin is unnecessary to assign a complete response. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a complete response would exist. If histologic features are suspicious or suggestive of mycosis fungoides/Sézary syndrome (see histologic criteria for early mycosis fungoides[7]), the response should be considered a partial response only.

†Whichever criterion occurs first.

8.1.2.6.6.2 Non-cutaneous: Lugano Criteria for Assessment of Disease

Response and progression will be evaluated in this study using the revised Lugano Classification lymphoma response criteria proposed by Cheson *et al.*(Cheson et al., 2016) The irradiated index lesion is not included in this determination; however, tumor response of this lesion will be assessed and tabulated separately using the revised Lugano Classification.(Cheson et al., 2016)

8.1.2.6.7 Measurement of Effect

8.1.2.6.7.1 Target Lesions

All measurable lesions up to a maximum of 6 lesions representative of all involved organs should be identified as target lesions and recorded and measured at baseline. If the protocol specified studies are performed, and there are fewer than 6 lesions identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions. For any one organ, no more than 2 lesions need to be measured. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

8.1.2.6.7.2 Non-target Lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline.

8.1.2.6.7.3 Response Criteria

All identified sites of disease must be followed on re-evaluation. Specifically, a change in objective status to either a PR or CR cannot be done without rechecking all identified sites (i.e., target and non-target lesions) of pre-existing disease.

8.1.2.6.7.3.1 Evaluation of target and non-target lesions

Evaluation of target and non-target lesions for response will be performed according to the revised Lugano Classification(Cheson et al., 2016) (criteria reproduced below):

Criteria	CR	PR	PD
Lugano	PET-CT, score 1, 2, or 3* with or without a residual mass on 5PS† OR on CT, target nodes/nodal masses must regress to ≤1.5 cm in LDi	PET-CT score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size. OR On CT ≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites	PET-CT score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment. OR On CT, 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 ≥2 cm from baseline. New or recurrent splenomegaly New or clear progression of preexisiting nonmeasured lesions Regrowth of previously resolved lesions A new node >1.5 cm in any axis or 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 AND/OR new or recurrent involvement of the bone marrow

8.1.2.6.7.3.2 Overall Objective Status

The overall objective response status for an evaluation is determined by combining the patient's status on target lesions, non-target lesions, and new disease.

Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic

deterioration that may include weight loss >10% of body weight, worsening of tumor-related symptoms, and/or decline in performance status of >1 level on ECOG scale.

8.1.2.7 Correlative Blood Sampling

- Biosamples (blood) obtained from patients before and at serial time points (as outlined in Section 7.0) during treatment will be analyzed. The primary goals for the basic studies with these human samples will be high dimensional (15-17 color) flow cytometry to analyze T cell subsets (including naïve, effector, memory (effector memory and central memory), effector memory RA, exhausted, Th1, Treg and Tfh), co-expression of sets of multiple inhibitory receptors by relevant T cell subsets, transcription factor expression, and T comprehensive functional analysis (expression of cytokines, chemokines, cytotoxic molecules, and degranulation). These studies will focus on sophisticated immune phenotyping and defining correlates of response.

    - In addition, the following markers will be studied: CD3, CD4, CD8, CD25, CD39, CD73, CD127, FOXP3, CD122, CD212 (IL-12R), HLA-DR, CD14, CD19, CD56, CD69, FAS-L, Granzyme B, IL-2, IL-4, IL-10, IL-12, Rantes, IFN- γ, TGF-β, GM-CSF, sIL-2R.

    - Circulating tumor material (e.g., circulating tumor cells, cell-free DNA, circulating tumor DNA, exosomes, etc.) will also be studied

Participants will additionally be screened for other companion biomarker studies.

8.1.3 Laboratory Procedures/Assessments

Standard-of-care laboratory tests will be ordered as specified in Table 6.

Table 6 Laboratory Tests

Hematology	Chemistry	Other
Hematocrit	Albumin	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	
WBC (total and differential)	Aspartate aminotransferase (AST)	Blood for correlative studies
Red Blood Cell Count	Lactate dehydrogenase (LDH)	
Absolute Neutrophil Count	Carbon Dioxide ‡	
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	
	Calcium	
	Chloride	
	Glucose	
	Potassium	
	Sodium	
	Total Bilirubin	
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*	
	Total protein	
	Blood Urea Nitrogen	

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.

