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Amendment 1	Version Date:	March 14, 2017
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Amendment 5	Version Date:	August 07, 2018
Amendment 6	Version Date:	January 28, 2019
Amendment 7	Version Date:	June 6, 2019

STUDY TITLE: A Phase II Trial of Pembrolizumab Sequentially Following Single Fraction Non-Ablative Radiation to One or More of the Target Lesions in patients with Stage IV NSCLC

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SPONSOR:	Cleveland Clinic/Case Comprehensive Cancer Center
SUPPORT/FUNDING:	Merck
SUPPLIED AGENT***:***	Pembrolizumab
IND #:	N/A
OTHER AGENT***:***	Single Fraction Radiation Therapy **(SFRT) (**8Gy x 1)

SUMMARY OF CHANGES

Protocol Date	Section/Page	Change	Rationale for Change
12/13/2016		Initial IRB approval	
03/14/2017		Merged all events that were labeled on study calendar as Prescreen Visit one to Visit2. All events will be done in one Visit. Added footnotes regarding screening labs and radiology consult. Local labs added to Visit 2 Screening. Both study calendars were updated and replaced page 4 and page 42. Section Number changed from 7.1.5.3.1 > 3.1.5.3.1.	
08/01/2017	P.5	Delete Correlative Studies	Duplicate entry
08/01/2017	P.13 on	Correct Section Header Numbering throughout document	Not sequential
08/01/2017	P.26	Added radiation to multiple lesions	Clarification
08/01/2017	P.26	Added exception to entry criteria	Clarification
08/01/2017	P.28	Exclusion Criterion 7,10	clarification
08/01/2017	P.31	Table 2 changed for consistency	clarification
08/01/2017	P.33	Removed 4D CT simulation	Not relevant
08/01/2017	P.33	Nonpreviously erradiated fields	Clarification
08/01/2017	P.34	SFRT 33 days to be consistent	Clarification
08/01/2017	P.35	Deleted Radiation Therapy Information	Not relevant
08/01/2017	P.48	Correletives Information added	Clarification
08/01/2017	P.47	StudyID vs. Registration Number	Clarification
08/01/2017	P.70	Deleted Reference	Erroneous
08/25/2017	P5, 43	Add blood draws	Missed in AM2
04/10/2018		Eligibility criteria changed to reflect new changes in clinical practice based on updated key trial results. Removed the language referring to one prior line of therapy.	Changed eligibility to meet current standard practice
4/10/2018		CTCAE updated to V.5	Updated
4/10/2018		Minor administrative changes throughout	Clarification
4/10/2018		Clarification provided as to the number of lesions that can be treated with SFRT	Clarification
8/7/2018		Updated PI throughout document	PI change
8/7/2018	P30	Updated Table 1 to remove PK	Erroneous
1/28/2019		Minor administrative changes throughout	Clarification
1/28/2019		CTCAE change back to V.4 throughout	Clarification
1/28/2019	P.3	Personnel changes	Updated

Protocol Date	Section/Page	Change	Rationale for Change
1/28/2019	P.6	Protocol Summary treatment section clarified	Clarification
1/28/2019	P.25	Added disease monitoring window to 9 weeks +/- 14 days	Updated
1/28/2019		Deleted Table 1 Laboratory Tests and renumbering of all subsequent tables	Duplicate entry, Updated
1/28/2019	P.32, 33	Exlusion criteria changed to reflect a recovered AE ≤ Grade 2 and add autoimmune disease as a separate exclusion criteria	Updated
1/28/2019	P.37	Clarification in following all treatment related AEs to resolution or new anti-neoplastic therapy	Clarification
1/28/2019	P.37	Added survival follow up window to +/- 14days	Updated
1/28/2019	P.38, 39	Table added SOC column and footnotes for clarification	Updated
1/28/2019	P.43	Prohibited Concomitant Medication section modified to allow an exception of steroid treatment at the discretion of the investigator	Updated
1/28/2019	P.50	6.9 revision to End of Treatment and Follow Up visit procedures	Clarification
1/28/2019	P.50	Deleted section 6.9.1 'Discontinuation of Study Therapy after Complete Response'	Erroneous
1/28/2019	P.53	Changed SAE reporting to Cancersaeinbox@ccf.org and updated Merk reporting fax number	Updated
06/06/2019		Minor administrative changes throughout	Clarification
06/06/2019	P.1, 2, 3	Change protocol number to version date. Update Personnel to reflect multisite format and add NYU Langone as a site and Jessica Pasko as research nurse to the protocol	Updated
06/06/2019	P. 20	Remove inconsistent inclusion/exclusion verbiage	Clarification
06/06/2019	P. 26	Figure 2 - Study Overview Flow Diagram	Updated
06/06/2019	P. 28	Treatment tumor tissue collection allows exception at the sponsor investigator's discretion	Updated
06/06/2019	P. 31	Allowed safety follow up visit to be earlier than 30 (+/- 7) days in the event of starting a new anti-cancer therapy	Updated
06/06/2019	P. 32, 33	Baseline archival tissue of any age now accepted; measurable lesion and tissue clarification	Updated
06/06/2019	P. 36	Pembrolizumab treatment windows clarified	Clarification
06/06/2019	P. 39	Table 3 study schema, C1 local laboratory procedures deleted	Duplicate entry, Clarification

Protocol Date	Section/Page	Change	Rationale for Change
06/06/2019	P. 40	Table 3 study schema: peripheral blood, serum, PBMC/IRC blood collection deleted at safety follow up, C8 treatment, and moved to C8/EOT. All correlative labs removed at C1. PBMC collection moved to screening. Duplicate tissue column deleted.	Updated, Erroneous
06/06/2019	P. 40	6.4 study schema bullet points updated: 'a' to reflect pembrolizumab clarification; 'c' removal of CT pelvis scan unless clinically indicated; 'd' baseline tissue and additional tissue updates; 'i' pregnancy test timeline added to schema	Updated, Clarification
06/06/2019	P. 42	Table 4 changed to reflect accurate CTCAE v4.0 verbiage: 'Infusion related reaction' and 'renal and urinary disorders- Other, specify'	Updated

PROTOCOL SUMMARY

Abbreviated Title	A Phase II Trial of Pembrolizumab Sequentially Following Focal Radiation to One or More of the Target Lesions in Previously Treated Patients with Stage IV NSCLC
Trial Phase	*Phase II*
Clinical Indication	1. Patients with metastatic NSCLC, with at least 2 measurable lesions
Objectives	Primary Objective: To determine the tumor responses outside the radiation field (abscopal effect) after radiation followed by pembrolizumab in metastatic NSCLC. Secondary Objectives: 1. To determine the progression-free and overall survival in patients with NSCLC receiving pembrolizumab, who receive Single Fraction Radiation Therapy (SFRT) 2. To determine the safety and toxicity of the combination of SFRT and pembrolizumab 3. To examine potential predictive biomarkers in tumor samples and peripheral blood in patients treated with pembrolizumab and SFRT 4. To determine the local control of SFRT in the radiated lesion(s), when SFRT is given with pembrolizumab 5. To evaluate the induction of a T-cell response in patients with metastatic NSCLC treated with radiation and the effect of radiation
Treatment	1. SFRT (8GYx1) to one or more sites of metastatic disease 2. Pembrolizumab, every 3 weeks for 8 cycles until progression or unacceptable toxicity. After cycle 8 (End of Treatment visit) patients will continue pembrolizumab as standard of care if they are tolerating and have no disease progression.
Number of trial subjects	48 patients

ABBREVIATIONS

CCCC	Case Comprehensive Cancer Center
CRF	Case Report Form
DCRU	Dahm's Clinical Research Unit
DSTC	Data Safety and Toxicity Committee
FDA	Food and Drug Administration
ICF	Informed Consent Form
IRB	Institutional Review Board
PRMC	Protocol Review and Monitoring Committee
SOC	Standard of Care
CCF	Cleveland Clinic Foundation
UH	University Hospitals

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1 INTRODUCTION

1.1 Background of Study Disease

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality in the United States with the majority of patients presenting with advanced disease. Despite improvements in survival with the addition of targeted agents to chemotherapy, the median survival for patients with advanced NSCLC remains a disappointing 12 months. (1) In patients who are able to tolerate treatment beyond first line, responses are even lower and median survival is only minimally improved with chemotherapy. Despite the development of new and effective therapies, the five-year survival rate for patients with advanced NSCLC remains less than 5%. (2) Strategies using monoclonal antibodies targeting the immune-checkpoint pathways have recently shown activity in several solid tumors including NSCLC. (3-6) Pembrolizumab is a fully human IgG4 monoclonal antibody targeting the Programmed death-1 receptor interfering with the binding with its ligands PD-L1 and PD-L2. Recent clinical trials with pembrolizumab demonstrated clinical activity in NSCLC. (4)

1.1.1 Name and Description of Investigational Agent Pembrolizumab

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1.

