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A phase II trial of ImmunotheRapy with non-ablative RADIAtion, in previously untreated patients with stage IV NSCLC. (IRRADIATE-Lung trial)

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ClinicalTrials.gov Number	*pending*

Initial: 12/20/2022
Amended: 5/4/2023
Amended: 1/9/2024

Statement of Compliance
This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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PROTOCOL APPROVAL SIGNATURES

Protocol Title: A phase II trial of ImmunotheRapy with upfront non-ablative radiation, in previously untreated patients with stage IV NSCLC**. (IRRADIATE-Lung trial)**

Protocol Number: s22-00673

This study will be conducted in compliance with the clinical study protocol (and amendments), International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for current Good Clinical Practice, and applicable regulatory requirements.

_____
Signature

_____
Date

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List of Abbreviations

Abbreviation	Definition
AE	Adverse Event/Adverse Experience
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
CBC	Complete Blood Count
CrCl	Creatinine Clearance
CFR	Code of Federal Regulations
CRF	Case Report Form
CTO	Clinical Trials Office
DHHS	Department of Health and Human Services
DSMC	Data and Safety Monitoring Committee
ECI	Events of Clinical Interest
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigative Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
MOP	Manual of Procedures
N	Number (typically refers to participants)
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0
NIH	National Institutes of Health
NSCLC	Non- small cell lung cancer
NYULH	New York University Langone Health
OHRP	Office for Human Research Protections
OS	Overall Survival
PCC	Perlmutter Cancer Center
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
PK/PD	Pharmacokinetic/Pharmacodynamics
PR	Partial Response

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QA	Quality Assurance
QC	Quality Control
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States
WBC	White Blood Cell

PROTOCOL SUMMARY

Title	A phase II trial of Immunotherapy with upfront non-ablative radiation, in previously untreated patients with stage IV NSCLC**. (IRRADIATE-Lung trial)**
Short Title	**IRRADIATE-Lung trial**
Brief Summary	This is a phase II clinical trial. Adult patients with metastatic non- small cell lung cancer (NSCLC), with at least 2 measurable lesions and those Patients with metastatic NSCLC who are previously untreated are eligible for the study if they meet all inclusion criteria, and do not satisfy any exclusion criteria. Subjects will receive standard of care immunotherapy of Pembrolizumab in addition to non-ablative radiation. The intervention is the low dose fractionation, 4Gy x 5, in the upfront treatment of de novo stage IV NSCLC in up to five distinct subsites of metastatic NSCLC.
Phase	*Phase II*
Objectives	Primary Objective: To estimate the best overall response rate by 4 cycles with the addition of upfront non-ablative radiation to chemo-immunotherapy in de novo metastatic NSCLC. Secondary Objectives: 1. To summarize the overall progression-free survival in patients with NSCLC receiving chemo-immunotherapy, who receive Radiation Therapy 2. To determine the safety and toxicity of the combination of radiation and pembrolizumab 3. To determine the local control of radiation in the radiated lesion, when radiation is given with pembrolizumab
Methodology	*Interventional, Single- open label trial*
Endpoint	Primary endpoint: 1. The Best Overall Response (BORR (CR or PR)) by 4 cycles in previously untreated stage IV NSCLC patients given non-ablative radiation followed by chemotherapy with pembrolizumab and safety and toxicity. Secondary endpoints: 1. Progression free survival, PFS is defined as the time from initiation of study drug post-radiation, until the first documented, confirmed progression of disease or death. 2. Overall Survival, OS will be measured from the initiation of study therapy 3. Durable Overall Response at 6 months and 12 months

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Study Duration	Patients will be followed for 1 year following the completion of the core study period of 6 cycles
Participant Duration	Participant involvement is about 18 months.
Enrollment Period	Up to 2 years
Duration of treatment	Radiation in concert with starting chemotherapy with pembrolizumab up to 6 cycles (18 weeks). Followed by continued treatment with pembrolizumab (SOC)
Study Population	Adults with untreated stage IV non-small cell lung cancer, able to tolerate a combination of immunotherapy (Pembrolizumab) and chemotherapy.
Study Centers/Sites	New York University Langone Health (NYULH) - *Manhattan* - *CyberKnife Center* - *Brooklyn* - *Long Island*
Number of participants	40 participants in 2 years
Description study rationale and Study intervention	**Study Interventions** 1) Radiation (4Gy x 5) to up to five metastatic subsites *2)* Chemotherapy with Pembrolizumab, every 3 weeks X 6 cycles followed by maintenance therapy until progression (Standard of Care)

