RADVAX™ FOR RELAPSED/REFRACTORY HODGKIN LYMPHOMA: A PHASE II TRIAL OF NIVOLUMAB + LOW DOSE RADIOTHERAPY FOR INCOMPLETE RESPONDERS

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UPCC Number:

04418

IRB Number:

828966

Version: 9/27/2018
Amend: 1/14/2019
Amend: 7/28/2020
Amend: 1/29/2021

Contents

List of Abbreviations

For example: LIST OF ABBREVIATIONS-list alphabetically.

ACC: American College of Cardiology

AE: Adverse event

DMC: Data Monitoring Committee

DM: Diabetes Mellitus

ECG: Electrocardiogram

Study Summary

Title	RADVAX™ FOR RELAPSED/REFRACTORY HODGKIN LYMPHOMA: A PHASE II TRIAL OF NIVOLUMAB + LOW DOSE RADIOTHERAPY FOR INCOMPLETE RESPONDERS
Short Title	Lymphoma RadVax™
Protocol Number	UPCC IRB
Phase	Phase II
Methodology	Open-label
Study Duration	2 years
Study Center(s)	Single Center
Objectives	This is a Phase II single-arm, single-site, open label clinical trial with r/r HL patients, aimed to determine whether a RadVax approach using low-dose RT added to nivolumab can improve response among patients who do not achieve a CR to nivolumab alone. The long-term goal is to develop an effective regimen for r/r HL patients.
Number of Subjects	25
Main Inclusion Criteria	• Pathologically confirmed Hodgkin lymphoma for whom nivolumab is clinically indicated. • Relapsed/refractory disease. • ≥2 sites of measurable disease, at least one outside of intended RT fields. • Age ≥ 18 years. • ECOG performance status of 0-2.

BACKGROUND AND STUDY RATIONALE

This study is a Phase II clinical trial that will be conducted in full accordance all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations including, as applicable, 45 CFR 46, 21 CFR Parts 50, 54, 56, 312, 314 and 812 and Good Clinical Practice: Consolidated Guidelines approved by the International Conference on Harmonisation (ICH). All episodes of noncompliance will be documented.

Introduction

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.[1]

1.1 Background and Relevant Literature

Immunotherapies have emerged as a very promising option for patients with relapsed/refractory (r/r) Hodgkin lymphoma (HL) who have progressed despite second line chemotherapy, stem cell transplants and/or surface-receptor targeted agents such as brentuximab. Activity of PD-1 inhibitors in r/r HL has been documented,[2, 3] resulting in FDA approval of nivolumab for this population in May 2016. Nivolumab 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 thought to be 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. 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) 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. 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. We plan to study the combination of low dose radiation with nivolumab in patients with relapsed/refractory Hodgkin lymphoma.

1.2 Name and Description of the Investigational Product

Nivolumab is a PD-1 inhibitor that is now FDA-approved for r/r HL and is considered a standard of care for select patients with r/r HL. Nivolumab was tested as single-agent monotherapy in a Phase II trial of 80 HL patients who progressed after stem cell transplant and BV, demonstrating 9% CR, 58% PR, and 23% SD rates with an impressive 6 month PFS of 76.9%.[3] Despite its FDA approval for r/r HL, patients who progress after nivolumab have limited additional options. Although pembrolizumab, also a PD-1 inhibitor, and more recently FDA-approved for r/r HL in March 2017, the study population was not previously exposed to PD-1 inhibition. Interestingly, the KEYNOTE 087 trial on which the approval was based, had a 22% CR and 47% PR for a similar overall response rate of 69%. We chose to use nivolumab for this study due to the greater experience our clinicians have in r/r HL patients with this agent due to the earlier FDA approval.

1.3 Radiotherapy and Immune Activation

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, whereas PD-L2 is expressed primarily on professional antigen presenting

cells.[4] 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. [5] 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.[6, 7]) 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.[8] 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, early results from our trial of ipilimumab and SBRT in melanoma showed disappointing abscopal effects (22%) when RT was delivered prior to initiating the drug (A. Maity, personal communication). Careful preclinical sequencing experiments have shown that PD-1 inhibition combined with fractionated RT is less effective when given after or near the end of a multi-fraction RT course.[9] 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.[6] Our plan is to deliver radiation after the first response assessment following 2 months of nivolumab. Assuming that immune modulation should already be in effect when RT is fractionated, we will deliver 2 fractions of 4 Gy at that time for patients who do not achieve anatomic CR. This strategy allows patients with complete anatomic response (CR) to remain on the drug alone while patients without CRs can be potentiated with low dose RT. Another potential strategy would be to wait to radiate after disease progression on immunomodulatory therapy, but preclinical observations support the early use of RT (approximately 2 months into therapy) 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 [6]. Ultimately, the timing of the addition of RT to a therapy with known efficacy comes down to clinical practicality. Thus, the study design allows integration of RT when less than a complete response (CR) is noted after initiating immunotherapy.

1.3.1 Clinical Data to Date

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.*[1] The impact of the therapy on the irradiated lesion and the non-irradiated lesion(s) was evaluated using two standard modalities: (i) ^{18}F-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.*[10].

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. However, ipilimumab-related side effects were significant, and the combination of ipilimumab and RT showed only modest improvement over what is reported in the literature. Although this study was not designed to assess response, the results do not show that the majority of the patients have substantially reduced size of their unirradiated lesions in response to radiation.

1.4 Dose Rationale

Nivolumab has been studied in r/r HL patients at a dose of 3 mg/kg, infused over 60 minutes, administered every 2 weeks.[2, 3] This had been a standard dose regimen for nivolumab across disease sites and was the manufacturer- and FDA-recommended dose regimen for r/r HL. (However, the FDA recently approved an every-4-week regimen of nivolumab, 480 mg infused over 30 minutes.) Treating physicians will have the discretion of treating every 2 weeks or every 4 weeks. Among patients tested for efficacy, grade 3 or higher toxicities included: thrombocytopenia in 33%, increased lipase in 12%, lymphopenia in 7%, neutropenia in 6%, and pneumonia in 5%.[11] Any grade toxicities included upper respiratory tract infection in 48%, fatigue in 43%, neutropenia in 37%, fever in 35%, cough in 35%, thrombocytopenia in 33%, lymphopenia in 32%, increased AST in 32%, and rash in 31%, among other toxicities.[11] For patients who subsequently undergo allogeneic hematopoietic stem cell transplantation, toxicity data are unclear, however there is a concern for increased severe acute graft versus host disease.[11]

1.5 Early FDG PET/CT Imaging

Following cancer response to immunotherapy presents unique challenges compared to conventional cytotoxic chemotherapies. Studies of anti-CTLA4 therapy with ipilimumab in melanoma revealed that a significant subset of responding tumors may exhibit non-traditional patterns of response that can confound interpretation on CT.[12] An example of a non-traditional response is the initial increase in size of the tumor over the course of several months with a later decrease in tumor size. In these cases, the initial increase in size of the tumor is thought to be on the basis of tumor infiltration by immune cells and can be mistaken for tumor growth on CT. Another example of a non-traditional tumor response to immunotherapy is a decrease in the size of the primary tumor with the development of new small lesions. This pattern has also been observed to correspond with favorable outcome in the setting of immunotherapy but would be considered disease progression by conventional measures.

An apparent increase in tumor burden that later resolves or decreases has been called a flare response, and is hypothesized to result from a transient immune-cell infiltrate in the tumor stroma. Several studies provide support for this hypothesis, including a case study of an ipilimumab-treated patient with apparent progressive disease at 12 weeks, in which the histological analysis of a lung nodule demonstrated a T-

cell infiltrate, extensive necrosis, and no residual tumor cells.[13] Thus, a different set of response criteria have been developed, termed immune-related response criteria (irRC), that incorporate the possibility of a transient flare response, as well as a delayed immune response, into the assessment.[12, 14] While irRC has been shown to be an improvement over conventional RECIST (Response Evaluation Criteria In Solid Tumors) in the setting of immunotherapy, irRC still does not accurately identify all responders and non-responders. This is partly due to the fact that morphological changes to the tumor from immunotherapy can take several months to manifest. Thus, a timelier and more accurate measure of response to immunotherapy is needed.

1.5.1 [^{18}F]FDG PET as a Marker of Cancer and Inflammation

2-Deoxy-2-[^{18}F]fluoro-D-glucose (FDG) is an ^{18}F analogue of glucose that serves as a PET radiotracer of cellular metabolism. FDG enters the cell through cell surface glucose transporters and becomes trapped within the cell following enzymatic phosphorylation by hexokinase. For decades, FDG has been employed to detect cancer exploiting a phenomenon known as the Warburg effect in which most malignancies preferentially produce ATP through a boost in extra- mitochondrial glycolysis, rather than mitochondrial oxidative phosphorylation, despite aerobic conditions. This metabolic switch, termed aerobic glycolysis, has a greater rate of glucose utilization albeit overall lower ATP yield, and provides the generation of key carbon precursors needed for the synthesis of nucleic acids, phospholipids, fatty acids, cholesterol and porphyrins.[15] As a result of the increased rate of glycolysis characteristic of the Warburg effect, most malignancies utilize more glucose (and FDG) than their non-transformed neighboring cells, which has led to the use of FDG PET/CT as a highly sensitive and moderately specific tool for the detection of occult metastatic disease.

It has recently been recognized that immune activation results in a similar cellular metabolic switch from oxidative phosphorylation to aerobic glycolysis. This occurs with both the innate and adaptive immune activation. For example, when activated using TLR ligands or proinflammatory cytokines, neutrophils, dendritic cells, and macrophages have been demonstrated to switch their metabolism from oxidative phosphorylation to aerobic glycolysis.[16] Similarly, following TCR stimulation, lymphocytes increase glucose utilization by several orders of magnitude and switch glucose metabolism from oxidative phosphorylation to aerobic glycolysis.[17, 18] Interestingly, anti-inflammatory subpopulations of both the innate and adaptive immune system, such as M2 macrophages, regulatory T cells and quiescent memory T cells, demonstrate a predominant use of oxidative phosphorylation rather than aerobic glycolysis as opposed to their inflammatory counterparts such as activated macrophages and T-helper cells.[19]

The upregulation of aerobic glycolysis in immune activation is readily visualized with FDG PET/CT imaging. Inflammatory conditions such as infection, rheumatoid arthritis and sarcoidosis yield intense avidity for FDG that compares with or exceeds that of most malignancies.[20, 21] In fact, a significant limitation to the use of FDG PET/CT in cancer restaging has been interference of the tumor FDG signal by post-therapeutic inflammatory tissues including surgical changes, talc pleurodesis, and radiation therapy.[22]

In this study, we propose utilizing FDG PET/CT to assess the immunotherapy response to nivolumab by detecting the superimposed increased metabolism within the tumor presented by a therapy-induced infiltrating population of glucose avid activated immune cells. FDG PET/CT studies are typically performed at approximately 8-12 weeks following the initiation of nivolumab, and the probability of seeing a flare response on these clinical studies is very low.

We propose looking for a flare response at about 1 week following the start of nivolumab. This time point is used in an ongoing clinical trial with lenalidomide and non-Hodgkin lymphoma. This was developed after a patient treated with lenalidomide for diffuse large B-cell lymphoma demonstrated a flare response on FDG PET/CT at 1 week, with a complete metabolic response on subsequent PET/CT at 5 weeks.