Pembrolizumab has an acceptable preclinical safety profile and is being advanced for clinical development as an intravenous immunotherapy for advanced malignancies. See investigator brochure for further details. (7)

1.1.2 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.(3, 8, 9)

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). (10, 11) The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic

tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade.(12, 13) The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. (14, 15) The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors.(16, 17). Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. (8) Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells has been shown to correlate with poor prognosis and survival in various malignancies. (18-21) PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). (18) This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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

Recently approval of nivolumab (MDX-1106, BMS-936558), an IgG4 antibody against PD-1, based on data in NSCLC has validated the role of PD-1 as an attractive target for clinical therapeutic intervention in NSCLC subjects. (22) The approval was based on phase III open-label CheckMate-017 study involved 272 previously treated patients with advanced or metastatic squamous cell NSCLC. Participants were randomized to the fully human IgG4 monoclonal antibody nivolumab at 3 mg/kg intravenously every 2 weeks (n = 135) or docetaxel at 75 mg/m2 (n = 137) intravenously every 3 weeks. Treatment with nivolumab improved OS by 41% versus docetaxel (9.2 vs 6.0 months; HR = 0.59; 95% CI, 0.44-0.79; P = .00025). This approval was further supported by phase II data of CheckMate -063 study presented at the 2014 Chicago Multidisciplinary Symposium in Thoracic Oncology. The study included 117 heavily pretreated patients with advanced squamous cell NSCLC. All patients had failed two or more systemic treatments and 65% of participants (n = 76) had previously failed three or more treatments. Seventy-six percent of patients were within 3 months of completion of most recent therapy. Nivolumab was administered at 3 mg/kg intravenously every 2 weeks until disease progression or treatment discontinuation. At 11 months follow-up ORR, as assessed by an independent panel, was 14.5% (95% CI, 8.7-22.2), with a median duration of response that was not yet reached. The

estimated 1-year survival rate was 41% (95% CI, 31.6-49.7) and the median OS was 8.2 months (95% CI, 6.05-0.91). An additional 26% of patients had stable disease for a median duration of 6 months (95% CI, 4.73-10.91), producing a disease control rate (ORR plus stable disease) of 41%. Responses were observed independent of PD-L1 status for patients with quantifiable PD-L1 expression. Adverse events (AEs) of all types and grades occurred in 74% of patients; however, 85% of patients were able to receive at least 90% of their planned dose intensity. Grade 3/4 drug-related AEs were reported in 17% of patients. The most common (≥2%) grade 3/4 AEs were fatigue (4.3%), pneumonitis (3.4%), and diarrhea (2.6%). Discontinuations due to drug-related AEs of any grade occurred in 12% of patients. Two drug-related deaths (pneumonia, ischemic stroke) occurred in patients with multiple comorbidities and progressive disease. (23)

Recently phase 1 data from Keynote-001 was published on the role of pembrolizumab in advance NSCLC. In this phase 1 study, 495 patients received at least one dose of pembrolizumab (at a dose of either 2 mg or 10 mg per kilogram of body weight every 3 weeks or 10 mg per kilogram every 2 weeks). The objective response rate was 19.4%, and the median duration of response was 12.5 months. The median duration of progression-free survival was 3.7 months, and the median duration of overall survival was 12.0 months. In a patient population with PD-L1 expression of at least 50% of tumor cells response rate was 45.2%, median progression-free survival of 6.3 months and overall survival was not reached. PD-L1 expression was assessed in tumor samples using immunohistochemical analysis, with results reported as the percentage of neoplastic cells with staining for membranous PD-L1 (proportion score). Common side effects attributed to pembrolizumab were fatigue, pruritus, and decreased appetite, with no clear difference according to dose or schedule. (24) Pembrolizumab is approved for use in patients with advanced chemotherapy refractory NSCLC expressing PD-L1. However, the role of PD-L1 expression in determining treatment with PD-1 inhibitors is unclear at this time. Nivolumab, another agent in the same class, is currently FDA approved for all patients with advanced chemotherapy refractory NSCLC irrespective of the PD-L1 status. No significant differences were seen between docetaxel and Nivolumab in patients who were PD-L1 negative. (25)

1.1.3 Preclinical Data

Due to the lack of cross-reactivity of pembrolizumab with PD-1 from rodents (or other nonprimate species), a commercially available, hamster anti-mouse PD-1 analog antibody (clone J43) was used for in vivo efficacy studies in mice. Anti-mouse PD-1 (J43) was tested as a monotherapy in several syngeneic murine tumor models. The tumor growth curves in Figure 1 show that anti-mouse PD-1, administered at 10 mg/kg, potently inhibited the subcutaneous growth of MC38 colon adenocarcinoma tumors in most animals. In addition to inhibiting tumor growth, anti-mouse PD-1 administered at 10 mg/kg induced complete tumor regression in 50% of the animals resulting in long-term tumor free survival (Figure 1).

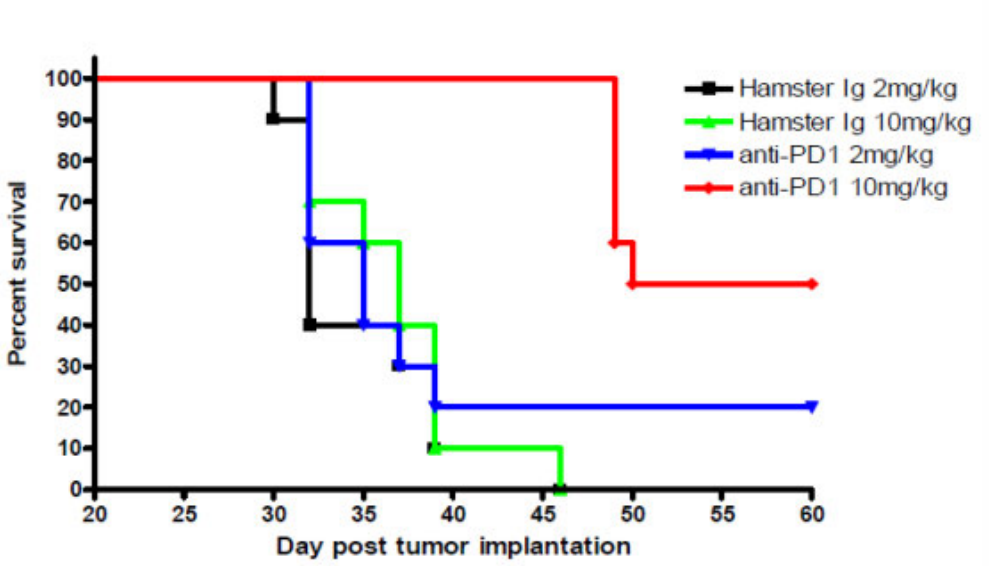

Figure 1 - The experiment described in Figure 1 was analyzed for the effects of anti-mouse PD-1 on the long-term survival of treated mice in each of the groups. Mice receiving 10 mg/kg of anti-mouse PD-1 demonstrated an increased chance of overall survival, with 50% of the mice surviving beyond 60 days with no evidence of tumor relapse

1.1.4 Clinical Trial Data

An open-label phase 1 trial (Keynote 001) was recently publishes in New England Journal of Medicine, in this large phase I trial side effects, safety, and antitumor activity of pembrolizumab was evaluated in patients with advanced NSCLC. A total of 495 patients received at least one dose of pembrolizumab between May 2012 and February 2014. With a primary objective of safety, side effect profile, and antitumor activity, patients were given intravenous pembrolizumab at a dose of 2 mg or 10 mg per kilogram of body weight every 3 weeks or 10 mg per kilogram every 2 weeks over a 30-minute period.

Overall treatment was well tolerated and the most common treatment related adverse events were fatigue, pruritus, and decreased appetite. Only 9.5% of patient experienced adverse events of grade 3 or higher. Pneumonitis of grade 3 or greater was observed in 9 patients and caused death in one patient.

At the time of the data cutoff, the median duration of follow-up was 10.9 months (range, 5.2 to 27.5), and 115 patients (23.2%) continued to receive treatment. Efficacy data from this study showed an overall response rate of 19.4% (95% confidence interval [CI], 16.0 to 23.2). The response rate was 18.0% (95% CI, 14.4 to 22.2) in the previously treated patients (n-394) and 24.8% (95% CI, 16.7 to 34.3) in the previously untreated patients (n-101). The median duration of response was 12.5 (range, 1.0 to 23.3) months in all patients, 23.2 months (range, 1.0 to 23.3) in previously untreated patients and 10.4 months (range, 1.0 to 10.4) in previously treated patients. Median progression-free survival was 3.7 months (95% CI, 2.9 to 4.1) for all the patients, 3.0 months (95% CI, 2.2 to 4.0) for previously treated patients, and 6.0 months (95% CI, 4.1 to 8.6) for previously untreated patients. Median overall survival was 12.0 months (95%

CI, 9.3 to 14.7) for all patients, 9.3 months (95% CI, 8.4 to 12.4) for previously treated patients, and 16.2 months (95% CI, 16.2 to not reached) for previously untreated patients

Subjects were required to submit a newly obtained tumor biopsy prior to initiating therapy with pembrolizumab to evaluate the tumors for expression of PD -L1, the presumptive predictive biomarker of pembrolizumab, using a preliminary immunohistochemistry assay. PD-L1 positivity was defined as membranous staining in at least 1% of cells (neoplastic and intercalated mononuclear inflammatory cells) within tumor nests or a distinctive staining pattern caused by the infiltration of mononuclear inflammatory cells in the stroma that formed a banding pattern adjacent to tumor nests. A modified H-score scoring system of PD-L1 expression was established for NSCLC by analyzing tumor specimens from resected NSCLC specimens. Results were reported as the percentage of neoplastic cells showing membranous staining of PD-L1 (proportion score).