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Schematic of Study Design

Flow diagram

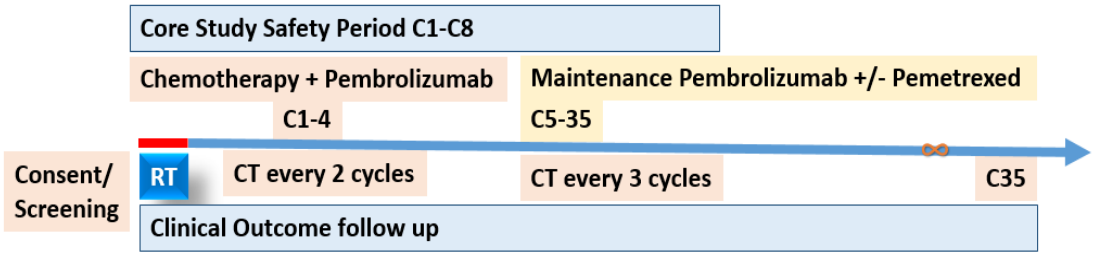

Table 1: Trial Treatment

Intervention	Dose	Dose Frequency	Route of Administration	Regimen/Treatment Period
RADIATION	4 Gy	x 5 fxs	3D-CRT, IMRT, or electrons	+/- 7 days of start of Pembrolizumab

a. Pembrolizumab treatment could begin on the same day as the Radiation but no greater than 7 days after the Radiation start
b. Pembrolizumab administration could be delayed up to 14 days for patient related factors or administrative reasons per physician discretion

1 Key Roles

Principal Investigator: Vamsidhar Velcheti, MD

Co- Principal Investigator: Jonathan Lischalk, MD

Co-Inv/Biostatistician: Judith D. Goldberg, ScD

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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality in the United States, with the majority of patients either 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). The latest paradigm shift from standard platinum-based doublets for NSCLC came with KN024, which established the use of pembrolizumab for patients with metastatic NSCLC whose tumors expressed high levels of PD-L1 (TPS ≥50%). The estimated rate of OS at 6 months was 80.2% for participants receiving pembrolizumab compared to 72.4% for participants receiving chemotherapy, the ORR was 44.8 % in participants receiving pembrolizumab compared to 27.8% in participants receiving chemotherapy, and the PFS was 10.3 months compared to 6 months for controls (64). KN042 lowered the TPS cutoff for 1L pembrolizumab monotherapy by demonstrating significantly improved OS for participants with NSCLC who have TPS ≥50% (HR 0.69, 95% CI 0.56–0.85), TPS ≥20% (HR 0.77, 95% CI 0.64–0.92), and TPS ≥1% (HR 0.81, 95% CI 0.71–0.93) compared with chemotherapy alone [Mok, T. S. K., et al 2019]. Likewise, Cohort G of KN021 had a 56.7% response rate in participants with any TPS score who had nonsquamous NSCLC in the pembrolizumab plus chemotherapy arm compared to 30.2% in the chemotherapy alone arm [Borghaei, H., et al 2018]. A PFS of 24 months was reported in the pembrolizumab plus chemotherapy arm compared to 9.3 months in the control arm with chemotherapy alone. The results of KN021G were extended in KN189 which reported a HR of 0.49 for OS (65). Despite these impressive results, patients with advanced NSCLC (both squamous and nonsquamous histologies) still have an urgent need for new immuno-oncology compounds that can be combined with a pembrolizumab backbone to increase response rates, decrease the risk of progression, and decrease the risk of death for those who do not respond to current treatments. (66,67,68)

2.2 Pembrolizumab Pharmaceutical and Therapeutic Background

2.2.1 Preclinical Data

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. Refer to the IB/approved label for detailed background information on pembrolizumab.

2.2.2 Clinical Data to Date

Refer to the IB/approved label for detailed background information on pembrolizumab.