8.1.4 Other Procedures

8.1.4.1 Withdrawal/Discontinuation

When a participant 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 8.2 - Assessing and Recording Adverse Events. Participants who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment. After discontinuing treatment following assessment of CR, these participants should return to the site for a Safety Follow-up Visit (described in Section 8.1.5.3.2) and then proceed to the Long term Follow-Up Phase of the study (described in Section 8.1.5.3.3).

At the end of study visit – the second response assessment, 8-12 weeks after the first response assessment – FDG-PET will be performed, the patient will be evaluated for toxicities, and a final blood draw will be taken for correlative biomarkers. Patient charts will be reviewed for progression, response, and overall survival.

8.1.4.1.1 Data Collection and Follow-up for Withdrawn Subjects

Subjects who withdraw consent to participate in the study will be seen for one final visit, during which they will be asked for permission to have the study team look into their survival status via publically available means.

8.1.4.1.2 Early Termination Visits

If a subject decides to leave the study early or is asked by the investigator to cease participation in the study, an early termination visit may be performed in person, by telemedicine, by telephone, or omitted at the discretion of the investigator, and will require only survival status, adverse event review, and tumor imaging as described in section 8.1.2.6.4 (End of Treatment and Follow-up Tumor Imaging).

8.1.5 Visit Requirements

Visit requirements are outlined in Section 7.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 8.1 - Trial Procedures.

8.1.5.1 Screening

An investigator must explain the nature of the study protocol and risks associated with the protocol in detail to the subject. The subject must sign and date the written informed consent prior to study participation. Informed consent process must be obtained before protocol procedures are performed. If a procedure required for screening was performed prior to signing the informed consent and the procedure meets the time limits of the protocol, this procedure may be used for the screening evaluation.

Screening will be completed prior to starting pembrolizumab.

Screening includes:

- Informed consent.
- Confirmed ECOG performance status of 0 or 1.
- Complete medical history.
- Standard-of-care laboratory tests appropriate for pembrolizumab (Table 6)
- Pregnancy test (required only for women of childbearing potential). If initiation of treatment is 15 days or more from eligibility, the pregnancy test should be repeated within 24 hours of treatment initiation.
- Documentation of pathological, imaging, and clinical confirmation of relapsed/refractory non-Hodgkin lymphoma.

8.1.5.1.1 Screening Period

8.1.5.1.1.1 Pregnancy Testing

Pregnancy test is required only for women of childbearing potential within 72 hours prior to the first fraction of radiation. A serum or urine test can be performed.

Females of childbearing potential must agree to use an effective contraception method during the study and for 120 days following the last dose of study drug; females of non-childbearing potential are those who are post-menopausal for more than 1 year or who have had a bilateral tubal ligation or hysterectomy. Female patients undergoing active fertility preservation therapy/egg harvesting which include hCG injections are expected to have mild elevation of hCG. These patients may be allowed to participate in the trial despite elevation of hCG after providing documentation of negative hCG prior the hCG injection and statement from her fertility specialist that they are not pregnant. Males who have partners of childbearing potential must agree to use an effective contraceptive method during the study and for 120 days following the last dose of study drug.

8.1.5.2 Treatment Period

8.1.5.2.1 Efficacy Evaluations

Efficacy will be evaluated based on the Response Criteria described in Section 8.1.2.5.

8.1.5.2.2 Safety Evaluations

Safety will be assessed based on the physical examination, vital signs, and laboratory evaluations.

8.1.5.2.3 Unscheduled Visits

Unscheduled visits may occur per patient request. If an unscheduled visit occurs within 1 week of the next scheduled visit, the unscheduled visit will substitute for the next scheduled visit, and that next scheduled visit will be canceled (with the exception of time elapsed between pembrolizumab infusion cycles, which will remain unchanged).

8.1.5.3 Post-Treatment Visits

8.1.5.3.1 End of Study Visit

At the end of study visit – the second response assessment, 8-12 weeks after the first response assessment – FDG-PET will be performed, the patient will be evaluated for toxicities, and a final blood draw will be taken for correlative biomarkers. Patient charts will be reviewed for progression, response, and overall survival.