For the training group, 136 patients were finally included and their associated clinical outcome data were used to assess an optimal cut point for PD-L1 positivity. An optimal PD-L1 cut point was identified by receiver operator characteristic curve analyses and by considering clinical implications of false positive and false negative results. Cut points were identified based upon a proportions score (PS) method of IHC analysis with the tumors expressing at or greater than the highest cut point (PS >50%) referred to as PD-L1 strongly positive tumors, and tumors expressing >1% but less than 50% referred to as the PD -L1 weak tumors. Outcomes based on irRC were used as the primary outcome for the analysis. 220 patients were included in validation group and the response rate was 45.2% (95% CI, 33.5 to 57.3) in the 73 patients with a proportion score of at least 50%. Among all the patients with a proportion score of at least 50%, median progression-free survival was 6.3 months; median overall survival was not reached.

Clinical data regarding combination of radiation with immunotherapy with a checkpoint inhibitor is limited to assess abscopal effect. Several case reports have described the role of abscopal effects, and several ongoing trials are further assessing it in various malignancies. (26-30)

Several other ongoing clinical trials are assessing the activity of pembrolizumab in NSCLC with a combination of chemotherapy and/or radiotherapy. Currently ongoing trials of pembrolizumab in NSCLC includes; NCT02220894- Study of MK-3475 (Pembrolizumab) Versus Platinum-based Chemotherapy for Participants With PD-L1-positive Advanced or Metastatic Non-small Cell Lung Cancer; NCT01840579- In Part B participants with advanced non-small cell lung cancer (NSCLC) will receive pembrolizumab in combination with either cisplatin/pemetrexed or carboplatin/paclitaxel by non-random assignment to assess the safety and tolerability of the combination therapy; NCT02422381- study will evaluate the safety of adding an investigational drug, pembrolizumab to standard treatment with gemcitabine; NCT02343952, assessing effect of Consolidation Pembrolizumab (MK-3475) following Chemoradiation in Patients With Inoperable/Unresectable Stage III NSCLC; NCT02085070 - to study the activity of pembrolizumab in untreated brain metastases from melanoma or non-small cell lung cancer; NCT02039674- study is to determine safety, tolerability, and efficacy of pembrolizumab (MK3475) in combination with chemotherapy or immunotherapy in participants with unresectable or metastatic non-small cell lung cancer (NSCLC); NCT02316002, Phase II Study of Pembrolizumab After Curative Intent Treatment for Oligometastatic Non-Small Cell Lung Cancer.

1.2 Single Fraction Radiation Therapy (SFRT)

1.2.1 Rationale

1.2.1.1 Rationale for the Trial and Selected Subject Population

NSCLC is the leading cause of cancer-related mortality in the United States, with the majority of patients presenting with advanced disease. Despite improvements in survival with the addition of targeted agents to chemotherapy the median survival for patients with advanced NSCLC remains a disappointing 12 months. (1) However, despite this aggressive therapy, the majority of patients will experience systemic recurrence and eventually die from their lung cancer. Tumors with high mutational burden present a wider array of tumor-specific antigens and prompt T-cell recognition and invasion. (31) Tumor evasion of immune surveillance is required for cancer progression. (32) The tumor milieu contains several suppressive mechanisms including the infiltration by specific immune inhibitory cells (e.g. Tregs and myeloid-derived suppressor cells), production of soluble factors/cytokines (IL-6, IL-10, and TGF-β), and activation of co-inhibitory pathways (e.g. PD-1/PDL-1, B7-H4, IDO-1, CTLA-4 etc). Recent evidence highlights the pivotal role of the immune checkpoint pathways in maintaining an immunosuppressive tumor microenvironment. (33) Strategies using monoclonal antibodies targeting the immune-checkpoint pathways have recently shown activity in several solid tumors including NSCLC. (3-6) Pembrolizumab is a fully human IgG4 monoclonal antibody targeting the Programmed death-1 receptor interfering with the binding with its ligands PD-L1 and PD-L2. Recent clinical trials with pembrolizumab demonstrated clinical activity in NSCLC. (4)

There is substantial evidence that radiotherapy (RT) is capable of converting the irradiated tumor into an immunogenic hub. The processes of antigen presentation and development of cellular immunity are complex, and subject to modulation due to the tumor microenvironment. Antigen presenting cells in the tumor microenvironment acquire the antigens from the tumor cells. The APCs mature with expression of MHC class I and II on cell surface for interaction with antigen specific T-cells. The antitumor effect of radiation is through DNA damage and insufficient repair resulting in apoptosis mediated by the BCL2, p53-dependent, and TRAIL (tumor necrosis factor (TNF)-related apoptosis-inducing ligand) dependent mechanisms. In addition to tumor cell apoptosis in the irradiated tumor, several mechanisms resulting in increased tumor specific immune responses have been described. Radiation depletes the suppressor T-cells in the tumor microenvironment (34) and produces pro-inflammatory cytokines that enhance the infiltration of effector (CD8+) T-cells. (35-37) Preclinical models demonstrate that radiation promotes the immunological recognition of the tumor and higher expression of different cancer testis family antigens and a higher expression of MHC-I in a dose-dependent scale. (38) In addition, preclinical data using B16 melanoma cells expressing the prototypic tumor stem cell marker CD133 revealed that hypofractional RT with anti-PD1 induced robust tumor T-cell infiltration and prolonged survival compared to RT or anti-PD1 alone.(39) The idea of enhanced systemic anti-tumor immune response following radiation is further supported by several anecdotal case reports of regressions of distant non-radiated tumor lesions, known as the abscopal effect. (27-30) The abscopal effect has also been observed in patient receiving anti-CTLA4 antibody, in both NSCLC and melanoma. (26, 30) In an ongoing single arm trial with radiation and ipilumumab in chemotherapy refractory NSCLC overall response rate (ORR) of non-ablative RT followed by ipilumumab was 18% in the intent to treat population and 33% in patients receiving 4 cycles of ipilimumab. (40) In addition to these responses a shift in T-cell receptor clonality

differentiated responders from non-responders to therapy in this trial. Beyond the above few case reports and small single arm combination trial with ipilimumab, this interaction has not been well studied in a prospective study and the details of the mechanism are unclear.

In this proposal, we plan to investigate this phenomenon of 'in-vivo immunization' with focal RT to one of the target tumor lesions and the potential for augmenting the anti-tumor immune response with pembrolizumab. The dose of radiation will be non-ablative and focal to one or more of the tumor lesions, and hence would expect minimal anticipated toxicity from the radiation. The preliminary clinical data from the pembrolizumab clinical trials are promising, and strategies such as this to augment tumor specific antigen presentation may augment the responses and clinical benefit from pembrolizumab.

1.2.1.2 Rationale for Dose Selection/Regimen/Modification

a) Dose of Pembrolizumab:

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

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

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on

exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

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

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

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

b) Dose of Radiation and Choice of Modality:

Most patients with metastatic NSCLC requiring palliative radiation receive 8 Gy SFRT or 20 Gy in 5 fractions. Several randomized controlled trials demonstrated that a single fraction of radiotherapy (8 Gy) is equivalent in palliation, and local control in comparison to a longer course of radiotherapy in patients with bone metastases. (41, 42) Similarly even in patients with lung or other visceral metastases no significant difference in symptom palliation and overall survival were noted with single fraction versus multiple fractions of radiation. (43) Moreover, SFRT is cost effective and prevents delays to initiation of systemic therapy. Animal studies suggest that low dose (2–4 Gy) SFRT can promote tumor immunity via major histocompatibility complex (MHC) up-regulation, antigen presentation, and vascular normalization. (44) At higher doses, SFRT likely retains these immunogenic effects, but also recruits T cells into the tumor and leads to greater direct tumor cell death due to apoptosis or necrosis. (45) Using a B16 mouse melanoma model, Lee et al. showed that SFRT (20 Gy) is more effective than fractionated radiation therapy (FRT; 45 Gy in 3 fractions) in controlling tumors though the total dose of radiation was far less. (45) In their model, the efficacy of SFRT was dependent on CD8 T-cells. Thus, we suspect that 8 Gy x 1 fx could potentially be well tolerated, effective, immunogenic, practical and cost effective regimen to evaluate for the immune-priming effect.

Patients with more than a single symptomatic lesion will be treated to some or all of their lesions, depending on disease burden, necessity for palliation of particular lesions, proximity to other major organs or neurovascular regions, and other patient considerations. There are no anatomic locations that will be deemed inappropriate for RT other than the brain.