No significant change is expected in the tumor's inherent basal glycolytic activity over the short interval between the baseline FDG PET/CT and the post-therapy PET/CT. Therefore, we hypothesize that the flare response can be visualized with FDG PET/CT by detection of a superimposed burst of tumoral glycolytic activity resulting from immunotherapy-induced immune infiltration. If successful, this data will help to determine the ideal time point for visualization of the flare response, test the potential for the flare response to serve as a biomarker for outcomes (e.g. which patients may stand to benefit from RT priming using RadVax concept), and contribute to our understanding of nivolumab's mechanism of action.

2 Study Objectives

This is a Phase II single-arm, single-site, open label clinical trial with r/r HL patients, aimed to determine whether a RadVax approach using low-dose RT added to nivolumab can improve response among patients who do not achieve a CR to nivolumab alone. The long-term goal is to develop an effective regimen for r/r HL patients.

2.1 Primary Objective

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

2.2 Secondary Objectives

1. To determine the nivolumab induction CR rate.
2. To determine the post-RT + continued nivolumab CR rate.
3. To determine the time to best response.
4. To determine duration of best response.
5. To estimate progression free survival, overall survival and disease free survival.
6. To evaluate safety and adverse events.

2.3 Exploratory Objectives

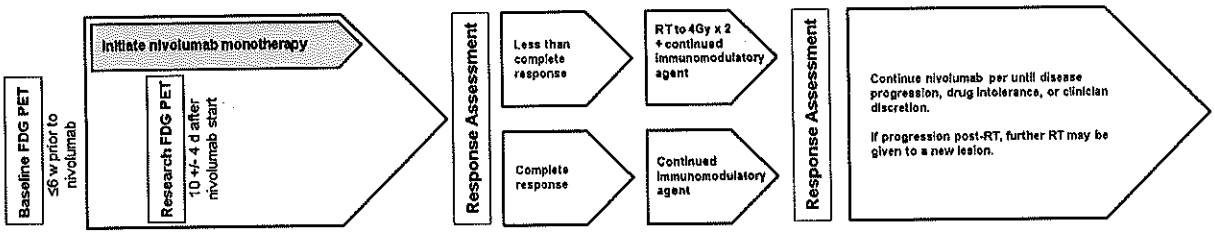
1. To evaluate baseline levels and post-treatment changes in biomarkers and determine whether biomarker changes are associated with clinical outcomes.
2. To evaluate tumor FDG uptake and determine whether FDG "flare" is associated with clinical outcomes.

3 Investigational Plan

3.1 General Design

This study is an open-label Phase II trial of Hodgkin lymphoma patients receiving initial treatment with the immunomodulatory agent, nivolumab, followed by low-dose (4 Gy x 2) involved-site radiotherapy in subjects with less than an anatomic CR after the first restaging scan. Patients with anatomic CR will continue nivolumab alone without radiotherapy. Eligible patients will have r/r disease with at least 2 sites of measurable disease, and must be eligible for treatment with nivolumab. Biosamples (blood and, where available, tumor) will be collected as outlined below. Nivolumab will be continued after RT until disease progression, drug intolerance, or at the discretion of the treating medical oncologist.

Research PET/CT will be performed approximately 1 week after nivolumab is started to assess for immunotherapy-related glycolytic activity (tumor "flare") at sites of disease using the FDA-approved clinical Positron Emission Tomography (PET) radiotracer, [^{18}F]fluorodeoxyglucose (FDG).



Registration

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Pre-study

- Initial baseline FDG PET/CT (standard of care) </=6 weeks prior to nivolumab administration.
- Collection of blood and, if available, tumor, for correlative biomarkers.

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Study Phase – Nivolumab

- Administration of nivolumab on day 1 and continued per standard of care and institutional practices.
- Continue blood sample collection for correlative biomarkers at week 1.
- Research FDG PET/CT at the time of week 2 blood sample collection.
- Continue blood sample collection for correlative biomarkers at weeks 4, 8, and 12.

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Study Phase – Response Assessment

- Repeat PET/CT at 8-12 weeks (standard of care response assessment).
- If CR, continue nivolumab (with continued biomarker collection) until confirmed disease progression, drug intolerance, or at the discretion of the treating medical oncologist.
- If less than CR, proceed to Study Phase – Radiotherapy.

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Study Phase – Radiotherapy

- Prior to RT, blood sample collection is done for correlative biomarkers.
- RT to 4 Gy x 2 fractions to a single lesion.
- Continue nivolumab on day 1 and continue per standard of care and institutional practices.

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Study Phase – Post-radiotherapy Follow Up

- Continue nivolumab.
- Continue blood sample collection for correlative biomarkers at 1, 4, 8, and 12 weeks post-RT.
- Repeat PET/CT (response assessment in non-target lesion) at 8-12 weeks post-RT.
- CR, PR or SD continue on nivolumab until confirmed disease progression, drug intolerance, or at the discretion of the treating medical oncologist.

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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.

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Primary Objective

- Determine the overall CR rate.

	Pre-trial	Induction Assessment					Post-induction Assessment				
		Week					Week				
		0	1	2	4	8-12	0	1	4	8	12
Nivolumab[3]		X			X	X	X		X	X	X
RT (if <CR)							X				
FDG PET/CT	X			X[1]		X				X	
Correlative biomarkers[2]	X		X	X	X	X	X	X	X	X	X

[1]Research FDG PET/CT to be done at time of week 1 correlative biomarkers blood draw.
[2]Collect times are approximate due to appointment scheduling.
[2] Nivolumab administration will be at the discretion of the treating physician.

3.1.1 Screening Phase

As described in greater detail in Section **Error! Reference source not found.**~~4.3~~, subjects will be recruited from the oncology practice at Penn Medicine. The treating radiation oncologist or medical oncologist will approach and inform the patient about the study, thereby initiating the informed consent process. A qualified member of the research team will initiate the formal consent process. A series of questions will be asked by the person obtaining consent to verify patient eligibility based upon the criteria outlined in Sections **Error! Reference source not found.**~~4.1~~ and **Error! Reference source not found.**~~4.2~~. Eligibility is confirmed with the study investigator or delegate.

3.1.2 Study Intervention Phase

Nivolumab 3 mg/kg will be administered on day 1 (pre-response assessment week 0) and on day 1 and continued per standard of care and institutional practices. At the week 1 biomarker collection, research FDG PET/CT will be performed to assess for FDG "flare." At week 8-12, PET/CT will be performed for the first response assessment. If a complete anatomic response is seen, nivolumab monotherapy will be continued on day 1 and continued per standard of care and institutional practices.

By contrast, if at week 8 less than a complete anatomic response is seen, radiotherapy to 4 Gy x 2 fractions will be administered (post-response assessment week 0). The patient will be evaluated by a radiation oncologist while on treatment, and toxicities will be recorded. Nivolumab will be continued on day 1 and continued per standard of care and institutional practices.

In either scenario, a second response assessment will be conducted ~8-12 weeks after the first response assessment. In either scenario, nivolumab monotherapy will be continued at the discretion of the treating medical oncologist.

If there is less than CR post-RT and there is an additional untreated non-target lesion that can be followed, radiotherapy can again be administered when disease progresses to a previously untreated lesion, after which the patient will continue on the post-RT follow-up algorithm.

3.1.3 *Follow Up Phase*

The patient will be seen in follow-up on the same day as nivolumab infusion. For those patients receiving RT, the patient will be seen once while on treatment. Patients will otherwise be seen at the discretion of the treating medical oncologist or designee and/or radiation oncologist. The patient will then continue to be followed off-study per the usual follow-up schedule at the discretion of the treating physician.

3.2 Study Endpoints

3.2.1 Primary Study Endpoint

- Overall CR rate.

3.2.2 *Secondary Study Endpoints*

- Nivolumab induction CR rate.
- Post-RT + nivolumab CR rate.
- Progression-free survival (PFS) for entire study population.
- Overall survival (OS) for the entire study population.
- Disease free survival (DFS) for the nivolumab induction CR cohort and for the RT + continued nivolumab CR cohort.
- Duration of immunotherapy use for the entire study population, nivolumab only cohort, and nivolumab + RT cohort.
- Time to best response.
    - Duration of response, Biosamples (blood and, where available, tumor) 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.
- Change from baseline in tumor FDG uptake on PET/CT after initiation of nivolumab.
- Association between change in tumor FDG uptake and progression-free and overall survival.
- Based on change in tumor FDG uptake after initiation of nivolumab, determine which patients have FDG "flare."
- Association between FDG flare and response, progression-free survival, overall survival, and biomarker changes.
- Exploratory analyses will be conducted in changes in markers between induction nivolumab responders (CR) and non-responders (<CR), between post-RT responders (CR/PR vs. <PR), and between RT and no-RT cohorts.

4 Study Population and Duration of Participation

4.1 *Inclusion Criteria*

- Pathologically confirmed Hodgkin lymphoma for whom nivolumab is clinically indicated.
- Relapsed/refractory disease.
- ≥2 sites of measurable disease, at least one outside of intended RT fields.
- Age ≥ 18 years.
- ECOG performance status of 0-2.
- Standard laboratory criteria for hematologic, and biochemical, and urinary indices within a range that, in the opinion of the physician, clinically supports enrollment of the subject on the trial.
- Patients of reproductive potential must agree to use an effective contraceptive method during participation in this trial.
- Ability to provide written informed consent.

4.2 *Exclusion Criteria*

- Subjects with contraindications to immune checkpoint therapy, as follows:

- Interstitial lung disease that is symptomatic or may interfere with the detection and management of suspected drug-related pulmonary toxicity.
- Prior organ allograft or allogeneic bone marrow transplantation.
- Pre-existing thyroid abnormality with thyroid function that cannot be maintained in the normal range with medication.
- Active autoimmune disease, except for vitiligo, type 1 diabetes mellitus, asthma, atopic
- dermatitis, or endocrinopathies manageable by hormone replacement; other autoimmune conditions may be allowable at the discretion of the principal investigator.
- Condition requiring systemic treatment with either corticosteroids.
    - Systemic steroids at physiologic doses (equivalent to dose of oral prednisone 10 mg) are permitted. Steroids as anti-emetics for chemotherapy are strongly discouraged
    - Intranasal, inhaled, topical, intra-articular, and ocular corticosteroids with minimal systemic absorption are permitted.
- Pregnant women, women planning to become pregnant and women that are nursing.

4.3 Subject Recruitment

Subjects will be recruited from the Oncology practices at Penn Medicine. The treating radiation oncologist or medical oncologist will approach and inform the patient about the study, thereby initiating the informed consent process. If the patient expresses interest in the study, the treating radiation oncologist or medical oncologist will contact a qualified member of the research team in the Radiation Oncology Department at the University of Pennsylvania and request availability for enrollment. A qualified member of the research team will initiate the formal consent process. This person will interview the potential subject with privacy considerations, explain the requirements of the study and provide a copy of the Informed Consent Form. The person obtaining consent will state the volunteer nature of research and advise the subject to take sufficient time to discuss the study if necessary before making their decision to sign the informed consent document. If a decision to participate is made, the informed consent form is signed. A series of questions will be asked by the person obtaining consent to verify patient eligibility. After eligibility is established, a subject study number will be issued. Eligibility is confirmed with the study investigator or delegate. All members of the research team will have successfully completed patient oriented research training. The consent process can be completed in person or via Telemedicine per University of Pennsylvania Health Systems telemedicine policy and procedures.