2.3 Rationale

2.3.1 Rationale for the Trial and Selected Subject Population

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) However despite, this aggressive therapy, the majority of patients will recur and eventually die from their lung cancer from systemic recurrence. 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

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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 RT is capable of converting the irradiated tumor into an immunogenic hub. The processes of antigen presentation and development of cellular immunity are complex processes, and subject to modulation because of 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 produce pro-inflammatory cytokines enhancing 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 ORR of non-ablative radiotherapy followed by ipilumumab demonstrated 18% (intent to treat population) and 33% (in patients receiving 4 cycles of ipilimumab).(40) In addition to 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. Most notable study was a retrospective analysis of the KEYNOTE-001 study that was published in Lancet Oncology in 2017 looked at patients included in this trial who received radiotherapy prior to receiving Pembrolizumab. This unique subgroup analysis found that median overall survival was doubled in patients who previously received radiotherapy prior to Pembrolizumab (10.7 months versus 5.3 months), as compared to their counterparts who were either treatment naive prior to enrollment or who received systemic therapy alone. Median overall survival in those who had received prior extracranial radiotherapy was higher at 11.6 months. (69) ; Following this there were a few trials designed to address this question of synergy of RT with immunotherapy in NSCLC. There were 2 trials both using SBRT with immunotherapy; One trial (PEMBRO-RT trial) used SBRT (24 Gy in 3 doses) followed by Pembrolizumab in previously untreated NSCLC which demonstrated; Median progression-free survival was 1.9 months in the control arm versus 6.6 months in the experimental arm, and median overall survival was 7.6 months in the control versus 15.9 months in the experimental arm; (70); Similar findings were noted in another study from U Penn done in patients with oligo-metastatic NSCLC again using SBRT. (71) There are a few other ongoing clinical trials exploring various different SBRT dosing strategies and exploring using SBRT in oligo progressive state. (NCT03693014, at MSK, NCT03431948 (MOSART trial), U Chicago, NCT03867175, at MD Anderson and NCT02318771 at Thomas Jefferson);

The majority of patients diagnosed with non-small cell lung cancer present in the stage IV setting. However, not all patients are diagnosed with widely metastatic disease at the outset and likely metastatic disease exists more as a spectrum rather than as a binary. A growing body of literature supports the categorization of a separate group of patients with limited sites of metastatic disease, termed oligometastatic, at presentation (Palma 2020, Gomez 2019, Li X 2021). This has been reflected in the most recent AJCC eighth edition staging of non-small cell lung cancer with the creation of the M1b designation. In the setting of limited metastatic disease, aggressive metastasis directed therapy (MDT) has demonstrated improvements in oncologic outcomes in several prospective trials. However, these trials have not explored the utilization of upfront radiation. Moreover, there is very limited data on the utilization of low-dose radiation to stimulate an immunogenic response earlier in the natural history of the disease. Our approach in the IRRIDIATE trial is unique and we attempt to evaluate a “pragmatic” “cost effective” and a dose that is non-ablative (doses below the threshold thought to physically damage DNA or kill cancer cells directly) and potentially superior antigenic dose of RT. Higher radiobiological doses are thought to result in major changes in vascularity and the tumor microenvironment beyond what we classically think of as radiation-induced post-mitotic cell death. This is true whether IO is included or not. There have been recent preclinical studies evaluating the pro-

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immunogenic impact of low-dose (non-ablative) of radiation on the tumor stroma by polarize macrophages into a immunoproliferative M1 subtype, which enhances T-cell responses (72) and also helps homing of T-cells and antigen presenting cells possibly by ameliorating TGF-β signaling, (presented at ASTRO 2018 meeting- Int J Radiat Oncol Biol Phys. 2018;102:3 S26) ; Preclinical data to support low-dose radiation for tumor priming and a handful of clinical trials exploring this dose range, which we referenced in our protocol.

Non-ablative radiotherapy used in a more comprehensive setting to treat de novo oligometastatic disease may provide improvements in cancer progression through standard radiation mechanisms in the absence of systemic therapy. However, when combined with standard of care systemic therapy which now includes immunotherapy, synergistic effects may be seen. The abscopal effect has been well-documented in the literature and radiation therapy has been shown to upregulate the expression of immunomodulatory factors that can alter the inherent immune response to malignancy as well as favorably alter the tumor microenvironment. To date, there is no clear preferred dose fractionation schedule utilized to augment the amplitude or frequency of the abscopal effect. There are several new investigations exploring low-dose external beam radiation to induce immune reprogramming in concert with immunotherapy as well as utilization in overcoming the tumor immunosuppressive stroma locally (Herrara FG 2021, Cancer Discov; Barsournian HB 2020, J Immunothera Cancer). Nevertheless, most of the ongoing prospective trials and existing data is published as it relates to larger more ablative doses of radiation and typically not in the initially diagnosed setting (Palma etc; NCT04238169).