Radiation will be delivered using electrons for subcutaneous lesions or rib lesions, and photons using 3D conformal planning and IMRT (intensity modulated radiation treatment) for deeper tumors in the neck, mediastinum, and retroperitoneal regions. None of the patients will be treated with stereotactic radiotherapy techniques. Standard doses of prophylactic antiemetic pre-medications including ondansetron and dexamethasone will be administered if thought to be clinically indicated before treatment of abdominal and retroperitoneal masses

1.2.1.3 Rationale for Biomarker Research

The relationship between PD-L1 and responses to PD1 inhibitors is not entirely clear at this time. (46, 47) In patients with NSCLC even though there appears to be an association between PD-L1 expression and response in some trials there has been no association in some trials. (23, 25, 46-50) The discrepancy in the predictive value of the PD-L1 assay are likely related to differences in the definition of positivity, variability of assays across clinical trials and the temporal and spatial heterogeneity of PD-L1. (51, 52) The expression of PD-L1 has also been correlated with the extent of tumor lymphocytic infiltrate. (51, 52) The latter has been observed to be increased after radiation therapy, suggesting one possible mechanism for an improved systemic response after SFRT. (39) We propose here to treat NSCLC patients without regard to PD-L1 expression on biopsies done just prior to initiation of pembrolizumab. When feasible, tissue specimens will be obtained before SFRT and pembrolizumab treatment, and again after SFRT, and local and systemic response will be correlated to expression. The majority of PD-L1 positive tumors were associated with CD4 and CD8 tumor infiltrating lymphocytes (TILs), while the minority of the PD-L1 negative tumors had associated TILs. Moreover, the staining pattern of PD-L1 on melanocytes differed based on proximity to TILs. Interferon-γ, a primary inducer of B7-H1 expression, can be detected at the interface of PDL1 positive melanocytes and TILs, possibly reflecting activation of PD-1 on the TILs. This interaction, therefore, might be predictive of antitumor response to PD-1 blockade. Additional mediators of this pathway that might be associated with anti-tumor response, and will be studied on pre-treatment specimens from patients enrolled in this trial. Expression of other members of the B7 super-family of ligands, including PD-L2 and B7-H4 on tumor cells, might be associated with activation of PD-1 on tumor cells.(53, 54) Galectin-9 (the ligand to TIM3), has been proposed as a mediator of PD-1 related T-cell exhaustion. (55) A more sophisticated and accurate predictive biomarker model might be built by incorporating markers on T cells, in addition to quantification of T cell tumor infiltrate. Specifically, co-expression of TIM-3 and PD-1 might be associated with sensitivity to PD-1 blockade.(55) LAG-3 (lymphocyte-activation gene 3) synergizes with PD-1 to inhibit T cell activation.(56, 57) Co-expression of PD-1 and CTLA-4 on T cells is thought to be co-inhibitory, and co-inhibition of these molecules is the basis of ongoing clinical trials. While the T-cell stimulatory role of PD-1H (PD-1 Homologue) on T cells was recently described, its association with anti-tumor response in the setting of PD-1 blockade has yet to be determined. We propose to evaluate several biomarkers studies in collaboration with the Yale Translational Immunology Lab, to characterize the nature of the tumor immune cell populations and several immune evasive pathways including PD-L1 and PD-1. We will use novel quantitative immunofluorescence based assays developed by our collaborators described in earlier publications. (51, 58-62)

Peripheral circulating immune cell phenotyping will be done by Genoptix Inc. In addition, MHC Dextramer® reagents will be used for detection of antigen-specific T cells pre and post

treatment. We will monitor changes of the circulating immune cell population's pre and post treatment and at the time of progression. Novel immune SEQ platforms will be used to interrogate T and B-cell receptor repertoire over time pre-post treatment and at progression. This will identify and define highly expanded clones and diversity of lymphocyte populations.

Correlations between genomic, transcriptomic and proteomic profiles of subjects tumors, and efficacy outcomes will be assessed to identify gene mutations, gene amplifications, RNA-expression levels, and protein-expression levels. Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be profiled to identify the genomic variances that may contribute to response or disease progression and provide an understanding of molecular abnormalities. RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations; Quantitative proteomics analysis will be conducted to determine the exact amounts of specific proteins and to confirm expression of genes that are correlative of response and disease progression.

A recent study (NCT01176461) with a mass spectroscopy based serum proteomic assay BDX008 took pre-nivolumab treated melanoma samples from 119 patients. The same assay was independently validated with pre-treatment serum of 30 patients from a non-protocol study using PD-1 blockade regimens. The evaluation showed that patients in the non-protocol study classified as having a high likelihood of good outcome had a 74 percent lower risk of death compared to those with a profile associated with low likelihood of good outcome (hazard ratio [HR] 0.26, p=0.002). Of the 119 patients in the nivolumab trial, those with a profile predicting high likelihood of good outcome had a 50 percent lower risk of disease progression (HR 0.50, p=0.001) and a 62 percent lower risk of death (HR 0.38, p=0.001) compared to those with a profile predicting low likelihood of good outcome. (63) We will evaluate the predictive value of this assay in our trial on all the pre-treatment samples. These studies will be done in collaboration with Biodesix Inc.

An additional potential biomarker of tumor response is cell-free tumor-derived circulating DNA (ctDNA). We will collaborate with BioCept Inc. to develop an ultrasensitive assay for measuring small amounts of cell-free mutant DNA released into the blood from dying tumor cells. The assay covers a broad panel of mutations and uses novel error suppression techniques applied to next-generation sequencing data to enable identification of rare mutant DNA down to a fractional abundance of ~0.02%. Because such ctDNA is highly tumor-specific and is rapidly cleared from the bloodstream, this assay exhibits excellent promise as a quantitative cancer biomarker. Rapid decreases in ctDNA levels have been observed following treatment with surgery, radiation therapy, and systemic therapy (sometimes with an initial spike from tumor kill). Thus, we hypothesize that quantitative changes in ctDNA may provide information that is complementary to radiologic studies for tracking the efficacy of treatment with the PD-1 inhibitor pembrolizumab in patients with non-small cell lung cancer.

We will also evaluate novel quantitative CT imaging algorithms developed in collaboration with the Case Biomedical engineering group to detect tumor inflammation. These imaging based biomarkers could potentially predict tumors with high tumor infiltrating lymphocytes, predict response based on pre-treatment imaging, and also help monitoring patients treated with immunotherapy and potentially help identify early responders and pseudo-progression.

1.2.1.4 Statistics and Sample Size

The primary goal of the trial is to assess the RECIST-defined tumor response rate outside the radiation field in previously treated NSCLC patients given radiation to an index lesion followed by pembrolizumab. Secondary goals include assessment of toxicity, other efficacy measures such as progression-free survival, response duration, overall survival, and local control of disease within the radiation field, immune response, and biomarkers such as PD-L1 expression.

In previous studies (KEYNOTE 001 and 010) the ORR to pembrolizumab monotherapy has been approximately 20% in this population. Based on this, an underlying ORR of **≥35%** would be considered positive in the current trial whereas a ≤20% ORR would be considered negative. A two-stage accrual design that allows for early stopping due to lack of efficacy will be employed to test this hypothesis. The maximum accrual goal is **48** eligible and evaluable patients. Initially **29** eligible and evaluable patients will be entered into the trial. If **≤6** patients respond (observed ORR **≤21%**) the trial will be stopped for (relative) lack of efficacy. If more than **6** patients respond an additional **19** eligible and evaluable patients will be entered. Pembrolizumab plus radiation will be considered effective if overall **12** or more patients respond (ORR **≥25%**). With this design the likelihood of stopping the trial early for lack of efficacy is **≥64%** if the underlying ORR is ≤20% and ≤7% if it is **≥35%**. The overall type I and II errors are **20% and 10%, respectively**.

Safety is an important secondary endpoint. Toxicity will be graded using CTCAE version 4.0 criteria, categorized by organ system, and summarized as frequency counts and percentages. Assuming the trial accrues all **48** patients, the risk of a particular type and/or grade of toxicity will be estimable using an exact 90% confidence interval that has a maximum half-width of **13%**. The likelihood of observing at least one such event is 86% even if the associated risk is only 5%.

Secondary efficacy endpoints such as progression-free survival, response duration, and overall survival will be summarized using the Kaplan-Meier method. Local control will be summarized as a frequency count and percentage. Other endpoints, such as PD-L1 expression, will be summarized as medians and ranges (e.g. proportion of cells expressing PD-L1) or frequency counts and percentages (e.g. number and percent of patient with PD-L1 expression in ≥50% of cells) as appropriate.

Methods such as Fisher's exact test, chi-square tests, logistic regression (categorical data), the logrank test and proportional hazards models (time to event data) will be used to compare patient groups. These analyses are primarily exploratory and it is acknowledged that they will have relatively low statistical power.

All genomic, transcriptomic, and proteomic molecular analyses will be exploratory. These studies would be analyzed using a prospective-retrospective statistical analysis plan (SAP).

2 STUDY OBJECTIVES AND ENDPOINTS

Hypothesis: *Focal radiation therapy to tumors can lead to improved tumor antigen presentation in patients with NSCLC. Such treatments could improve tumor responses to pembrolizumab in patients, by enhancing the host immune response.*

2.1 Study Objectives

2.1.1 Primary Objective

Objective: To determine the tumor responses outside the radiation

2.1.2 Secondary Objective

Objective:

1. To determine the progression-free and overall survival in patients with NSCLC receiving pembrolizumab, who receive Single Fraction Radiation Therapy (SFRT)

2. To determine the safety and toxicity of the combination of SFRT and pembrolizumab

3. To examine potential predictive biomarkers in tumor samples and peripheral blood in patients treated with pembrolizumab and SFRT

4. To determine the local control of SFRT in the radiated lesion(s), when SFRT is given with pembrolizumab

5. To evaluate the induction of a T-cell response in patients with metastatic NSCLC treated with radiation and the effect of radiation

2.1.3 Exploratory Objectives

To examine potential predictive biomarkers in tumor samples and peripheral blood in patients treated with pembrolizumab and SFRT.