In addition, this trial will be listed on our web site as a formal protocol and information of its availability will be made known to treating professionals throughout our satellites and referring physicians.

4.4 Duration of Study Participation

The duration of the study is approximately 22-25 weeks, from the time of pre-trial assessment through the final end-of-study visit. The duration of the intervention phase of the study is approximately 20-23 weeks: 8-12 weeks for nivolumab monotherapy, 8-12 weeks for continued nivolumab monotherapy vs. RT plus nivolumab, with 3 weeks allowed for RT simulation and planning. An additional 8-12 weeks is appended for patients undergoing additional RT.

4.5 Total Number of Subjects and Sites

Recruitment will end when 25 subjects are enrolled with lesions that are measurable as defined in section 6.3.2. Based on published CR rates,[2, 3] it is expected that the induction CR rate in this study population is expected to be approximately 10%.

4.6 Vulnerable Populations:

Vulnerable populations are not specifically included in this research study. We do not anticipate enrolling prisoners.

5 Study Intervention

5.1 Description

Nivolumab is a highly selective, humanized monoclonal antibody (IgG4) that blocks PD-1. Nivolumab was tested as single-agent monotherapy in a Phase II trial of 80 HL patients who progressed after stem cell transplant and BV, demonstrating 9% CR, 58% PR, and 23% SD rates with an impressive 6 month PFS of 76.9%.[3] Nivolumab is now FDA-approved for r/r HL. The combination of nivolumab with radiation is based on the observation that RT can enhance immunomodulators in lymphoma.[5-7] Based on preclinical sequencing experiments,[6, 9] RT will be given after the first response assessment after 8-12 weeks of nivolumab in patients with less than CR. RT will be given in 2 fractions of 4 Gy each, to be delivered to an index site using an involved site paradigm.

5.2 Intervention Regimen

5.2.1 Nivolumab Administration

Nivolumab (3 mg/kg) will be administered as an IV infusion on day 1 and continued per standard of care and institutional practices. Nivolumab 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.

5.2.2 Radiotherapy Administration

Involved-site radiotherapy will be administered after the first response assessment following induction nivolumab. RT will be delivered in the Department of Radiation Oncology. All subjects will be immobilized as needed in a custom designed device in the appropriate position to isolate the index lesion. 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.

5.2.3 Target Contouring

Gross Tumor Volume (GTV) is defined as all known gross disease encompassing the selected index lesion. The GTV will consist of the index lesion 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. Volumes must be designed to allow for an additional measurable lesion to be excluded from the radiated volume (non-target lesion).

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.

5.2.4 Normal Structures

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

5.2.5 Dose Fractionation

All patients will be given 2 fractions of 4 Gy each over a period of 2-4 days, depending on the radiation oncology schedule, to the PTV as defined above.

5.2.6 External Beam Equipment and Beam Delivery

Radiation treatments will be administered at the University of Pennsylvania Department of Radiation Oncology. A radiation oncologist will check the first film on all fields. All set-up films will be permanently filed for all subjects.

5.2.7 Quality Assurance

Daily portal films or online radiographic imaging will be performed during therapy. 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).

5.3 Investigational Product

Clinical supplies of nivolumab will be provided by Bristol-Myers Squibb as part of standard of care as summarized below

Product Description.

Product Name and Potency	Dosage Form
NIVOLUMAB 3mg/kg	Solution for Injection

5.4 Storage

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

5.5 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 Study Procedures

	Eligibility	Pre-response Assessment			Post-response Assessment				
		Week (from start of nivo.)			Week				
		1	4	8-12	0 (if RT)	1	4, 8	12	FU[2]
Tests and Observations									
History, PE, VS	X		X	X	X		X	X	X
ECOG Performance Status	X		X	X	X		X	X	X
Toxicity Assessment			X	X			X	X	X
FDG PET/CT	X		X[1]	X			X[2]		X[3]
Laboratory									
Correlative Biomarkers	X	X	X	X	X	X	X	X	
CBC w/ differential	X		X	X	X		X	X	X
Complete metabolic panel	X		X	X	X		X	X	X
Standard-of-care laboratory tests appropriate for nivolumuab	X		X	X	X		X	X	X
Pregnancy Test	[4]				X[4]				

[1]Research FDG PET/CT at time of week 1 correlative biomarkers blood draw.
[2]Week 8-12.
[3]As clinically indicated.

[4]Pregnancy test is required only for women of child-bearing potential. A serum or urine test can be performed.

6.1 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 nivolumab.

Screening includes:

- Informed consent.
- Confirmed ECOG performance status of 0, 1 or 2.
- Complete medical history.
- Standard-of-care laboratory tests appropriate for nivolumab.
- Documentation of pathological, imaging, and clinical confirmation of relapsed/refractory Hodgkin lymphoma.

6.2 Study Intervention Phase

6.2.1 Procedures Prior to Protocol Therapy

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

Baseline standard of care procedures that include:

- Standard-of-care history, physical examination, and laboratory tests as clinically indicated
- FDG-PET
- Correlative biomarkers

6.2.2 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.

All women of child-bearing potential will be asked on the day of the PET/CT scan if they might be pregnant; this is a standard question for all patients who will be undergoing PET/CT scans due to the radiation exposure associated with the scan. If the patient is unsure about whether she might be pregnant then a urine pregnancy test will be performed prior to the injection of FDG.

The patient will be made comfortable in a preparatory room. Approximately 15 mCi of FDG will be administered according to the standard procedures used for clinical FDG PET/CT at the Hospital of the University of Pennsylvania. All patients will undergo a skull base to thighs PET/CT scan starting at approximately 60 minutes after FDG injection. A brief low-dose CT scan will be acquired according to standard PET/CT imaging procedures; this is used for attenuation correction and anatomical localization of findings in the PET scan. This can be performed either before or after the PET transmission scan. There are no separate diagnostic CT scans performed as part of this research.

A total of at least 3 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 nivolumab 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.

- Post-therapy: Approximately 1 week following the start of nivolumab, a post-therapy FDG PET/CT will be obtained. This PET/CT will be obtained for study purposes, to assess glycolytic activity at sites of metastatic disease at an early time point. The results from this scan will not be reported to the participant, and will have no impact on the treatment decisions made by the treating physician.

- Response assessment: At weeks 8-12 after the start of nivolumab, FDG PET/CT will be obtained for response assessment. For patients undergoing radiotherapy, an additional FDG PET/CT will be obtained at weeks 8-12 after the delivery of radiation. Subsequent FDG PET/CT(s) will be obtained as clinically indicated in follow-up.

Adverse events that are grade 3 or higher will be recorded post injection of the radiotracer to the completion of the imaging exam.

6.2.3 Procedures During Nivolumab Administration

As per standard of care, patients will be seen by a physician, advanced practice provider, or registered nurse prior to nivolumab infusion and a toxicity assessment will be performed. The following laboratories will be performed prior to infusion every 4 weeks:

- Standard-of-care laboratory tests appropriate for nivolumab
- Correlative biomarkers

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

6.2.4 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 study coordinator in conjunction with the PI to determine toxicities, including the grade and attribution to radiation.

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

6.3 Follow Up Phase of the Study

6.3.1 Image Interpretation

Static images will be reconstructed using standard procedure and analyzed by visual inspection and standardized uptake value (SUV) analysis. The tumor avidity, as estimated by the SUVmax, of up to 6 lesions will be measured on each FDG PET/CT scan. Patients will also be grouped based on a positive flare response (greater than 20% increase in SUVmax) or negative flare response (less than 20% increase in SUVmax).

6.3.2 Response Criteria

Response and progression will be evaluated in this study using the revised International Working Group criteria proposed by Cheson *et al.* (Revised Response Criteria for Malignant Lymphoma).[23] The irradiated index lesion is not included in this determination; however, tumor response of this lesion will be assessed and tabulated separately using criteria from Cheson *et al.*[23]

6.3.2.1 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.

6.3.2.2 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.

6.3.2.3 Measurement of Effect

6.3.2.3.1 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).

6.3.2.3.2 Non-Target Lesions

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

6.3.2.4 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.

6.3.2.4.1 Evaluation of target and non-target lesions

Evaluation of target and non-target lesions for response will be performed according to Cheson *et al.*[23] (criteria reproduced below):

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

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

6.3.2.4.2 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.

6.3.3 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.

6.4 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.

6.5 Subject Withdrawal

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward event occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 – Other Procedures. A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment

- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

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

6.5.1 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.

6.6 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 will include all of the items indicated for the planned final visit.

7 Study Evaluations and Measurements

7.1 Physical Examination

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.2 Vital Signs

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

7.3 Pregnancy Testing

Females of childbearing potential must have a negative serum or urine beta human chorionic gonadotropin (β-hCG) pregnancy test result within 15 days prior to the starting radiation therapy and must agree to use an effective contraception method during the study and for 6 months following the last dose of nivolumab; 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 6 months following the last dose of study drug.

7.4 Efficacy Evaluations

Efficacy will be evaluated based on the Response Criteria described in Section 6.3.2~~6.3.1~~

7.5 Safety Evaluations

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

8 Statistical Design

This is a single arm Phase II clinical trial for relapsed/refractory Hodgkin lymphoma patients receiving nivolumab followed by either: a) continued nivolumab monotherapy if patient achieves an induction complete response (CR) scored at week 8, or b) RT (4 Gy x 2 fractions) plus continued nivolumab for patients who achieve <CR after induction. In the RT group, a second response assessment is undertaken at week 16, to determine the number of patients who have achieved CR. In both groups, nivolumab is continued until disease progression, drug intolerance, or at the discretion of the treating medical oncologist.

8.1 Primary Objective

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

8.2 Secondary Objectives

1. To determine the nivolumab induction CR rate
2. To determine the post-RT + continued nivolumab CR rate
3. To determine the time to best response
4. To determine duration of best response
5. To estimate progression free survival, overall survival and disease free survival
6. To evaluate safety and adverse events

8.3 Exploratory Objectives

1. To evaluate baseline and post-treatment changes in biomarkers and determine whether biomarker changes are associated with clinical outcomes.
2. To evaluate tumor FDG uptake and determine whether FDG "flare" is associated with clinical outcomes.

8.4 Primary Endpoint

The primary endpoint is the overall CR rate, defined as the total number of CRs after nivolumab induction plus the total number of CRs after RT + continued nivolumab in those patients with <CR after induction, divided by the total number of patients treated on the study. The Cheson criteria will be used to score response.

8.5 Secondary Endpoints

1. The nivolumab induction CR rate is defined as the proportion of patients who achieve CR after nivolumab induction, at the week 8 evaluation.
2. The post-RT + continued nivolumab CR rate is defined as the proportion of patients who achieve CR after RT + continued nivolumab, at the week 16 evaluation (8-12 weeks post-RT). All patients who had <CR are eligible to receive RT. The denominator will include all eligible patients, regardless of whether 2 fractions of RT were administered.
3. 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 nivolumab for another 8 weeks.
4. Duration of best response is defined from date of best response to date of of disease progression, death due to any cause of last patient contact alive and progression-free.
5. 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.
6. Overall survival is defined from date of study entry to date of death due to any cause of last patient contact alive.