In this proposal, we plan to investigate the phenomenon of 'in-vivo immunization' with focal RT to up to five lesions and the potential for augmenting the anti-tumor immune response with pembrolizumab and chemotherapy. In combining the standard of care chemotherapy and immunotherapy in the upfront setting we explore the use of safe and non-ablative doses of radiation therapy to induce a favorable immunological alteration and determine if induction of this state in the upfront setting can ultimately change the disease course of metastatic lung cancer. **Hypothesis:** Upfront low dose non-ablative 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.

2.3.2 Dose Rationale

a)Dose of Pembrolizumab and chemotherapy:
Pembrolizumab and chemotherapy will be administered per institutional standard of care; please refer to Refer to the approved label for detailed background information on Pembrolizumab and chemotherapy. For non-squamous the standard chemotherapy option of choice is carboplatin and pemetrexed and for Squamous cell carcinoma, the chemotherapy used would be carboplatin and paclitaxel or nab-paclitaxel. The chemotherapy regimen is at the discretion of the investigator and institutional standards.

b) Dose of Radiation and choice of modality:
Many patients with metastatic NSCLC requiring radiation of 4 Gy x 5 fraction in the palliative settings . Utilization of non-ablative low-dose radiotherapy is cost effective and prevents delays to initiation of systemic therapy. Animal studies suggest that low dose (2–4 Gy) radiation can promote tumor immunity via major histocompatibility complex (MHC) up-regulation, antigen presentation, and vascular normalization.(44) At higher doses, radiation 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 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 radiation was dependent on CD8 T-cells. Thus, we suspect that these fractionation schedules could be well tolerated, effective, immunogenic, practical and cost effective regimen to evaluate for the immune-priming effect.

Herein we propose utilizing standardized 4 Gy x 5 dose fractionation schedule delivered in the upfront treatment of de novo stage IV NSCLC in up to five distinct subsites of metastatic NSCLC. This dose fractionation schedule offers non-ablative radiation therapy, which would be expected to yield minimal radiation-related toxicity. Moreover, this dose remains low enough such that were a situation to arise in the future where additional radiation, either palliative or curative, was necessary, reirradiation would be feasible. The preliminary clinical data from the pembrolizumab are promising and strategies such as this to augment tumor specific antigen presentation may augment the responses and clinical benefit from pembrolizumab.

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All patients included will have de novo stage IV non-small cell lung cancer, and those who previously had overlapping radiation therapy in any form, including for a prior metachronous malignancy or otherwise, will be ineligible. Patients with symptomatic lesions will be eligible for palliative radiotherapy and these lesions may be included within the treated quota, assuming palliation is delivered in the sanctioned dose fractionation schedule.

Radiation modality and technique will be determined at the discretion of the treating radiation oncologist. Radiation will be delivered using electrons for superficial lesions, and photons using 3D conformal planning or IMRT (intensity modulated radiation treatment) for deeper tumors. Stereotactic body radiation therapy will not be permitted in the present study. 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.

Definition of "distinct subsites":
Patients diagnosed with metastatic NSCLC will be eligible for the trial and upfront non-ablative radiation therapy will be delivered to up to a maximum of five "distinct metastatic subsites," with the location of treatment at the discretion of the treating radiation oncologist. Distinct metastatic subsites are defined as follows:

- Lung
- Axial skeleton
- Appendicular skeleton
- Adrenal
- Liver
- Non-regional lymph nodes
- Soft tissue

No patient will receive radiation to more than two sites of metastatic disease within the *same* metastatic subsite with the exception of skeletal disease. For those patients who undergo radiotherapy to multiple sites of metastatic disease within the same subsite, standard TG 101 dose constraints will be utilized to ensure safe radiation delivery to the adjacent organs at risk. Brain disease is not included within the "distinct subsite" designation given intracranial disease will require treatment prior to enrollment. Patients with intracranial disease treated with stereotactic radiosurgery and/or neurosurgical resection will be candidates for enrollment. However, patient's treated with whole brain radiation therapy will be excluded from eligibility.

Number of lesions irradiated:

- The number of treated lesions will ultimately be dictated by the attending radiation oncologist and will not exceed five lesions.
- We encourage irradiation of the maximal number of distinct subsites that can safely be treated while respecting the geographical distribution of involved sites at presentation, not exceeding a total of five metastatic lesions.
- No patient will receive radiation to more than two sites of metastatic disease within the same metastatic subsite (not applicable to bone lesions). That is, for a patient diagnosed with one bone metastasis and one adrenal metastasis, we encourage treatment of both the bone and adrenal metastases with non-ablative radiotherapy.
- Patients with symptomatic disease requiring palliative radiotherapy will be eligible, withstanding the dose fractionation schedule is in accordance with the present trial.
- At least one lesion, metastatic or locoregional disease, must remain untreated.