2.2 Efficacy Endpoints

2.2.1 Primary Endpoint

The **Best Overall Response** is the best response recorded from the start of the treatment until disease progression (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The anti-tumor activity will be evaluated as an efficacy endpoints based on radiographic (CT). RECIST 1.1 will be applied for evaluation of tumor response.

2.2.2 Secondary Endpoints:

1. **Progression Free Survival (PFS)** is defined as the time from initiation of study drug post-SFRT, until the first documented, confirmed progression of disease. PFS will also be measured and report from the initiation of study drug, pre-SFRT.

2. **Overall Survival (OS)** will be measure from the initiation of study therapy

3. Durable Overall Response at 6 months and 12 months

4. **Local Control with SFRT:** The target lesion(s) selected for SFRT will be followed for local control. For the purpose of the study, local control will be defined as a complete response, partial response, or stable disease within the planning target volume. The duration of local control will be measured from the time of SBRT treatment fraction.

2.2.3 Safety Endpoints

1. Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.0), timing, seriousness and relationship to study treatments

2. For patients receiving SFRT to lung lesions, the development of grade 3 or greater pneumonitis that is probably or definitely attributable to either SFRT or pembrolizumab within the follow-up period will be monitored

2.2.4 Biomarker Research

1. Evaluate predictive biomarkers on pre-treatment biopsies and peripheral blood samples

   Tissue based biomarkers: PD-L1 expression will be evaluated using chromogenic staining using the FDA approved DAKO PDL-1 IHC assay (22C3) and using novel quantitative immunofluorescence (QIF) based platforms. In addition to PD-L1, we will evaluate the predictive value of several other immune evasion and/or activation markers in the tumor and immune infiltrate compartments. These assays will be done in the Translational Immuno-oncology lab at the Yale University, New Haven, CT and in Collaboration with Genoptix Inc.

   Peripheral Blood based biomarkers:

   a) Proteomic assays in collaboration with Biodesix and Pandey lab at Johns Hopkins will be used and validated to determine predictive value

   b) Frequency and phenotypic character of PBMC subsets including DCs, MDSCs, T-cells and Natural killer (NK) cells, these will be done in collaboration with Genoptix Inc.

In addition, exploratory biomarkers using imaging-derived quantitative measurements of responses; these will be done in collaboration with the Center for Computational Imaging and Personalized Diagnostics at the Case Western Reserve University, Cleveland, OH.

3 STUDY DESIGN

3.1 Study Design

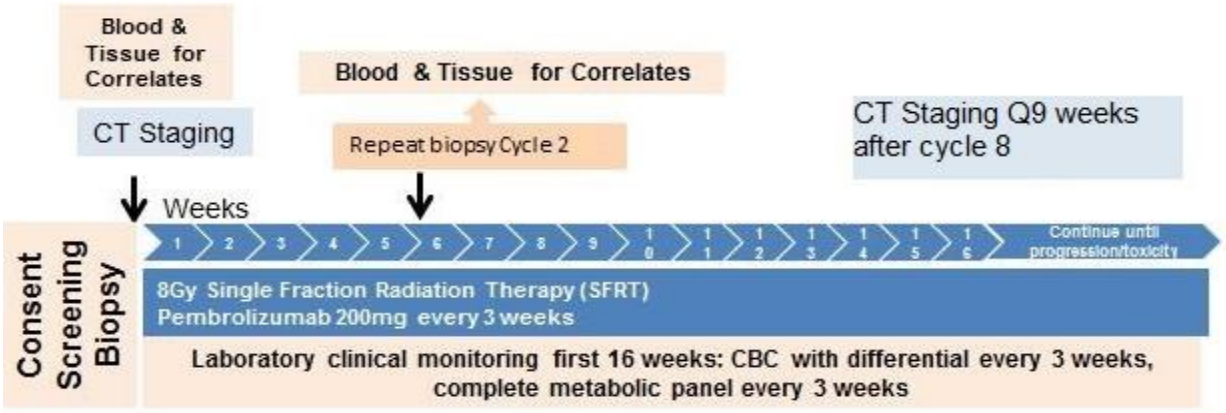

Figure 2 - Study Overview Flow Diagram

This is a phase II trial of pembrolizumab sequentially following focal radiation to one or more of the target lesions, in patients with stage IV Non-Small Cell Lung Cancer (NSCLC). The primary goal of this trial is to evaluate the efficacy of focal radiation (RT) to index lesion(s) as a way of enhancing the anti-tumor immune response to pembrolizumab. The primary efficacy endpoint is overall RECIST-defined response outside the radiation field. To accomplish this goal 48 patients will be enrolled in this study.

3.1.1 Tumor Imaging and Assessment of Disease

The initial tumor imaging will be performed within 30 days prior to the first dose of trial treatment. CT scans are the required modality for measureable disease unless a subject has a clinical condition e.g. severe contrast allergy, or the lesions are significantly better visualized through the use of an MRI. The same imaging technique must be used for a subject throughout the study. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 30 days prior to the first dose of trial treatment. Repeat imaging would be performed after every 2 cycles of therapy for the remainder of the on-study treatment period or more frequently if clinically indicated. CT timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies. This protocol recommends that patients receiving pembrolizumab as standard of care after EOT will have CT scans every 9 weeks +/- 14 days until the subject experiences confirmed disease progression or starts a new antineoplastic therapy.

Subjects who discontinue trial treatment for reasons other than disease progression should also receive tumor imaging every 9 weeks +/- 14 days until the subject experiences confirmed disease progression or starts a new antineoplastic therapy.

Disease progression for trial eligibility will be according to RECIST 1.1 criteria. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management. De-identified imaging will also be obtained from all participating sites for

imaging correlative studies to be done by collaborators at Case Western Reserve University Biomedical Engineering group.

3.1.2 Tumor Tissue Collection and Correlative Studies Blood Sampling

3.1.2.1 *Correlatives in Biopsy Tissue*

All the tissue based immunological correlatives PD-L1 expression and other exploratory correlatives will be performed by NavigateBiopharma and in the Translational Immuno-oncology Laboratory lab at the Yale University. Both these laboratories are specialized in measurement of immune biomarkers and have access to CLIA-compliant facilities.

i. *Measurement of Tumor infiltrating immune cells on pre-treatment and post treatment biopsies:* The automated quantitative spectral multiplexing platform for evaluation of immune biomarkers is highly novel. We have previously developed and validated ways to reproducibly measure and quantify TILs and immune biomarkers by QIF. (51, 59, 61) To understand the tumor immune landscape, we will characterize the immune infiltrates in the samples using a previously described and validated assay to objectively interrogate different lymphocyte subsets. (59) This assay comprises the simultaneous staining and measurement of tumor cells (cytokeratin), T cells (CD3), cytotoxic T cells (CD8) and B lymphocytes (CD20). The signal intensity and amount of cells will be measured using informatic tools as described for PD-L1. These will be done in collaboration with Tumor immunology lab at Yale to develop and validate several immune biomarker panels for potential use in the clinical setting. This collaboration will expand on our previous work.

ii. *Measurement of several immune biomarkers in the tumor and stromal compartments on pre-treatment and post treatment biopsies*: PD-L1 expression will be determined for all patients on pre-treatment samples per standard of care using the DAKO PD-L1 assay in the Yale CLIA lab. Positivity will be determined by the presence of any (non-nuclear) PD-L1 signal present in intact tumor and/or stromal cells within the tumor region of the tissue examined, as evaluated by a pathologist in preparations stained with chromogenic immunohistochemistry for PD-L1 and counterstained with hematoxylin. Operationally, a positivity threshold of signal present in >1% of cells will be used. An additional 3-tiered semi-quantitative categorical result will be rendered by the pathologist based in the estimation of the percentage of positive cells including 1+ (<30%), 2+ (30-<60%) and 3+ (60-100%). PD-L1 negative cases will be those with absence of any detectable signal in the sample tested and with appropriate tissue and staining controls.