7. Disease-free survival is defined from date of CR to date of disease progression, death due to any cause of last patient contact alive and disease-free. DFS is only computed for CR patients.
8. Toxicities will be graded and tabled separately by induction or post-RT.

8.6 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. Tumor FDG uptake will be measured on PET/CT at baseline and at 1-2 weeks after initiation of nivolumab. Based on change in tumor FDG uptake after initiation of nivolumab, FDG "flare", will be score as absent/present. FDG "flare" will likely be defined by >20% increase in tumor FDG uptake. This definition may be modified for the observed distribution of changes in tumor FDG uptake on our study.

8.7 Interim Analysis

No interim analysis is planned.

8.8 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 overall CR rate and 95% exact confidence interval will be calculated. Following an intent to treat analysis, all patients who received at least 1 dose of nivolumab are included in the analysis of the primary endpoint. Based on an exact binomial test, the number of patients with CR will determine whether the null hypothesis will be rejected (see Sample Size/Power below).
3. The nivolumab induction CR rate and post-RT + continued nivolumab CR rate and 95% confidence intervals will also be calculated.
4. Time to best response and duration of best response will be calculated and summarized separately for CR, PR, SD and PD patients.
5. Progression free survival, overall survival and disease-free survival will be estimated by the Kaplan-Meier method. Disease free survival will be computed by landmark analysis for two distinct groups: 1) DFS from week 8, for patients who achieved induction CR and 2) DFS from week 16, for patients who achieved CR after RT + nivolumab.
6. 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 induction nivolumab, post-induction nivolumab or post-induction RT + continued nivolumab

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 nivolumab 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). Tumor FDG uptake on PET/CT, from baseline to 1 week after nivolumab will be compared. Student's t-test or non-parametric Wilcoxon rank sum test will be employed.

2. Change in tumor FDG uptake from baseline to week 1, will be assessed by paired t-test or Wilcoxon signed rank test.
3. The association between binary FDG "flare" and progression-free & overall survival will be tested using log rank test. Cox regression will be used to assess the effect of continuously scaled FDG change. For all survival analyses, a landmark analysis will be performed. Here, PFS or OS are defined from a landmark, which is 1-2 weeks after initiation of nivolumab.
4. The association between binary FDG "flare" and response will be tested by Fisher's exact test.
5. The association between binary FDG "flare" and biomarker changes will be assessed by Wilcoxon rank sum test.

8.9 Sample Size/Power

With 25 patients, there is 81% power to detect a difference of 20% assuming a null hypothesis that the CR rate = 10% versus an alternative hypothesis that the CR rate = 30% using a one-sided exact test with a 5% significance level. We will reject the null hypothesis if 6 or more of 25 patients achieve a CR. The actual significance level for this exact test procedure is 3%.

9 Safety and Adverse Events

9.1 Definitions

9.1.1 Adverse Event

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Concurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the

other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

9.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

9.3 Relationship of AE to Study

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal

relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the study product, is also an adverse event. The Principal Investigator or an appropriate designee will determine the relationship of the adverse event.

9.4 Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

Investigators must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

9.4.1 Investigator Reporting: Notifying the Penn IRB

This section describes the requirements for safety reporting by investigators who are Penn faculty, affiliated with a Penn research site, or otherwise responsible for safety reporting to the Penn IRB. The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Penn IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

  Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

  AND

  Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Reporting Process

Unanticipated problems posing risks to subjects or others as noted above will be reported to the Penn IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding

its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Serious, unexpected drug-related adverse events will be reported to the University of Pennsylvania IRB, and the University of Pennsylvania Cancer Center Data and Safety Monitoring Committee (DSMC) reporting guidelines as is required by each board. Grade 3 or higher adverse events must be reported within 10 days of knowledge of the event. All unexpected deaths must be reported within 24 hours of knowledge of this event. All other deaths must be reported within 30 days of knowledge of this event. The DSMC has outlined the following exceptions:

- Grade 3 or 4 events that are judged by a study investigator to be clearly unrelated to protocol therapy andoccur in organ systems receiving less than 5% of the prescribed treatment dose.The reason for determining that the event is unrelated must be clearly documented in the EMR.
- Grade 3 or 4 events that are probably or definitely related to progression of disease as judged by a study investigator. The fact that this event is related to disease progression must be clearly document in the EMR.
- Grade 3 or 4 events that are probably or definitely related to an FDA approved agent used in conjunction with radiation based on its current labeling and occur in organ systems receiving less than 5% of the prescribed treatment dose. The fact that this event is related to the FDA approved agent must be clearly documented in the EMR.

Adverse events (AE) and Serious Adverse Events (SAE) will use the descriptions and grading scales found in the revised **NCI Common Terminology Criteria for Adverse Events (CTCAE)**. This study will utilize the CTCAE v5.0 for adverse event reporting. All appropriate treatment areas will have access to a copy of the CTCAE v5.0 and a copy can be accessed at the web site: http://ctep.cancer.gov/.

9.5 Stopping Rules

There are no stopping rules in this Phase II trial.

9.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9.6.1~~9.7.1~~). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

The Medical Monitor will be Dr. Andrzej Wojcieszynski, a physician who is not directly involved in the trial and is not part of the Lymphoma Oncology Group at Penn. Because of Dr. Wojcieszynski'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, appropriateness of dose escalation 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 a minimum of every 6 months (or more 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.

9.6.1 Data and Safety Monitoring Plan

The Abramson Cancer Data and Safety Monitoring Committee is charged with the responsibility of reviewing all SAEs, deviations, Medical/Safety Monitoring reports for all cancer based protocols conducted at the University of Pennsylvania. The DSMC reviews these document and data and makes recommendation necessary to ensure subject safety and study integrity. Additionally, the DSMC monitors and audits the progress and conduct of all cancer based studies in accordance with their NCI approved Institutional Data and Safety Monitoring Plan.

10 Study Administration, Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.2 Data Collection and Management

Source data is all information, original records of clinical findings, observations, or other activities in a research study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents and may be paper, electronic or a combination of both. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Electronic case report forms will be developed and completed in Velos in lieu of paper case report forms.

10.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

10.4 Records Retention

Federally Funded Research or Non-IND/IDE Research:
The DHHS regulation (45 CFR 46.115) states that records relating to research conducted or supported by any Federal department or agency shall be retained for at least 3 years after completion of the research.

The FDA regulation (21 CFR 56.115) is virtually identical; it also states that IRB records must be retained for at least 3 years after completion of the research for these same types of studies.

Records for this study will be maintained in a secure location with access limited to the investigators and the study specific research team for 3 years from the date of full study terminations. If necessary, after the first year of termination, records may be moved to an off-site secure storage facility.

HIPAA Retention Period (45 CFR164.530(j):
Protected Health Information (PHI) Research Requests (HIPAA1-008): Records documenting research requests, privacy board review or privacy officer expedited review, background material, and acceptance or denial of request. Retain 6 years after research completed.

Protected Health Information Disclosure Records (HIPAA1-009): Documenting the release of PHI, including **both authorized and unauthorized** releases. Should include the date of release, to whom the information was released, and the circumstances of the release. Retain 6 years after research completed.

Maintenance of HIPAA records is independent of the regulations for clinical study records. All records of PHI research requests and any type of release will be maintained for 6 years after the research is fully terminated.

11 Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring Plan

The study PI is responsible for ensuring the ongoing quality and integrity of the research study. In addition, this study will be monitored or audited in accordance with Abramson Cancer Center's NCI approved Institutional Data and Safety Monitoring Plan.

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be maintained in the study specific Regulatory Binder which contains "Essential Study Documents". In addition, NCI requires all cancer based studies to have an independent scientific review. This protocol must be reviewed and fully approved by the Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) prior to enrolling any subjects. Documentation of CTSRMC approval must also be maintained in the study specific Regulatory Binder.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB and CTSRMC for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed and dated by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12.1 Risks

There are potential risks both from nivolumab and from low-dose radiotherapy.

Risks of nivolumab include fatigue, dermatitis, and such autoimmune dysfunction as pneumonitis, colitis, hepatitis, nephritis, thyroid dysfunction, pituitary dysfunction, and others. There is also the risk of myalgias, arthralgias, weakness, renal failure, ophthalamic dysfunction, and other toxicities. As with any medication, there is a risk of hypersensitivity reaction; medications to treat hypersensitivity reactions should be immediately available, including epinephrine, diphenhydramine, methylprednisolone and nebulized albuterol. Finally, there is a risk of toxicities not listed, as well as CTCAE grade 3 or higher toxicities, up to and including death. Pre-infusion examinations and laboratory assessment, as well as peri-infusion monitoring, are carried out with the express goal of detecting toxicities.

Risks of low-dose radiotherapy are very low, both in frequency and in severity. Nonetheless, there are rare risks to organs at risk proximal to the treatment field, both in the acute phase and in the late phase. Finally, there is a risk of toxicities not listed, as well as CTCAE grade 3 or higher toxicities, up to and including death. Radiation treatment planning, as described in Section **Error! Reference source not found.**6, is carried out with the express goal of minimizing toxicity to organs at risk, and low-dose radiotherapy is extremely safe and well-tolerated.

The risk of one additional FDG PET/CT poses a very small risk related to radiation exposure from FDG positron emission. This radiation exposure is orders of magnitude smaller than the low-dose radiotherapy described above. FDG PET/CT scans are a standard clinical procedure for patients with HL.

12.2 Benefits

This trial may have benefits both for the study participants and for society in general.

Study participants may have improved treatment response with the addition of radiation to nivolumab, leading to improved overall survival.

Society in general may benefit from the knowledge generated by this trial. Such knowledge includes understanding whether:

- The addition of radiation to nivolumab can improve treatment response in patients with r/r HL
- The addition of radiation to nivolumab can improve overall survival in patients with r/r HL
- Phase III clinical trials can be undertaken to assess the addition of radiation to nivolumab to improve r/r/ HL treatment response and overall survival

12.3 Risk Benefit Assessment

The most serious risks listed above are felt to be less likely to occur. Moreover, as outlined above, there are a number of mechanisms in place to limit potential risks and maximize patient safety. Ultimately, for the study overall and for study participants individually, the potential benefits outweigh the potential risks.

12.4 Informed Consent Process / HIPAA Authorization

Subjects will be recruited from investigator clinical practices. Subjects will undergo an informed consent process in accordance with Good Clinical Practice Guidelines and be given ample time to make an informed decision. Informed consent will be obtained prior to the performance of any study procedures. Subjects must meet all of the inclusion and none of the exclusion criteria. Eligibility will be verified by a study investigator on a case report form. Subjects will be encouraged to ask questions of the investigator and research team as they arise throughout the duration of study participation. Consent will be obtained by an investigator or a member of the trained research staff designated by the principal investigator.

13 Study Finances

13.1 Funding Source

This study will be supported with internal funds from the Department of Radiation Oncology.

13.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

13.3 Subject Stipends or Payments

We will pay for the cost of parking for patients parking in the PCAM patient garage, if not already covered through the hospital, on the day of the research PET/CT scan. We will not pay the patient for participation.

14 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study. Rule regarding the publication of results from this study are covered in the sponsored research agreement between Merck and the University of Pennsylvania.