8.1.5.3.2 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever comes first. Participants will be considered off study/ withdrawn after the safety follow up period has ended. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Participants 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-cancer 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. Participants who are eligible for retreatment/crossover with pembrolizumab (as described in Section 6.2.3) may have up to two safety follow-up visits, one after the Initial Treatment Period and one after the Second Course Treatment.

8.1.5.3.3 Follow-Up Visits

Participants who discontinue study treatment for a reason other than disease progression will move into the Long term Follow-Up Phase after completing the Safety Follow up visit (described in Section 8.1.5.3.2)and should be assessed in follow-up per standard of care. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study or if the participant begins retreatment with pembrolizumab as detailed in Section 6.2.3. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 6.2.3 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

8.1.5.3.4 Survival Follow-Up

Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and will be followed in the EMR for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

8.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant 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. AEs, SAEs, and other reportable safety events will be recorded and reported to Merck within 3 months as noted below.

● All AEs from the time of treatment initiation through 30 days following cessation of study treatment must be reported by the investigator.

● All AEs meeting serious criteria, from the time of treatment initiation through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.

● All pregnancies and exposure during breastfeeding, from the time of treatment initiation through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.

● Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately by the investigator if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify Merck and the ACC DSMC committee in accordance with the ACC Data and Safety Monitoring Plan.

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

For purposes of this study, 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. In the event of overdose, the participant 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 to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

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

Although pregnancy and infant exposure during breast-feeding are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them) that occurs during the study.

Pregnancies and infant exposures during breastfeeding that occur after the consent form is signed but before treatment initiation must be reported by the investigator if they cause the participant to be excluded from the trial or are the result of a protocol-specified intervention.

Pregnancies and infant exposures during breastfeeding that occur from the time of treatment initiation through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the participant 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 215-661-6229)

8.2.3 Immediate Reporting of Adverse Events to Merck

8.2.3.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other 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 7 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment initiation, any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any participant must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial or is the result of a protocol-specified intervention.

For the time period beginning at treatment initiation through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant 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 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 Merck Global Safety.

All participants 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: +1-215-661-6229

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 215-661-6229) at the time of submission to FDA.

8.2.3.2 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 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

For the time period beginning when the consent form is signed until treatment initiation, any ECI, or follow up to an ECI, that occurs to any participant must be reported within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial or is the result of a protocol-specified intervention.

For the time period beginning at treatment initiation through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 2 working days to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 8.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck, that is not associated with clinical symptoms or abnormal laboratory results.

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

> *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.

8.2.4 Evaluating Adverse Events

An investigator who is a qualified physician, nurse practitioner, physician associate, or nurse will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. 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 7 Evaluating Adverse Events

An investigator who is a qualified physician, nurse practitioner, physician associate, or nurse will evaluate all adverse events as to:

V5.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mild 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 participant, 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 participant 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 participant 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 participant 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 participant 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 PARTICIPANT, 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		Participant 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 participant with overdose without an associated AE.)

8.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to the ACC DSMC committee in accordance with the ACC Data and Safety Monitoring Plan, regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

9.0 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

This is a single arm Phase II clinical trial for relapsed/refractory non-Hodgkin lymphoma patients receiving RT and pembrolizumab followed by continued pembrolizumab monotherapy if patient achieves a CR, PR or SD. Pembrolizumab is continued until disease progression, drug intolerance, or at the discretion of the treating medical oncologist.

9.2 Statistical Analysis Plan

9.2.1 Primary Objective

1. To determine the complete response (CR) rate for the study.

9.2.2 Secondary Objectives

1. To determine the time to best response
2. To determine duration of best response
3. To estimate progression free survival and overall survival
4. To evaluate safety and adverse events

9.2.3 Exploratory Objectives

1. To evaluate baseline and post-treatment changes in biomarkers and determine whether biomarker changes are associated with clinical outcomes.

9.2.4 Primary Endpoint

The primary endpoint is the CR rate, defined as the total number of CRs after RT + pembrolizumab induction (first course of RT if multiple courses are delivered), divided by the total number of evaluable patients treated on the study. Evaluable implies that the patient received one dose of pembrolizumab and at least two fractions of radiotherapy. The revised Lugano Classification criteria will be used to score response.