   In addition to chromogenic PD-L1 IHC using a novel platform, we can increase specific staining of multiple tissue biomarkers (PD-L2, B7H4, TIM-3, VISTA, LAG-3, IDO-1 etc.), and are able to reach 6-plex and beyond in a single image retaining the morphologic context of the tumor. The incorporation of such novel approaches could positively impact the value of tissue biomarker determination for anti-cancer immunotherapies. Finally, additional correlative studies using novel approaches with higher sensitivity and throughput, such as the Luminex assay69 and CyTOF massspect based cytometry70, will be pursued once these platforms are appropriately standardized.

iii. *Omics Testing*: We will evaluate the genomic, transcriptomic, and proteomic profile of subjects' tumors to identify gene mutations, gene amplifications, RNA-expression, and protein-expression using the Nantomics "Omics platform". The exploratory genomics, transcriptomic, and proteomics molecular profiling will be performed on formalin-fixed, paraffin embedded (FFPE) tumor tissue and whole blood samples (subject matched normal comparator against the tumor tissue) by next-generation sequencing and mass spectrometry-based quantitative proteomics. Collection of tumor tissue and whole blood is mandatory for this study, unless an exception is approved by the sponsor investigator. See lab manual for tissue collection requirements.

iv. *Next Generation Sequencing for T-cell receptor clonality*: TCR sequencing and clonality quantification on pre-and post-treatment samples will be performed using ImmunoSeq assay in a multiplexed PCR method using forward primers specific to TCR Vβ gene segments and reverse primers specific to TCR Jβ gene segments. In addition, using Immune Repertoire Capture™ (IRC™) technology we will evaluate immune response, enabling the identification and generation of functional human antibodies and TCRs. This delivers an unparalleled quantitation of the adaptive immune response. This will be done in collaboration with Atreca Inc.

v. *Pharmacodynamic analyses*: The intended molecular pharmacodynamic effect of oral THU-decitabine is depletion of DNMT1 in tumor tissue. This will be measured by QIF. DNMT1-depletion is expected to induce p53-independent cell cycle exits, with downregulation of MYC and upregulation of p27/CDKN1B. This will be measured by QIF also. Finally, the intracellular accumulation of decitabine to deplete DNMT1 depends on relative expression in the cancer cells of pyrimidine metabolism enzymes DCK, CDA and UCK2, and also the growth fraction of the malignancy, measured by surrogates such as KI67. These parameters will also be measured by QIF.

3.1.2.2 Correlatives in Blood

i. *Phenotypic character of PBMC*: To be performed by GenOptix. Multiplex T cell phenotyping flow cytometry panels. We will design a broad T-cell flow cytometry panel composed of multiple exhaustion markers, checkpoint receptors and activation markers. Non-biased automated algorithms will be used to determine T-cell signatures predictive of response and resistance to immunotherapies. The putative markers in the panel may include CD3, CD4, CD8, CD45RO, CD45RA, CCR7, CD95, CD27, CD25, CD57, CD107, CD69 CD11A, TIM3, HLA-DR, PD-1, LAG3, OX40, ICOS, CCR4, CXCR3, CCR6, BIM, EOMES, CTLA-4. In addition to T-cells, we will evaluate other immune cell subsets including dendritic cells (DCs), monocyte populations, and NK cells. A whole blood immunophenotyping assay will quantify the absolute number and proportion of NK cells (CD56+CD3-), NKT cells (CD56+CD3+), B cells (CD19+), and monocytes (CD16+). In addition, both myeloid (CD45+HLADR+ CD11c+CD123-) and plasmacytoid (CD45+HLA-DR+CD11c-CD123+) DC frequencies will be measured in this precision-validated multiparameter flow cytometric assay. In addition, PBMCs will be cryopreserved for future potential studies using platforms such as Mass cytometry

(CyTOF), IRC™ and CIBERSORT, and will be correlated to the immunologic response, clinical response, and survival data.

ii. *Serum proteomic and ctDNA correlatives:* Exploratory proteomic analysis using MALDI ToF mass-spectrometry and ProTS will be performed in collaboration with Biodesix and the Pandey lab at Johns Hopkins on baseline and on treatment plasma samples at time points defined in the protocol from patients in the study.

PBMCs, Serum and plasma will be banked for other potential correlatives

3.1.3 Laboratory Procedures/Assessments

Laboratory Safety Evaluations (Hematology and Chemistry) are to be performed.

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

3.2 Number of Subjects

The maximum accrual goal is 48 eligible and evaluable patients. Initially 29 eligible and evaluable patients will be entered into the trial. If $\leq$6 patients respond (observed ORR $\leq$21%) the trial will be stopped for (relative) lack of efficacy. If more than 6 patients respond an additional 19 eligible and evaluable patients will be entered

3.3 Replacement of Subjects

Patients who do not receive treatment on study, e.g. do not receive C1D1 of study treatment, will not be counted towards the accrual goal of 48 participants and will be replaced.

3.4 Expected Duration of Treatment and Subject Participation

Subjects will complete 8 cycles (28 weeks) of on study treatment. Before they begin study treatment they will receive SFRT to one or more target lesions. If participants experience complete response while on study treatment they will stop treatment with pembrolizumab. If they experience recurrence after this time they have the option of re-starting treatment on trial as long as all eligibility requirements are still met.

3.5 Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug

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

4 SUBJECT SELECTION

4.1 Entry Criteria

4.1.1 Informed Consent

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

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

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

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

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

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

4.1.2 Inclusion/Exclusion Criteria

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

4.1.3 Medical History

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

4.1.4 Prior and Concomitant Medications Review

4.1.4.1 Prior Medications

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

4.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.

4.1.5 Disease Details and Treatments

4.1.5.1 Disease Details

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

4.1.5.2 Prior Treatment Details

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

4.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatments. The safety follow-up visit should occur 30-days (+/- 7 days) after discontinuation of Pembrolizumab or prior to the start of a new anti-cancer therapy, whichever occurs first. Once new anti-cancer therapy has been initiated, the subject will move into survival follow-up.

4.1.6 Diagnosis/Condition for Entry into the Trial

1. Histologically documented, metastatic NSCLC

2. Patients with EGFR and ALK alterations should have been treated with at least 1 line of targeted tyrosine kinase inhibitor

3. At least 2 distinct measurable metastatic sites; patients can have radiation to multiple measurable disease sites as clinically indicated, however, there must be at least 1 measurable non-radiated target lesion for primary endpoint assessment of abscopal response.

4. Agreeable and clinically feasible pre-treatment biopsy if archival tissue is not available and an exception is not granted by the sponsor investigator.

4.2 Subject Inclusion Criteria

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

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

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

3. Have measurable disease based on RECIST 1.1.

4. Be willing to provide archival tissue of any age or tissue from a newly obtained core or excisional biopsy of a tumor lesion if an exception is not granted by the sponsor investigator.

5. Have a performance status of ≤1 ECOG Performance Scale.

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

Table 1 - Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL

[a]Creatinine clearance should be calculated per institutional standard.

7. Have one measurable lesion outside of the planned radiation field (defined as not receiving direct beam from any of the treatment portals).

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

9. Female subjects of childbearing potential (Section 6.7.2) must be willing to use an adequate method of contraception as outlined in Section 6.7.2.1, for the course of the study through 120 days after the last dose of study medication.

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

10. Male subjects of childbearing potential (Section 6.7.2) must agree to use an adequate method of contraception as outlined in Section 6.7.2.1, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

4.3 Subject Exclusion Criteria

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

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

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

4. Hypersensitivity to pembrolizumab or any of its excipients.

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

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

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

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

Exception: any AEs related to adequate organ function laboratory values that are within parameters in Table 1 adequate organ function is met per Laboratory Values

7. Patients who have previously received radiation overlapping with the current planned radiation treatment fields are ineligible. Overlap is defined as any tissue falling within the direct path of both prior and current planned radiation fields.

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

9. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are clinically stable for at least 4 weeks and, have no evidence of new or enlarging brain metastases and also are off steroids 3 days prior to dosing with study medication. Stable brain metastases by this definition should be established prior to the first dose of pembrolizumab.

10. Has had prior chemotherapy, within 2 weeks prior to study treatment. Patients on targeted therapy (tyrosine kinase inhibitor) may go on the study after 5 days off therapy. Patients can be screened but cannot start study treatment until after the above washout period.

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

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

13. Has an active infection requiring systemic therapy.

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

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

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

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

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

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

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

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

5 REGISTRATION

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects. Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit. If the subject is found to be eligible he/she will retain screening number as the on study identification number.

6 TREATMENT PLAN

The Study Schema (Section 6.4) summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

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

6.1 Screening

Approximately 30 days prior to study treatment, potential subjects will be evaluated to determine that they fulfill the entry requirements. Screening procedures may be repeated after consultation with the Sponsor. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

1. Laboratory tests are to be performed within 10 days prior to the first dose of trial treatment.

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

3. Tumor imaging must be performed within 30 days prior to the first dose of trial treatment.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria.

Results from assessments performed during the initial screening period are acceptable in lieu of repeating a screening test if performed within the specified time frame and the results meet the inclusion/exclusion criteria.

6.2 Treatment/Core Study Period

6.2.1 Timing of Dose Administration

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

Table 2 - Trial Treatment

Drug	Dose	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
SFRT + Pembrolizumab	8 Gy	Single Fraction	External Beam Radiation	Within 3 days from first dose of Pembrolizumab	Study Arm
	200 mg [a]	Q3W[b]	IV infusion	Day 1 of each 3 week cycle	

a) Initial Pembrolizumab treatment could begin on the same day as the SFRT but no greater than 3 days after the SFRT.

b) Proceeding the initial C1 treatment, Pembrolizumab can be administered up to +/- 7 days to the scheduled Day 1 of each cycle for patient related factors or administrative reasons per physician discretion

The first fraction of SFRT should be delivered as soon as feasible after planning and simulation. Pembrolizumab will be administered within 3 days **after** SFRT administration.

Trial treatment should be administered on Day 1 of each subsequent cycle after all procedures/assessments have been completed as detailed on the Study Schema. Trial treatment may be administered up to 7 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments may be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible.