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RADVAX™ FOR RELAPSED/REFRACTORY HODGKIN LYMPHOMA: A PHASE II TRIAL OF NIVOLUMAB + LOW DOSE RADIOTHERAPY FOR INCOMPLETE RESPONDERS

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UPCC Number:

04418

IRB Number:

828966

Version: 9/27/2018
Amend: 1/14/2019
Amend: 7/28/2020
Amend: 1/29/2021

Contents

List of Abbreviations

For example: LIST OF ABBREVIATIONS-list alphabetically.

ACC: American College of Cardiology

AE: Adverse event

DMC: Data Monitoring Committee

DM: Diabetes Mellitus

ECG: Electrocardiogram

Study Summary

Title	RADVAX™ FOR RELAPSED/REFRACTORY HODGKIN LYMPHOMA: A PHASE II TRIAL OF NIVOLUMAB + LOW DOSE RADIOTHERAPY FOR INCOMPLETE RESPONDERS
Short Title	Lymphoma RadVax™
Protocol Number	UPCC IRB
Phase	Phase II
Methodology	Open-label
Study Duration	2 years
Study Center(s)	Single Center
Objectives	This is a Phase II single-arm, single-site, open label clinical trial with r/r HL patients, aimed to determine whether a RadVax approach using low-dose RT added to nivolumab can improve response among patients who do not achieve a CR to nivolumab alone. The long-term goal is to develop an effective regimen for r/r HL patients.
Number of Subjects	25
Main Inclusion Criteria	• Pathologically confirmed Hodgkin lymphoma for whom nivolumab is clinically indicated. • Relapsed/refractory disease. • ≥2 sites of measurable disease, at least one outside of intended RT fields. • Age ≥ 18 years. • ECOG performance status of 0-2.

BACKGROUND AND STUDY RATIONALE

This study is a Phase II clinical trial that will be conducted in full accordance all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations including, as applicable, 45 CFR 46, 21 CFR Parts 50, 54, 56, 312, 314 and 812 and Good Clinical Practice: Consolidated Guidelines approved by the International Conference on Harmonisation (ICH). All episodes of noncompliance will be documented.

Introduction

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.[1]

1.1 Background and Relevant Literature

Immunotherapies have emerged as a very promising option for patients with relapsed/refractory (r/r) Hodgkin lymphoma (HL) who have progressed despite second line chemotherapy, stem cell transplants and/or surface-receptor targeted agents such as brentuximab. Activity of PD-1 inhibitors in r/r HL has been documented,[2, 3] resulting in FDA approval of nivolumab for this population in May 2016. Nivolumab 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 thought to be 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. 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) 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. 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. We plan to study the combination of low dose radiation with nivolumab in patients with relapsed/refractory Hodgkin lymphoma.

1.2 Name and Description of the Investigational Product

Nivolumab is a PD-1 inhibitor that is now FDA-approved for r/r HL and is considered a standard of care for select patients with r/r HL. Nivolumab was tested as single-agent monotherapy in a Phase II trial of 80 HL patients who progressed after stem cell transplant and BV, demonstrating 9% CR, 58% PR, and 23% SD rates with an impressive 6 month PFS of 76.9%.[3] Despite its FDA approval for r/r HL, patients who progress after nivolumab have limited additional options. Although pembrolizumab, also a PD-1 inhibitor, and more recently FDA-approved for r/r HL in March 2017, the study population was not previously exposed to PD-1 inhibition. Interestingly, the KEYNOTE 087 trial on which the approval was based, had a 22% CR and 47% PR for a similar overall response rate of 69%. We chose to use nivolumab for this study due to the greater experience our clinicians have in r/r HL patients with this agent due to the earlier FDA approval.

1.3 Radiotherapy and Immune Activation

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, whereas PD-L2 is expressed primarily on professional antigen presenting

cells.[4] 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. [5] 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.[6, 7]) 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.[8] 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, early results from our trial of ipilimumab and SBRT in melanoma showed disappointing abscopal effects (22%) when RT was delivered prior to initiating the drug (A. Maity, personal communication). Careful preclinical sequencing experiments have shown that PD-1 inhibition combined with fractionated RT is less effective when given after or near the end of a multi-fraction RT course.[9] 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.[6] Our plan is to deliver radiation after the first response assessment following 2 months of nivolumab. Assuming that immune modulation should already be in effect when RT is fractionated, we will deliver 2 fractions of 4 Gy at that time for patients who do not achieve anatomic CR. This strategy allows patients with complete anatomic response (CR) to remain on the drug alone while patients without CRs can be potentiated with low dose RT. Another potential strategy would be to wait to radiate after disease progression on immunomodulatory therapy, but preclinical observations support the early use of RT (approximately 2 months into therapy) 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 [6]. Ultimately, the timing of the addition of RT to a therapy with known efficacy comes down to clinical practicality. Thus, the study design allows integration of RT when less than a complete response (CR) is noted after initiating immunotherapy.

1.3.1 Clinical Data to Date

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.*[1] The impact of the therapy on the irradiated lesion and the non-irradiated lesion(s) was evaluated using two standard modalities: (i) ^{18}F-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.*[10].

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. However, ipilimumab-related side effects were significant, and the combination of ipilimumab and RT showed only modest improvement over what is reported in the literature. Although this study was not designed to assess response, the results do not show that the majority of the patients have substantially reduced size of their unirradiated lesions in response to radiation.

1.4 Dose Rationale

Nivolumab has been studied in r/r HL patients at a dose of 3 mg/kg, infused over 60 minutes, administered every 2 weeks.[2, 3] This had been a standard dose regimen for nivolumab across disease sites and was the manufacturer- and FDA-recommended dose regimen for r/r HL. (However, the FDA recently approved an every-4-week regimen of nivolumab, 480 mg infused over 30 minutes.) Treating physicians will have the discretion of treating every 2 weeks or every 4 weeks. Among patients tested for efficacy, grade 3 or higher toxicities included: thrombocytopenia in 33%, increased lipase in 12%, lymphopenia in 7%, neutropenia in 6%, and pneumonia in 5%.[11] Any grade toxicities included upper respiratory tract infection in 48%, fatigue in 43%, neutropenia in 37%, fever in 35%, cough in 35%, thrombocytopenia in 33%, lymphopenia in 32%, increased AST in 32%, and rash in 31%, among other toxicities.[11] For patients who subsequently undergo allogeneic hematopoietic stem cell transplantation, toxicity data are unclear, however there is a concern for increased severe acute graft versus host disease.[11]

1.5 Early FDG PET/CT Imaging

Following cancer response to immunotherapy presents unique challenges compared to conventional cytotoxic chemotherapies. Studies of anti-CTLA4 therapy with ipilimumab in melanoma revealed that a significant subset of responding tumors may exhibit non-traditional patterns of response that can confound interpretation on CT.[12] An example of a non-traditional response is the initial increase in size of the tumor over the course of several months with a later decrease in tumor size. In these cases, the initial increase in size of the tumor is thought to be on the basis of tumor infiltration by immune cells and can be mistaken for tumor growth on CT. Another example of a non-traditional tumor response to immunotherapy is a decrease in the size of the primary tumor with the development of new small lesions. This pattern has also been observed to correspond with favorable outcome in the setting of immunotherapy but would be considered disease progression by conventional measures.

An apparent increase in tumor burden that later resolves or decreases has been called a flare response, and is hypothesized to result from a transient immune-cell infiltrate in the tumor stroma. Several studies provide support for this hypothesis, including a case study of an ipilimumab-treated patient with apparent progressive disease at 12 weeks, in which the histological analysis of a lung nodule demonstrated a T-

cell infiltrate, extensive necrosis, and no residual tumor cells.[13] Thus, a different set of response criteria have been developed, termed immune-related response criteria (irRC), that incorporate the possibility of a transient flare response, as well as a delayed immune response, into the assessment.[12, 14] While irRC has been shown to be an improvement over conventional RECIST (Response Evaluation Criteria In Solid Tumors) in the setting of immunotherapy, irRC still does not accurately identify all responders and non-responders. This is partly due to the fact that morphological changes to the tumor from immunotherapy can take several months to manifest. Thus, a timelier and more accurate measure of response to immunotherapy is needed.

1.5.1 [^{18}F]FDG PET as a Marker of Cancer and Inflammation

2-Deoxy-2-[^{18}F]fluoro-D-glucose (FDG) is an ^{18}F analogue of glucose that serves as a PET radiotracer of cellular metabolism. FDG enters the cell through cell surface glucose transporters and becomes trapped within the cell following enzymatic phosphorylation by hexokinase. For decades, FDG has been employed to detect cancer exploiting a phenomenon known as the Warburg effect in which most malignancies preferentially produce ATP through a boost in extra- mitochondrial glycolysis, rather than mitochondrial oxidative phosphorylation, despite aerobic conditions. This metabolic switch, termed aerobic glycolysis, has a greater rate of glucose utilization albeit overall lower ATP yield, and provides the generation of key carbon precursors needed for the synthesis of nucleic acids, phospholipids, fatty acids, cholesterol and porphyrins.[15] As a result of the increased rate of glycolysis characteristic of the Warburg effect, most malignancies utilize more glucose (and FDG) than their non-transformed neighboring cells, which has led to the use of FDG PET/CT as a highly sensitive and moderately specific tool for the detection of occult metastatic disease.

It has recently been recognized that immune activation results in a similar cellular metabolic switch from oxidative phosphorylation to aerobic glycolysis. This occurs with both the innate and adaptive immune activation. For example, when activated using TLR ligands or proinflammatory cytokines, neutrophils, dendritic cells, and macrophages have been demonstrated to switch their metabolism from oxidative phosphorylation to aerobic glycolysis.[16] Similarly, following TCR stimulation, lymphocytes increase glucose utilization by several orders of magnitude and switch glucose metabolism from oxidative phosphorylation to aerobic glycolysis.[17, 18] Interestingly, anti-inflammatory subpopulations of both the innate and adaptive immune system, such as M2 macrophages, regulatory T cells and quiescent memory T cells, demonstrate a predominant use of oxidative phosphorylation rather than aerobic glycolysis as opposed to their inflammatory counterparts such as activated macrophages and T-helper cells.[19]

The upregulation of aerobic glycolysis in immune activation is readily visualized with FDG PET/CT imaging. Inflammatory conditions such as infection, rheumatoid arthritis and sarcoidosis yield intense avidity for FDG that compares with or exceeds that of most malignancies.[20, 21] In fact, a significant limitation to the use of FDG PET/CT in cancer restaging has been interference of the tumor FDG signal by post-therapeutic inflammatory tissues including surgical changes, talc pleurodesis, and radiation therapy.[22]

In this study, we propose utilizing FDG PET/CT to assess the immunotherapy response to nivolumab by detecting the superimposed increased metabolism within the tumor presented by a therapy-induced infiltrating population of glucose avid activated immune cells. FDG PET/CT studies are typically performed at approximately 8-12 weeks following the initiation of nivolumab, and the probability of seeing a flare response on these clinical studies is very low.

We propose looking for a flare response at about 1 week following the start of nivolumab. This time point is used in an ongoing clinical trial with lenalidomide and non-Hodgkin lymphoma. This was developed after a patient treated with lenalidomide for diffuse large B-cell lymphoma demonstrated a flare response on FDG PET/CT at 1 week, with a complete metabolic response on subsequent PET/CT at 5 weeks.