9.2.5 Secondary Endpoints

1. Time to best response is defined from date of study entry to date of best response. For progressive disease patients, time to best response will be defined from study entry to date taken off study due to PD. It is assumed that most patients who are scored PD at 8-12 weeks will continue pembrolizumab for another 8 weeks.

2. Duration of best response is defined from date of best response to date of disease progression, death due to any cause of last patient contact alive and progression-free.

3. Progression free survival is defined from date of study entry to date of disease progression, death due to any cause of last patient contact alive and progression-free.

4. Overall survival is defined from date of study entry to date of death due to any cause of last patient contact alive.

5. Toxicities will be graded and tabled separately for pembrolizumab pre- or post-RT.

9.2.6 Exploratory Endpoints

1. Biosamples (blood and, where available, tumor) obtained will be obtained before treatment and at serial time points during treatment. Flow cytometry is used to analyze T cell subsets (including naïve, effector, memory (effector memory and central memory), effector memory RA, exhausted, Th1, Treg and Tfh), co-expression of sets of multiple inhibitory receptors by relevant T cell subsets, transcription factor expression, and T comprehensive functional analysis (expression of cytokines, chemokines, cytotoxic molecules, and degranulation).

2. Additional markers will be studied: CD3, CD4, CD8, CD25, CD39, CD73, CD127, FOXP3, CD122, CD212 (IL-12R), HLA-DR, CD14, CD19, CD56, CD69, FAS-L, Granzyme B, IL-2, IL-4, IL-10, IL-12, Rantes, IFN- γ, TGF-β, GM-CSF, sIL-2R.

3. Circulating tumor material (e.g., circulating tumor cells, cell-free DNA, circulating tumor DNA, exosomes, etc.) will also be studied

9.2.7 Interim Analysis

No interim analysis is planned.

9.2.8 Plans for Data Analysis

1. Baseline and demographic characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables such as age and frequency and percentage for categorical variables such as gender).

2. The CR rate and 95% exact confidence interval will be calculated. Based on an exact binomial test, the number of evaluable patients with CR will determine whether the null hypothesis will be rejected (see Sample Size/Power below).

3. Time to best response and duration of best response will be calculated and summarized separately for CR, PR and SD patients.

4. Progression free survival and overall survival will be estimated by the Kaplan-Meier method.

5. All subjects entered into the study will have detailed information collected on adverse events for the overall study safety analysis. Toxicities will be graded and tabled separately by pembrolizumab pre- and post-XRT.

Exploratory Analyses

1. Longitudinal changes in biomarkers will be assessed by plots over time and descriptive statistics (mean, median, standard deviation, range and coefficient of variation). Change in markers from baseline to week 8, will be compared between pembrolizumab + RT induction responders (CR) and non-responders (<CR). Change in markers from week 8 to week 16, will be compared between post-radiotherapy responders (CR) and non-responders (<CR). Student's t-test or non-parametric Wilcoxon rank sum test will be employed.

2. Primary, secondary, and exploratory study analyses will be further stratified by histology (e.g. DLBCL, PMBCL, FL, TCL, etc.), and for patients with DLBCL, prior vs. no prior CART therapy.

9.2.9 Sample Size/Power

With 40 evaluable patients, there is 82% power to detect a difference of 15% assuming a null hypothesis that the CR rate = 10% versus an alternative hypothesis that the CR rate = 25% using a one-sided exact test with a 5% significance level. We will reject the null hypothesis if 8 or more of 40 evaluable patients achieve a CR. The actual significance level for this exact test procedure is 4.2%.

10.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

10.1 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.

Pembrolizumab will be provided by Merck as summarized in Table 8.

Table 8 Product Descriptions

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

10.2 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

10.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the participant, 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.

10.4 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.

10.5 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 participants 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.

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12.0 APPENDICES

Appendix 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.

Appendix 2: Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

Appendix 3: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following for 120 days following the completion of study treatment:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 10 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10 for 120 days following the completion of study treatment.

Table 10 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly).

b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 120 days after the last dose of study treatment .
c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected; at the time points specified in the Schedule of Activities, and as required locally.