However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Please see the Pharmacy Manual for specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

6.2.1.1 SFRT Planning

Patients will undergo CT simulation and treatment planning per standard practice. Patient immobilization should be sufficient to ensure minimal intra- and inter-fraction set-up error, and is otherwise left to the discretion of the treating radiation oncologist. The treating physician will define a planning target volume (PTV) to which the dose will be described, and which will be used to define local control or local failure. 3D conformal beam arrangement is encouraged, though advanced techniques are allowed at the discretion of the treating radiation oncologist. At least 90% of the PTV should receive 90% or more the prescription dose. All organs at risk within 5 cm of the PTV will be contoured, and dose-volume histograms produced. For the treatment dose of 8 Gy x 1 in a non-previously irradiated field it is not expected that normal tissue dose-limits would be exceeded, however, the treatment field should be evaluated at the discretion of the treating radiation oncologist.

This will be followed by pembrolizumab 200mg solution intravenously every 3 weeks until progression of disease (PD) (RECIST) or unacceptable toxicity (protocol defined). Treatment cycles will be every 21 days, and formal radiographic assessment will be performed at baseline and then after every 2 cycles i.e. end of C2, C4, etc. Tumor measurements will be performed according to RECIST criteria.

6.2.2 Treatment Regimen Overview

Refer to the study schema in section 6.4 for a full list of tests and procedures during the screening, treatment, and follow-up periods.

6.2.2.*1* *Clinical Procedures/Assessments*

6.2.2.1.1 Adverse Event Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Study Schema, and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 7). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs). Refer to the ECI guidance document regarding the identification, evaluation and management of potential irAEs.

Please refer to section 7 for detailed information regarding the assessment and recording of AEs.

6.2.2.1.2 Full Physical Exam

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

6.2.2.1.2 Directed Physical Exam

The investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration for each visit.

6.2.2.1.2 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 Study Schema. Vital signs should include temperature, pulse, respiratory rate, weight, and blood pressure. Height will be measured at screening only.

6.2.2.1.2 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix I) at screening, prior to the administration of each dose of trial treatment, and at treatment discontinuation of trial treatment as specified in the Study Schema.

6.3 Post-Study Follow-Up Period

6.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted 30 days +/- 7 days after the last dose of core study (i.e. after 8 cycles) treatment or EOT visit, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with a treatment related AE of Grade ≥ 1 will be followed until the resolution of the AE to Grade 0 or until the beginning of a new anti-neoplastic therapy, whichever occurs first.

6.3.1.1 Survival Follow-Up

Subjects will be followed every 12 weeks +/- 14 days post study for survival status and record of anti-cancer treatments for up to 5 years in follow-up until death, withdrawal of consent, or the end of the study, whichever occurs first. If the subject has any anti-cancer treatments subsequent to study completion at any time during that five year follow-up period, their subsequent treatment would be recorded. This will be done by review of patients' medical records, communication with patients treating physicians, review of public obituary records or contact of patients by telephone.

Table 3 - STUDY SCHEMA

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post Study Treatment**		
Treatment Cycle/Title:	Main Study Screening Visit	1	2	3	4	5	6	7	8	Cycle 8 or off study due to progression/toxicity	Safety Follow-up	SOC Treatment Period (if applicable)	Survival Follow Up[b]
Scheduling Window (Days):	-28 to -1		± 7	± 7	±7	± 7	± 7	±7	± 7	At time of Discontinuation	30 days (± 7) post discontinuation	Per SOC guidelines	Every 12 weeks (± 14 days) post discontinuation
Administrative Procedures													
Informed Consent/ Inclusion/Exclusion Criteria	X												
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X		
Pembrolizumab		X	X	X	X	X	X	X	X			X	
SFRT		X											
Survival Status/ Post-study anticancer therapy status											X	X	X
Clinical Procedures/Assessment													
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X		
Full Physical Examination	X[e]												
Directed Physical Examination	X	X	X	X	X	X	X	X	X	X	X		
ECOG Performance Status	X	X	X	X	X	X	X	X	X				
Local Laboratory Procedures/Assessments													
Pregnancy Test – Urine or Serum β-HCG	X[i]												
CBC with Differential	X[f]		X	X	X	X	X	X	X				
Comprehensive Metabolic Panel	X[f]		X	X	X	X	X	X	X				
T3, FT4 and TSH	X[f]			X		X		X					
Efficacy Measurements													
Tumor Imaging[c]	X[g]			X		X		X				X[h]	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood													
Archival or Newly Obtained Tissue Collection	X[d]			X[d]									

Peripheral Blood/Flow	X			X		X				X			
Serum	X			X		X				X			
PBMC/IRC	X		X	X	X	X	X	X		X			

6.4 Study Schema

a) Patients will begin pembrolizumab on the same day as the SFRT but no greater than 3 days after the SFRT. Patients will receive subsequent Pembrolizumab every 3 weeks (± 7 days per protocol) until progression or unacceptable toxicity. A treatment break for up to 6 weeks will be allowed upon discussion with study PI. The core study period will end at 8 cycles. After cycle 8 (End of Treatment visit) patients will continue pembrolizumab as standard of care if they are tolerating and have no disease progression.

b) Patients will be monitored post study every 12 weeks (± 14 days) for survival status; these could be done by review of patient's medical records or contacting patient's medical provider or the subject. Patients on standard of care pembrolizumab will begin survival follow up after pembrolizumab progression or start of new anti-neoplastic therapy.

c) Patient's disease will be monitored with CT scans of the chest and abdomen after every 2 cycles (i.e. prior to every odd cycle ± 7 days) or sooner, if clinically indicated, while on study treatment. CT scans of the pelvis will be completed only for known pelvic disease or pelvic symptoms as clinically indicated.

d) Patients must be willing to provide archival tissue of any age or obtain a fresh biopsy at screening. If available, tissue collected <6 weeks from the start of study treatment is recommended. If a previous PDL1 status is obtained, a patient may be eligible for a tissue exemption from the sponsor investigator. Patients must be willing to provide a repeat treatment biopsy after 2 cycles of pembrolizumab, before cycle 3 imaging is performed. Both baseline and treatment biopsies can be evaluated on a case by case basis and an exception may be made at the discretion of the sponsor investigator.

e) Consult radiation oncologist for radiation simulation consult. This can be done on the same day or a different day of patient's oncology physical exam as long as it is within the 28 day screening window.

f) Screening laboratory tests are to be performed within 10 days prior to the first dose of study drug.

g) Imaging can be done within 30 days of start of treatment

h) Patients on standard of care pembrolizumab beyond the 8 cycles of study treatment, will have CT scans every 9 weeks (± 14 days).

i) For female subjects of reproductive potential, a urine or serum pregnancy test must be performed within 72 hours prior to first dose of trial treatment.

6.5 Definition of Dose Limiting Toxicity

For the purpose of determining the safety of SFRT and pembrolizumab combination, a DLT will be considered to be any of the following adverse events which are probably or definitely attributable to study treatment, and which occur between the SFRT and within 60 days of the last fraction of SFRT.

1. Any non-hematologic, non-laboratory toxicity which is grade 3 or greater and does not resolve to grade 2 or lower with supportive care within 14 days.

2. Any non-hematologic, non-laboratory toxicity which is grade 4 or greater

For patients with lung targets, the development of grade 3 or greater pneumonitis that is probably or definitely attributable to either SFRT or pembrolizumab within the follow-up period will be considered a DLT, regardless of whether it resolves

6.5.1 Pembrolizumab Dose Selection/Modification

6.5.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Sections 1.1 and 1.3.

Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

6.5.1.2 Dose Modification (Escalation/Titration/Other)

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 4. See Section 6.6 for supportive care guidelines, including use of corticosteroids.

Table 4 - Dose Modification Guidelines for Drug-Related Adverse Events

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

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

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

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

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

6.5.1.3 Dosing Interruptions

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

6.5.2 SFRT Dose Modification and Supportive Care

SFRT with 8Gy is considered a palliative dose and we do not anticipate any significant unexpected adverse events from treatment. However, if any grade 3 or greater adverse event occurs during radiation treatment that are probably or definitely attributable to radiation, this will be counted as a DLT. These patients will be allowed to continue with trial therapy pembrolizumab if the toxicity resolves to grade 0 or 1 with supportive measures within 12 weeks. If greater than 20% (2/10) SFRT related DLTs are seen in the first 10 patients; the study will be put on hold for safety review by the DSMB.

6.6 Concomitant Medications and Supportive Care Guidelines

6.6.1 Concomitant Medications

6.6.1.1 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

6.6.1.2 Acceptable Concomitant Medications

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

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.

6.6.1.3 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids, or short courses of corticosteroid treatment unrelated to study treatment, may be approved after consultation with the Sponsor.

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

The Exclusion Criteria (Section 4.3) describes other medications which are prohibited in this trial.

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

6.6.2 Supportive Care Guidelines

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

Note: If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 6.5.1.2 for dose modification.

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

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

  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For **Grade 2 or higher diarrhea**, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
    - For **T1DM** or **Grade 3-4** Hyperglycemia
        - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
        - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis**:

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

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

- **Hyperthyroidism or Hypothyroidism**:

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

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):

    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.

    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.

  - **Grade 3-4** hyperthyroidism

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

- **Hepatic**:

  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).

    - Treat with IV or oral corticosteroids

  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.

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

- **Renal Failure or Nephritis**:

  - For **Grade 2** events, treat with corticosteroids.