No significant change is expected in the tumor's inherent basal glycolytic activity over the short interval between the baseline FDG PET/CT and the post-therapy PET/CT. Therefore, we hypothesize that the flare response can be visualized with FDG PET/CT by detection of a superimposed burst of tumoral glycolytic activity resulting from immunotherapy-induced immune infiltration. If successful, this data will help to determine the ideal time point for visualization of the flare response, test the potential for the flare response to serve as a biomarker for outcomes (e.g. which patients may stand to benefit from RT priming using RadVax concept), and contribute to our understanding of nivolumab's mechanism of action.

2 Study Objectives

This is a Phase II single-arm, single-site, open label clinical trial with r/r HL patients, aimed to determine whether a RadVax approach using low-dose RT added to nivolumab can improve response among patients who do not achieve a CR to nivolumab alone. The long-term goal is to develop an effective regimen for r/r HL patients.

2.1 Primary Objective

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

2.2 Secondary Objectives

1. To determine the nivolumab induction CR rate.
2. To determine the post-RT + continued nivolumab CR rate.
3. To determine the time to best response.
4. To determine duration of best response.
5. To estimate progression free survival, overall survival and disease free survival.
6. To evaluate safety and adverse events.

2.3 Exploratory Objectives

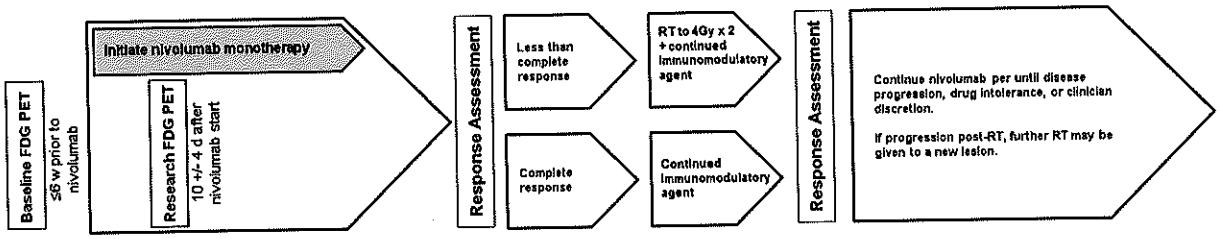
1. To evaluate baseline levels and post-treatment changes in biomarkers and determine whether biomarker changes are associated with clinical outcomes.
2. To evaluate tumor FDG uptake and determine whether FDG "flare" is associated with clinical outcomes.

3 Investigational Plan

3.1 General Design

This study is an open-label Phase II trial of Hodgkin lymphoma patients receiving initial treatment with the immunomodulatory agent, nivolumab, followed by low-dose (4 Gy x 2) involved-site radiotherapy in subjects with less than an anatomic CR after the first restaging scan. Patients with anatomic CR will continue nivolumab alone without radiotherapy. Eligible patients will have r/r disease with at least 2 sites of measurable disease, and must be eligible for treatment with nivolumab. Biosamples (blood and, where available, tumor) will be collected as outlined below. Nivolumab will be continued after RT until disease progression, drug intolerance, or at the discretion of the treating medical oncologist.

Research PET/CT will be performed approximately 1 week after nivolumab is started to assess for immunotherapy-related glycolytic activity (tumor "flare") at sites of disease using the FDA-approved clinical Positron Emission Tomography (PET) radiotracer, [^{18}F]fluorodeoxyglucose (FDG).



Registration

↓

Pre-study

- Initial baseline FDG PET/CT (standard of care) </=6 weeks prior to nivolumab administration.
- Collection of blood and, if available, tumor, for correlative biomarkers.

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Study Phase – Nivolumab

- Administration of nivolumab on day 1 and continued per standard of care and institutional practices.
- Continue blood sample collection for correlative biomarkers at week 1.
- Research FDG PET/CT at the time of week 2 blood sample collection.
- Continue blood sample collection for correlative biomarkers at weeks 4, 8, and 12.

↓

Study Phase – Response Assessment

- Repeat PET/CT at 8-12 weeks (standard of care response assessment).
- If CR, continue nivolumab (with continued biomarker collection) until confirmed disease progression, drug intolerance, or at the discretion of the treating medical oncologist.
- If less than CR, proceed to Study Phase – Radiotherapy.

↓

Study Phase – Radiotherapy

- Prior to RT, blood sample collection is done for correlative biomarkers.
- RT to 4 Gy x 2 fractions to a single lesion.
- Continue nivolumab on day 1 and continue per standard of care and institutional practices.

↓ ↑

Study Phase – Post-radiotherapy Follow Up

- Continue nivolumab.
- Continue blood sample collection for correlative biomarkers at 1, 4, 8, and 12 weeks post-RT.
- Repeat PET/CT (response assessment in non-target lesion) at 8-12 weeks post-RT.
- CR, PR or SD continue on nivolumab until confirmed disease progression, drug intolerance, or at the discretion of the treating medical oncologist.

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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.

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Primary Objective

- Determine the overall CR rate.

	Pre-trial	Induction Assessment					Post-induction Assessment				
		Week					Week				
		0	1	2	4	8-12	0	1	4	8	12
Nivolumab[3]		X			X	X	X		X	X	X
RT (if <CR)							X				
FDG PET/CT	X			X[1]		X				X	
Correlative biomarkers[2]	X		X	X	X	X	X	X	X	X	X

[1]Research FDG PET/CT to be done at time of week 1 correlative biomarkers blood draw.
[2]Collect times are approximate due to appointment scheduling.
[2] Nivolumab administration will be at the discretion of the treating physician.

3.1.1 Screening Phase

As described in greater detail in Section Error! Reference source not found.4.3, subjects will be recruited from the oncology practice at Penn Medicine. The treating radiation oncologist or medical oncologist will approach and inform the patient about the study, thereby initiating the informed consent process. A qualified member of the research team will initiate the formal consent process. A series of questions will be asked by the person obtaining consent to verify patient eligibility based upon the criteria outlined in Sections Error! Reference source not found.4.1 and Error! Reference source not found.4.2. Eligibility is confirmed with the study investigator or delegate.

3.1.2 Study Intervention Phase

Nivolumab 3 mg/kg will be administered on day 1 (pre-response assessment week 0) and on day 1 and continued per standard of care and institutional practices. At the week 1 biomarker collection, research FDG PET/CT will be performed to assess for FDG "flare." At week 8-12, PET/CT will be performed for the first response assessment. If a complete anatomic response is seen, nivolumab monotherapy will be continued on day 1 and continued per standard of care and institutional practices.

By contrast, if at week 8 less than a complete anatomic response is seen, radiotherapy to 4 Gy x 2 fractions will be administered (post-response assessment week 0). The patient will be evaluated by a radiation oncologist while on treatment, and toxicities will be recorded. Nivolumab will be continued on day 1 and continued per standard of care and institutional practices.

In either scenario, a second response assessment will be conducted ~8-12 weeks after the first response assessment. In either scenario, nivolumab monotherapy will be continued at the discretion of the treating medical oncologist.

If there is less than CR post-RT and there is an additional untreated non-target lesion that can be followed, radiotherapy can again be administered when disease progresses to a previously untreated lesion, after which the patient will continue on the post-RT follow-up algorithm.

3.1.3 *Follow Up Phase*

The patient will be seen in follow-up on the same day as nivolumab infusion. For those patients receiving RT, the patient will be seen once while on treatment. Patients will otherwise be seen at the discretion of the treating medical oncologist or designee and/or radiation oncologist. The patient will then continue to be followed off-study per the usual follow-up schedule at the discretion of the treating physician.

3.2 Study Endpoints

3.2.1 Primary Study Endpoint

- Overall CR rate.

3.2.2 *Secondary Study Endpoints*

- Nivolumab induction CR rate.
- Post-RT + nivolumab CR rate.
- Progression-free survival (PFS) for entire study population.
- Overall survival (OS) for the entire study population.
- Disease free survival (DFS) for the nivolumab induction CR cohort and for the RT + continued nivolumab CR cohort.
- Duration of immunotherapy use for the entire study population, nivolumab only cohort, and nivolumab + RT cohort.
- Time to best response.
    - Duration of response, Biosamples (blood and, where available, tumor) 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.
- Change from baseline in tumor FDG uptake on PET/CT after initiation of nivolumab.
- Association between change in tumor FDG uptake and progression-free and overall survival.
- Based on change in tumor FDG uptake after initiation of nivolumab, determine which patients have FDG "flare."
- Association between FDG flare and response, progression-free survival, overall survival, and biomarker changes.
- Exploratory analyses will be conducted in changes in markers between induction nivolumab responders (CR) and non-responders (<CR), between post-RT responders (CR/PR vs. <PR), and between RT and no-RT cohorts.

4 Study Population and Duration of Participation

4.1 *Inclusion Criteria*

- Pathologically confirmed Hodgkin lymphoma for whom nivolumab is clinically indicated.
- Relapsed/refractory disease.
- ≥2 sites of measurable disease, at least one outside of intended RT fields.
- Age ≥ 18 years.
- ECOG performance status of 0-2.
- Standard laboratory criteria for hematologic, and biochemical, and urinary indices within a range that, in the opinion of the physician, clinically supports enrollment of the subject on the trial.
- Patients of reproductive potential must agree to use an effective contraceptive method during participation in this trial.
- Ability to provide written informed consent.

4.2 *Exclusion Criteria*

- Subjects with contraindications to immune checkpoint therapy, as follows:

- Interstitial lung disease that is symptomatic or may interfere with the detection and management of suspected drug-related pulmonary toxicity.
- Prior organ allograft or allogeneic bone marrow transplantation.
- Pre-existing thyroid abnormality with thyroid function that cannot be maintained in the normal range with medication.
- Active autoimmune disease, except for vitiligo, type 1 diabetes mellitus, asthma, atopic
- dermatitis, or endocrinopathies manageable by hormone replacement; other autoimmune conditions may be allowable at the discretion of the principal investigator.
- Condition requiring systemic treatment with either corticosteroids.
    - Systemic steroids at physiologic doses (equivalent to dose of oral prednisone 10 mg) are permitted. Steroids as anti-emetics for chemotherapy are strongly discouraged
    - Intranasal, inhaled, topical, intra-articular, and ocular corticosteroids with minimal systemic absorption are permitted.
- Pregnant women, women planning to become pregnant and women that are nursing.

4.3 Subject Recruitment

Subjects will be recruited from the Oncology practices at Penn Medicine. The treating radiation oncologist or medical oncologist will approach and inform the patient about the study, thereby initiating the informed consent process. If the patient expresses interest in the study, the treating radiation oncologist or medical oncologist will contact a qualified member of the research team in the Radiation Oncology Department at the University of Pennsylvania and request availability for enrollment. A qualified member of the research team will initiate the formal consent process. This person will interview the potential subject with privacy considerations, explain the requirements of the study and provide a copy of the Informed Consent Form. The person obtaining consent will state the volunteer nature of research and advise the subject to take sufficient time to discuss the study if necessary before making their decision to sign the informed consent document. If a decision to participate is made, the informed consent form is signed. A series of questions will be asked by the person obtaining consent to verify patient eligibility. After eligibility is established, a subject study number will be issued. Eligibility is confirmed with the study investigator or delegate. All members of the research team will have successfully completed patient oriented research training. The consent process can be completed in person or via Telemedicine per University of Pennsylvania Health Systems telemedicine policy and procedures.