  - For **Grade 3-4** events, treat with systemic corticosteroids.

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

- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

  Table 5 shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 5 - Infusion Reaction Treatment Guidelines

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

6.7 Diet, Sexual Activity, and Other Considerations

6.7.1 Diet

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

6.7.2 Sexual Activity

6.7.2.1 Contraception

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

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

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

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

OR

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

OR

3. Has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

Practice abstinence[†] from heterosexual activity

OR

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

Acceptable methods of contraception are[‡]:

<u>Single method (one of the following is acceptable):</u>

- Intrauterine device (IUD)
- Vasectomy of a female subject's male partner
- Contraceptive rod implanted into the skin

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

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

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

6.7.2.2 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 7.4.

6.7.2.3 Use in Nursing Women

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

6.8 Trial Compliance (Medication/Diet/Sexual Activity/Other)

Interruptions from the protocol specified treatment plan for > 3 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

The total volume of trial treatment infused will be compared to the total volume prepared to determine compliance with each dose administered. The instructions for preparing and administering pembrolizumab will be provided in the Pharmacy Manual. Standard of care therapy will be prepared and administered as per the approved product label

6.9 Withdrawal/Discontinuation

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 weeks of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 6.9.1. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 6.3.1) and then proceed to the Follow-Up Period of the study (described in Section 6.3.1.1).

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

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

- Confirmed radiographic disease progression

Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved.

- Unacceptable adverse experiences as described in Section 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 6.2.2 (Treatment Regimen Overview). After the end of study treatment, each subject will be followed for 30 days for adverse event monitoring. Subjects who discontinue study treatment for reasons other than progressive disease will have post-treatment follow-up visits for disease status every 9 weeks +/- 14 days until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. Additionally, subjects who continue to receive pembrolizumab as standard of care will be followed for disease status every 9 weeks +/- 14 days until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. After documented disease progression or initiation of a non-study cancer treatment, each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

7 ADVERSE EVENTS

7.1 Evaluating Adverse Events

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

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

7.2 Assessing and Recording Adverse Events

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

and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

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

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal. Progression of the cancer under study is not considered an adverse event.

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

From the time of treatment through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.5.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.4 Reporting Pregnancy and Lactation to the Sponsor and to Merck

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

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

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

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

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

7.5.1 Serious Adverse Events

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

- Results in death
- Is life threatening
- Results in persistent or significant disability/incapacity
- Results in or prolongs an existing inpatient hospitalization

- Is a congenital anomaly/birth defect
- Is another important medical event

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.

- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose.

Refer to Table 7 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2 for additional details) that occurs to any subject must be reported within 1 business day to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study whether or not related to the Merck product, must be reported within 1 business day to the Sponsor and within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period (Section 6.3) must be reported immediately to the Sponsor and to Merck Global Safety.

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

SAE reports and any other relevant safety information are to be emailed to the Sponsor, Dr. Pennell, at [redacted] and to the Cleveland Clinic SAE inbox at [redacted]

SAE reports and any other relevant safety information are also to be forwarded to the Merck Global Safety facsimile number: [redacted]

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to

the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

7.5.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

For the time period beginning when the consent form is signed until treatment, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined in Section 7.3, that is not associated with clinical symptoms or abnormal laboratory results.

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

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

7.6 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 7.5 Immediate Reporting of Adverse Events to the Sponsor and to Merck, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

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

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

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

7.7 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations. Please refer to the Manual of Operations for more details on SAE routing procedures.

Table 6 Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days..	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done.	

<table>
<tr><td rowspan="7">Relationship to Merck Product (continued)</td><td colspan="2">This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information.
The following components are to be used to assess the relationship between Merck product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):</td></tr>
<tr><td>Exposure</td><td>Is there evidence that the subject was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?</td></tr>
<tr><td>Time Course</td><td>Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?</td></tr>
<tr><td>Likely Cause</td><td>Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors</td></tr>
<tr><td colspan="2">The following components are to be used to assess the relationship between the test drug and the AE: (continued)</td></tr>
<tr><td>Dechallenge</td><td>Was Merck product discontinued or dose/exposure/frequency reduced?
If yes, did the AE resolve or improve?
If yes, this is a positive dechallenge. If no, this is a negative dechallenge.

Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.</td></tr>
<tr><td></td><td>Rechallenge</td><td>Was the subject re-exposed to Merck product in this study?
If yes, did the AE recur or worsen?
If yes, this is a positive rechallenge. If no, this is a negative rechallenge.

Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time

Note: if a rechallenge is planned for an adverse event which was serious and which may have been caused by Merck product, or if re-exposure to Merck product poses additional potential significant risk to the subject, then the rechallenge must be approved in advance by the sponsor as per dose modification guidelines in the protocol.</td></tr>
<tr><td></td><td>Consistency with Trial Treatment Profile</td><td>Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?</td></tr>
<tr><td colspan="3">The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.</td></tr>
</table>

8 STATISTICAL ANALYSIS PLAN

The primary goal of the trial is to assess the RECIST-defined tumor response rate outside the radiation field in previously treated NSC lung cancer patients given radiation to an index lesion followed by pembrolizumab. Secondary goals include assessment of toxicity, other efficacy measures such as progression-free survival, response duration, overall survival, and local control of disease within the radiation field, immune response, and biomarkers such as PD-L1 expression.

In previous studies (KEYNOTE 001 and 010) the overall response rate (ORR) to pembrolizumab monotherapy has been approximately 20% in this population. Based on this an underlying ORR in the current trial >35% would be considered positive whereas a <20% ORR would be considered negative. A two-stage accrual design that allows for early stopping due to lack of efficacy will be employed to test this hypothesis. The maximum accrual goal is 48 eligible and evaluable patients. Initially 29 eligible and evaluable patients will be entered into the trial. If <6 patients respond (observed ORR <21%) the trial will be stopped for (relative) lack of efficacy. If more than 6 patients respond an additional 19 eligible and evaluable patients will be entered. Pembrolizumab plus radiation will be considered effective if overall 12 or more patients respond (ORR >25%). With this design the likelihood of stopping the trial early for lack of efficacy is >64% if the underlying ORR is <20% and <7% if it is >35%. The overall type I and II errors are 20% and 10%, respectively.

Safety is an important secondary endpoint. Toxicity will be graded using CTCAE version 4.0 criteria, categorized by organ system, and summarized as frequency counts and percentages. Assuming the trial accrues all 48 patients the risk of a particular type and/or grade of toxicity will be estimable using an exact 90% confidence interval that has a maximum half-width of 13%. The likelihood of observing at least one such event is 86% even if the associated risk is only 5%.

Secondary efficacy endpoints such as progression-free survival, response duration, and overall survival will be summarized using the Kaplan-Meier method. Local control will be summarized as a frequency count and percentage. Other endpoints, such as PD-L1 expression, will be summarized as medians and ranges (e.g. proportion of cells expressing PD-L1) or frequency counts and percentages (e.g. number and percent of patient with PD-L1 expression in >50% of cells) as appropriate.

Methods such as Fisher's exact test, chi-square tests, logistic regression (categorical data), the logrank test and proportional hazards models (time to event data) will be used to compare patient groups. These analyses are primarily exploratory and it is acknowledged that they will have relatively low statistical power.

All genomic, transcriptomic, and proteomic molecular analyses will be exploratory. These studies would be analyzed using a prospective-retrospective statistical analysis plan (SAP).

8.1 Pre-Planned Subset Analysis

Preplanned sub-set analysis will be performed based on (1) histology, (2) number of disease sites at the time of study treatment (≤4 versus >4), (3) PD-L1 status (TPS < 50 and TPS ≥ 50) pre-treatment, and (4) TILs status on pre-treatment samples.

9 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations. Clinical Supplies will be provided by Merck as summarized in Table 7.

Table 7 - Product Descriptions

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

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

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

9.5 Returns and Reconciliation

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

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

10 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history. The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with local, national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

10.2 Compliance with Financial Disclosure Requirements

All investigators will follow institutional policy for financial disclosure relating to the study and will be in compliance with federal and institutional guidelines for human research studies.

10.3 Compliance with Law, Audit and Debarment

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

10.4 Compliance with Trial Registration and Results Posting Requirements

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

10.5 Quality Management System

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and

accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. For multicenter studies, participating sites must inform the sponsor-investigator of pending audits.

10.6 Data Management

The Overture and OnCore™ Databases will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. Overture and OnCore™ are Clinical Trials Management Systems housed on secure servers maintained at Case Western Reserve University. Access to data through Overture and OnCore™ is restricted by user accounts and assigned roles. Once logged into the Overture or OnCore™ system with a user ID and password, Overture and OnCore™ define roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore™ Administrator at OnCore-registration@case.edu.

Overture and OnCore™ are designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. This study will utilize electronic Case Report Form completion in the Overture database. A calendar of events and required forms are available in Overture and OnCore™.

11 APPENDICES

11.1 Common Terminology Criteria for Adverse Events V 4.0 (CTCAE)

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

11.2 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* *As published in the European Journal of Cancer:*
E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

In addition, volumetric analysis will be explored by central review for response assessment**.**

APPENDIX I

PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Description	Percent	Description
0	Normal activity. Full active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% if waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead

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