In addition, this trial will be listed on our web site as a formal protocol and information of its availability will be made known to treating professionals throughout our satellites and referring physicians.

4.4 Duration of Study Participation

The duration of the study is approximately 22-25 weeks, from the time of pre-trial assessment through the final end-of-study visit. The duration of the intervention phase of the study is approximately 20-23 weeks: 8-12 weeks for nivolumab monotherapy, 8-12 weeks for continued nivolumab monotherapy vs. RT plus nivolumab, with 3 weeks allowed for RT simulation and planning. An additional 8-12 weeks is appended for patients undergoing additional RT.

4.5 Total Number of Subjects and Sites

Recruitment will end when 25 subjects are enrolled with lesions that are measurable as defined in section 6.3.2. Based on published CR rates,[2, 3] it is expected that the induction CR rate in this study population is expected to be approximately 10%.

4.6 Vulnerable Populations:

Vulnerable populations are not specifically included in this research study. We do not anticipate enrolling prisoners.

5 Study Intervention

5.1 Description

Nivolumab is a highly selective, humanized monoclonal antibody (IgG4) that blocks PD-1. Nivolumab was tested as single-agent monotherapy in a Phase II trial of 80 HL patients who progressed after stem cell transplant and BV, demonstrating 9% CR, 58% PR, and 23% SD rates with an impressive 6 month PFS of 76.9%.[3] Nivolumab is now FDA-approved for r/r HL. The combination of nivolumab with radiation is based on the observation that RT can enhance immunomodulators in lymphoma.[5-7] Based on preclinical sequencing experiments,[6, 9] RT will be given after the first response assessment after 8-12 weeks of nivolumab in patients with less than CR. RT will be given in 2 fractions of 4 Gy each, to be delivered to an index site using an involved site paradigm.

5.2 Intervention Regimen

5.2.1 Nivolumab Administration

Nivolumab (3 mg/kg) will be administered as an IV infusion on day 1 and continued per standard of care and institutional practices. Nivolumab 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.

5.2.2 Radiotherapy Administration

Involved-site radiotherapy will be administered after the first response assessment following induction nivolumab. RT will be delivered in the Department of Radiation Oncology. All subjects will be immobilized as needed in a custom designed device in the appropriate position to isolate the index lesion. 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.

5.2.3 Target Contouring

Gross Tumor Volume (GTV) is defined as all known gross disease encompassing the selected index lesion. The GTV will consist of the index lesion 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. Volumes must be designed to allow for an additional measurable lesion to be excluded from the radiated volume (non-target lesion).

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.

5.2.4 Normal Structures

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

5.2.5 Dose Fractionation

All patients will be given 2 fractions of 4 Gy each over a period of 2-4 days, depending on the radiation oncology schedule, to the PTV as defined above.

5.2.6 External Beam Equipment and Beam Delivery

Radiation treatments will be administered at the University of Pennsylvania Department of Radiation Oncology. A radiation oncologist will check the first film on all fields. All set-up films will be permanently filed for all subjects.

5.2.7 Quality Assurance

Daily portal films or online radiographic imaging will be performed during therapy. 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).

5.3 Investigational Product

Clinical supplies of nivolumab will be provided by Bristol-Myers Squibb as part of standard of care as summarized below

Product Description.

Product Name and Potency	Dosage Form
NIVOLUMAB 3mg/kg	Solution for Injection

5.4 Storage

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

5.5 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 Study Procedures

	Eligibility	Pre-response Assessment			Post-response Assessment				
		Week (from start of nivo.)			Week				
		1	4	8-12	0 (if RT)	1	4, 8	12	FU[2]
Tests and Observations									
History, PE, VS	X		X	X	X		X	X	X
ECOG Performance Status	X		X	X	X		X	X	X
Toxicity Assessment			X	X			X	X	X
FDG PET/CT	X		X[1]	X			X[2]		X[3]
Laboratory									
Correlative Biomarkers	X	X	X	X	X	X	X	X	
CBC w/ differential	X		X	X	X		X	X	X
Complete metabolic panel	X		X	X	X		X	X	X
Standard-of-care laboratory tests appropriate for nivolumuab	X		X	X	X		X	X	X
Pregnancy Test	[4]				X[4]				

[1]Research FDG PET/CT at time of week 1 correlative biomarkers blood draw.
[2]Week 8-12.
[3]As clinically indicated.

[4]Pregnancy test is required only for women of child-bearing potential. A serum or urine test can be performed.

6.1 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 nivolumab.

Screening includes:

- Informed consent.
- Confirmed ECOG performance status of 0, 1 or 2.
- Complete medical history.
- Standard-of-care laboratory tests appropriate for nivolumab.
- Documentation of pathological, imaging, and clinical confirmation of relapsed/refractory Hodgkin lymphoma.

6.2 Study Intervention Phase

6.2.1 Procedures Prior to Protocol Therapy

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

Baseline standard of care procedures that include:

- Standard-of-care history, physical examination, and laboratory tests as clinically indicated
- FDG-PET
- Correlative biomarkers

6.2.2 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.

All women of child-bearing potential will be asked on the day of the PET/CT scan if they might be pregnant; this is a standard question for all patients who will be undergoing PET/CT scans due to the radiation exposure associated with the scan. If the patient is unsure about whether she might be pregnant then a urine pregnancy test will be performed prior to the injection of FDG.

The patient will be made comfortable in a preparatory room. Approximately 15 mCi of FDG will be administered according to the standard procedures used for clinical FDG PET/CT at the Hospital of the University of Pennsylvania. All patients will undergo a skull base to thighs PET/CT scan starting at approximately 60 minutes after FDG injection. A brief low-dose CT scan will be acquired according to standard PET/CT imaging procedures; this is used for attenuation correction and anatomical localization of findings in the PET scan. This can be performed either before or after the PET transmission scan. There are no separate diagnostic CT scans performed as part of this research.

A total of at least 3 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 nivolumab 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.

- Post-therapy: Approximately 1 week following the start of nivolumab, a post-therapy FDG PET/CT will be obtained. This PET/CT will be obtained for study purposes, to assess glycolytic activity at sites of metastatic disease at an early time point. The results from this scan will not be reported to the participant, and will have no impact on the treatment decisions made by the treating physician.

- Response assessment: At weeks 8-12 after the start of nivolumab, FDG PET/CT will be obtained for response assessment. For patients undergoing radiotherapy, an additional FDG PET/CT will be obtained at weeks 8-12 after the delivery of radiation. Subsequent FDG PET/CT(s) will be obtained as clinically indicated in follow-up.

Adverse events that are grade 3 or higher will be recorded post injection of the radiotracer to the completion of the imaging exam.

6.2.3 Procedures During Nivolumab Administration

As per standard of care, patients will be seen by a physician, advanced practice provider, or registered nurse prior to nivolumab infusion and a toxicity assessment will be performed. The following laboratories will be performed prior to infusion every 4 weeks:

- Standard-of-care laboratory tests appropriate for nivolumab
- Correlative biomarkers

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

6.2.4 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 study coordinator in conjunction with the PI to determine toxicities, including the grade and attribution to radiation.

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

6.3 Follow Up Phase of the Study

6.3.1 Image Interpretation

Static images will be reconstructed using standard procedure and analyzed by visual inspection and standardized uptake value (SUV) analysis. The tumor avidity, as estimated by the SUVmax, of up to 6 lesions will be measured on each FDG PET/CT scan. Patients will also be grouped based on a positive flare response (greater than 20% increase in SUVmax) or negative flare response (less than 20% increase in SUVmax).

6.3.2 Response Criteria

Response and progression will be evaluated in this study using the revised International Working Group criteria proposed by Cheson *et al.* (Revised Response Criteria for Malignant Lymphoma).[23] The irradiated index lesion is not included in this determination; however, tumor response of this lesion will be assessed and tabulated separately using criteria from Cheson *et al.*[23]

6.3.2.1 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.

6.3.2.2 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.

6.3.2.3 Measurement of Effect

6.3.2.3.1 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).

6.3.2.3.2 Non-Target Lesions

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

6.3.2.4 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.

6.3.2.4.1 Evaluation of target and non-target lesions

Evaluation of target and non-target lesions for response will be performed according to Cheson *et al.*[23] (criteria reproduced below):

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

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

6.3.2.4.2 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.

6.3.3 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.

6.4 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.

6.5 Subject Withdrawal

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward event occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 – Other Procedures. A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment

- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

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

6.5.1 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.

6.6 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 will include all of the items indicated for the planned final visit.

7 Study Evaluations and Measurements

7.1 Physical Examination

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.2 Vital Signs

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

7.3 Pregnancy Testing

Females of childbearing potential must have a negative serum or urine beta human chorionic gonadotropin (β-hCG) pregnancy test result within 15 days prior to the starting radiation therapy and must agree to use an effective contraception method during the study and for 6 months following the last dose of nivolumab; 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 6 months following the last dose of study drug.

7.4 Efficacy Evaluations

Efficacy will be evaluated based on the Response Criteria described in Section 6.3.2~~6.3.1~~

7.5 Safety Evaluations

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

8 Statistical Design

This is a single arm Phase II clinical trial for relapsed/refractory Hodgkin lymphoma patients receiving nivolumab followed by either: a) continued nivolumab monotherapy if patient achieves an induction complete response (CR) scored at week 8, or b) RT (4 Gy x 2 fractions) plus continued nivolumab for patients who achieve <CR after induction. In the RT group, a second response assessment is undertaken at week 16, to determine the number of patients who have achieved CR. In both groups, nivolumab is continued until disease progression, drug intolerance, or at the discretion of the treating medical oncologist.

8.1 Primary Objective

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

8.2 Secondary Objectives

1. To determine the nivolumab induction CR rate
2. To determine the post-RT + continued nivolumab CR rate
3. To determine the time to best response
4. To determine duration of best response
5. To estimate progression free survival, overall survival and disease free survival
6. To evaluate safety and adverse events

8.3 Exploratory Objectives

1. To evaluate baseline and post-treatment changes in biomarkers and determine whether biomarker changes are associated with clinical outcomes.
2. To evaluate tumor FDG uptake and determine whether FDG "flare" is associated with clinical outcomes.

8.4 Primary Endpoint

The primary endpoint is the overall CR rate, defined as the total number of CRs after nivolumab induction plus the total number of CRs after RT + continued nivolumab in those patients with <CR after induction, divided by the total number of patients treated on the study. The Cheson criteria will be used to score response.

8.5 Secondary Endpoints

1. The nivolumab induction CR rate is defined as the proportion of patients who achieve CR after nivolumab induction, at the week 8 evaluation.
2. The post-RT + continued nivolumab CR rate is defined as the proportion of patients who achieve CR after RT + continued nivolumab, at the week 16 evaluation (8-12 weeks post-RT). All patients who had <CR are eligible to receive RT. The denominator will include all eligible patients, regardless of whether 2 fractions of RT were administered.
3. 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 nivolumab for another 8 weeks.
4. Duration of best response is defined from date of best response to date of of disease progression, death due to any cause of last patient contact alive and progression-free.
5. 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.
6. Overall survival is defined from date of study entry to date of death due to any cause of last patient contact alive.

7. Disease-free survival is defined from date of CR to date of disease progression, death due to any cause of last patient contact alive and disease-free. DFS is only computed for CR patients.
8. Toxicities will be graded and tabled separately by induction or post-RT.

8.6 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. Tumor FDG uptake will be measured on PET/CT at baseline and at 1-2 weeks after initiation of nivolumab. Based on change in tumor FDG uptake after initiation of nivolumab, FDG "flare", will be score as absent/present. FDG "flare" will likely be defined by >20% increase in tumor FDG uptake. This definition may be modified for the observed distribution of changes in tumor FDG uptake on our study.

8.7 Interim Analysis

No interim analysis is planned.

8.8 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 overall CR rate and 95% exact confidence interval will be calculated. Following an intent to treat analysis, all patients who received at least 1 dose of nivolumab are included in the analysis of the primary endpoint. Based on an exact binomial test, the number of patients with CR will determine whether the null hypothesis will be rejected (see Sample Size/Power below).
3. The nivolumab induction CR rate and post-RT + continued nivolumab CR rate and 95% confidence intervals will also be calculated.
4. Time to best response and duration of best response will be calculated and summarized separately for CR, PR, SD and PD patients.
5. Progression free survival, overall survival and disease-free survival will be estimated by the Kaplan-Meier method. Disease free survival will be computed by landmark analysis for two distinct groups: 1) DFS from week 8, for patients who achieved induction CR and 2) DFS from week 16, for patients who achieved CR after RT + nivolumab.
6. 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 induction nivolumab, post-induction nivolumab or post-induction RT + continued nivolumab

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 nivolumab 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). Tumor FDG uptake on PET/CT, from baseline to 1 week after nivolumab will be compared. Student's t-test or non-parametric Wilcoxon rank sum test will be employed.

2. Change in tumor FDG uptake from baseline to week 1, will be assessed by paired t-test or Wilcoxon signed rank test.
3. The association between binary FDG "flare" and progression-free & overall survival will be tested using log rank test. Cox regression will be used to assess the effect of continuously scaled FDG change. For all survival analyses, a landmark analysis will be performed. Here, PFS or OS are defined from a landmark, which is 1-2 weeks after initiation of nivolumab.
4. The association between binary FDG "flare" and response will be tested by Fisher's exact test.
5. The association between binary FDG "flare" and biomarker changes will be assessed by Wilcoxon rank sum test.

8.9 Sample Size/Power

With 25 patients, there is 81% power to detect a difference of 20% assuming a null hypothesis that the CR rate = 10% versus an alternative hypothesis that the CR rate = 30% using a one-sided exact test with a 5% significance level. We will reject the null hypothesis if 6 or more of 25 patients achieve a CR. The actual significance level for this exact test procedure is 3%.

9 Safety and Adverse Events

9.1 Definitions

9.1.1 Adverse Event

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Concurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the

other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

9.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

9.3 Relationship of AE to Study

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal

relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the study product, is also an adverse event. The Principal Investigator or an appropriate designee will determine the relationship of the adverse event.

9.4 Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

Investigators must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

9.4.1 Investigator Reporting: Notifying the Penn IRB

This section describes the requirements for safety reporting by investigators who are Penn faculty, affiliated with a Penn research site, or otherwise responsible for safety reporting to the Penn IRB. The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Penn IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

  Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

  AND

  Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Reporting Process

Unanticipated problems posing risks to subjects or others as noted above will be reported to the Penn IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding

its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Serious, unexpected drug-related adverse events will be reported to the University of Pennsylvania IRB, and the University of Pennsylvania Cancer Center Data and Safety Monitoring Committee (DSMC) reporting guidelines as is required by each board. Grade 3 or higher adverse events must be reported within 10 days of knowledge of the event. All unexpected deaths must be reported within 24 hours of knowledge of this event. All other deaths must be reported within 30 days of knowledge of this event. The DSMC has outlined the following exceptions:

- Grade 3 or 4 events that are judged by a study investigator to be clearly unrelated to protocol therapy andoccur in organ systems receiving less than 5% of the prescribed treatment dose.The reason for determining that the event is unrelated must be clearly documented in the EMR.
- Grade 3 or 4 events that are probably or definitely related to progression of disease as judged by a study investigator. The fact that this event is related to disease progression must be clearly document in the EMR.
- Grade 3 or 4 events that are probably or definitely related to an FDA approved agent used in conjunction with radiation based on its current labeling and occur in organ systems receiving less than 5% of the prescribed treatment dose. The fact that this event is related to the FDA approved agent must be clearly documented in the EMR.

Adverse events (AE) and Serious Adverse Events (SAE) will use the descriptions and grading scales found in the revised **NCI Common Terminology Criteria for Adverse Events (CTCAE)**. This study will utilize the CTCAE v5.0 for adverse event reporting. All appropriate treatment areas will have access to a copy of the CTCAE v5.0 and a copy can be accessed at the web site: http://ctep.cancer.gov/.

9.5 Stopping Rules

There are no stopping rules in this Phase II trial.

9.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9.6.1~~9.7.1~~). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

The Medical Monitor will be Dr. Andrzej Wojcieszynski, a physician who is not directly involved in the trial and is not part of the Lymphoma Oncology Group at Penn. Because of Dr. Wojcieszynski'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, appropriateness of dose escalation 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 a minimum of every 6 months (or more 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.

9.6.1 Data and Safety Monitoring Plan

The Abramson Cancer Data and Safety Monitoring Committee is charged with the responsibility of reviewing all SAEs, deviations, Medical/Safety Monitoring reports for all cancer based protocols conducted at the University of Pennsylvania. The DSMC reviews these document and data and makes recommendation necessary to ensure subject safety and study integrity. Additionally, the DSMC monitors and audits the progress and conduct of all cancer based studies in accordance with their NCI approved Institutional Data and Safety Monitoring Plan.

10 Study Administration, Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.2 Data Collection and Management

Source data is all information, original records of clinical findings, observations, or other activities in a research study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents and may be paper, electronic or a combination of both. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Electronic case report forms will be developed and completed in Velos in lieu of paper case report forms.

10.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

10.4 Records Retention

Federally Funded Research or Non-IND/IDE Research:
The DHHS regulation (45 CFR 46.115) states that records relating to research conducted or supported by any Federal department or agency shall be retained for at least 3 years after completion of the research.

The FDA regulation (21 CFR 56.115) is virtually identical; it also states that IRB records must be retained for at least 3 years after completion of the research for these same types of studies.

Records for this study will be maintained in a secure location with access limited to the investigators and the study specific research team for 3 years from the date of full study terminations. If necessary, after the first year of termination, records may be moved to an off-site secure storage facility.

HIPAA Retention Period (45 CFR164.530(j):
Protected Health Information (PHI) Research Requests (HIPAA1-008): Records documenting research requests, privacy board review or privacy officer expedited review, background material, and acceptance or denial of request. Retain 6 years after research completed.

Protected Health Information Disclosure Records (HIPAA1-009): Documenting the release of PHI, including **both authorized and unauthorized** releases. Should include the date of release, to whom the information was released, and the circumstances of the release. Retain 6 years after research completed.

Maintenance of HIPAA records is independent of the regulations for clinical study records. All records of PHI research requests and any type of release will be maintained for 6 years after the research is fully terminated.

11 Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring Plan

The study PI is responsible for ensuring the ongoing quality and integrity of the research study. In addition, this study will be monitored or audited in accordance with Abramson Cancer Center's NCI approved Institutional Data and Safety Monitoring Plan.

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be maintained in the study specific Regulatory Binder which contains "Essential Study Documents". In addition, NCI requires all cancer based studies to have an independent scientific review. This protocol must be reviewed and fully approved by the Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) prior to enrolling any subjects. Documentation of CTSRMC approval must also be maintained in the study specific Regulatory Binder.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB and CTSRMC for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed and dated by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12.1 Risks

There are potential risks both from nivolumab and from low-dose radiotherapy.

Risks of nivolumab include fatigue, dermatitis, and such autoimmune dysfunction as pneumonitis, colitis, hepatitis, nephritis, thyroid dysfunction, pituitary dysfunction, and others. There is also the risk of myalgias, arthralgias, weakness, renal failure, ophthalamic dysfunction, and other toxicities. As with any medication, there is a risk of hypersensitivity reaction; medications to treat hypersensitivity reactions should be immediately available, including epinephrine, diphenhydramine, methylprednisolone and nebulized albuterol. Finally, there is a risk of toxicities not listed, as well as CTCAE grade 3 or higher toxicities, up to and including death. Pre-infusion examinations and laboratory assessment, as well as peri-infusion monitoring, are carried out with the express goal of detecting toxicities.

Risks of low-dose radiotherapy are very low, both in frequency and in severity. Nonetheless, there are rare risks to organs at risk proximal to the treatment field, both in the acute phase and in the late phase. Finally, there is a risk of toxicities not listed, as well as CTCAE grade 3 or higher toxicities, up to and including death. Radiation treatment planning, as described in Section Error! Reference source not found.6, is carried out with the express goal of minimizing toxicity to organs at risk, and low-dose radiotherapy is extremely safe and well-tolerated.

The risk of one additional FDG PET/CT poses a very small risk related to radiation exposure from FDG positron emission. This radiation exposure is orders of magnitude smaller than the low-dose radiotherapy described above. FDG PET/CT scans are a standard clinical procedure for patients with HL.

12.2 Benefits

This trial may have benefits both for the study participants and for society in general.

Study participants may have improved treatment response with the addition of radiation to nivolumab, leading to improved overall survival.

Society in general may benefit from the knowledge generated by this trial. Such knowledge includes understanding whether:

- The addition of radiation to nivolumab can improve treatment response in patients with r/r HL
- The addition of radiation to nivolumab can improve overall survival in patients with r/r HL
- Phase III clinical trials can be undertaken to assess the addition of radiation to nivolumab to improve r/r/ HL treatment response and overall survival

12.3 Risk Benefit Assessment

The most serious risks listed above are felt to be less likely to occur. Moreover, as outlined above, there are a number of mechanisms in place to limit potential risks and maximize patient safety. Ultimately, for the study overall and for study participants individually, the potential benefits outweigh the potential risks.

12.4 Informed Consent Process / HIPAA Authorization

Subjects will be recruited from investigator clinical practices. Subjects will undergo an informed consent process in accordance with Good Clinical Practice Guidelines and be given ample time to make an informed decision. Informed consent will be obtained prior to the performance of any study procedures. Subjects must meet all of the inclusion and none of the exclusion criteria. Eligibility will be verified by a study investigator on a case report form. Subjects will be encouraged to ask questions of the investigator and research team as they arise throughout the duration of study participation. Consent will be obtained by an investigator or a member of the trained research staff designated by the principal investigator.

13 Study Finances

13.1 Funding Source

This study will be supported with internal funds from the Department of Radiation Oncology.

13.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

13.3 Subject Stipends or Payments

We will pay for the cost of parking for patients parking in the PCAM patient garage, if not already covered through the hospital, on the day of the research PET/CT scan. We will not pay the patient for participation.

14 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study. Rule regarding the publication of results from this study are covered in the sponsored research agreement between Merck and the University of Pennsylvania.

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