Example patient #1: Patient with two metastases in the same subsite, we encourage non-ablative radiation to both lesions in the same subsite at the discretion of the treating radiation oncologist.

Example patient #2: Patient with two metastases within two different subsites, we encourage non-ablative radiation to both lesions in each distinct subsite at the discretion of the treating radiation oncologist.

Example patient #3: Patient with innumerable asymptomatic metastases in a single subsite. We encourage non-ablative radiation to up to two lesions within this subsite. However, if this subsite is axial or appendicular skeletal

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disease, a two lesion limit does not apply and up to five lesions within the skeleton may be treated at the discretion of the treating radiation oncologist.

Example patient #4: Patient with innumerable asymptomatic metastases in every aforementioned subsite. We encourage non-ablative radiation to five distinct subsites targeting five distinct metastatic lesions at the discretion of the treating radiation oncologist.

2.3.3 Rationale for Biomarker Research

Though the exploratory biomarker work up is planned; the samples will be banked in the Wong lab and analysis will be done after the completion of the study when funding for the correlative studies is secured.

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

Potential risks of the combination of immunotherapy with radiation may be increased toxicity, intolerability, or unanticipated adverse drug reactions.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and ICF documents.

The risks of pembrolizumab, pemexetred, carboplatin, paclitaxel, and nab-paclitaxel can be found in their package inserts uploaded in RNav.

Potential risks of the combination of immunotherapy with radiation may be increased toxicity, intolerability, or unanticipated adverse drug reactions.

Immunotherapy and the chemotherapy in the study is considered standard treatment for treating metastatic lung cancer. As with any drug, an allergic reaction can occur. Allergic reactions can be mild or more serious and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat or trouble breathing.

The body forms antibodies when there is something unusual in the blood. This may include medications. An antibody is a type of protein that helps protect the body from bacteria and viruses. Subjects may form antibodies because of the name of study drug.

Risks of Radiation Therapy (RT): Radiation induced fibrosis (RIF) of the skin and subcutaneous tissues is a potential complication that can occur months after RT and progress over several years. RIF is a common adverse outcome in breast cancer patients. The skin and superficial tissues receive almost full dose of radiation and are at risk for RIF. RIF is characterized by skin thickening, shrinkage of the breast, and problems with healing.

Risks of Washout Period: Without your regular medication(s), your disease may get worse. We will monitor your health closely to make sure your disease and symptoms are adequately managed.

2.4.2 Known Potential Benefits

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of a specific intervention. The potential benefit from the study is that the radiation will increase the tumor responsiveness to immunotherapy. The combination of radiation may improve responsiveness in tumors that may otherwise be resistant or refractory to either chemotherapy and/or anti-PD-(L)1 therapy.

3 Objectives and Purpose

3.1 Primary Objective

To estimate the best overall response rate with the addition of upfront non-ablative radiation to chemo-immunotherapy in de novo metastatic NSCLC.

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3.2 Secondary Objectives

1. To summarize the overall progression-free survival in patients with NSCLC receiving chemo-immunotherapy, who receive Radiation Therapy
2. To determine the safety and toxicity of the combination of radiation and chemo-pembrolizumab
3. To determine the local control of radiation in the radiated lesion, when radiation is given with pembrolizumab

3.3 Exploratory Objectives

1. To examine potential predictive biomarkers in tumor samples and peripheral blood in patients treated with chemo-pembrolizumab and radiation exploratory
2. To evaluate the induction of a T-cell response in patients with metastatic NSCLC treated with radiation and the effect of radiation

4 Study Design and Endpoints

4.1 Description of Study Design

This is a phase II open label trial of pembrolizumab sequentially following upfront non-ablative focal therapy to up to five distinct metastatic subsites in de novo stage IV Non-Small Cell Lung Cancer (NSCLC). The primary goal of this trial is to evaluate the efficacy defined by time to progression or death with upfront non-ablative focal radiation (RT) to index lesions as a way of enhancing the anti-tumor immune response to pembrolizumab. To accomplish this goal 40 patients will be enrolled in this study.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

1. To estimate the best overall response rate by 4 cycles with the addition of upfront non-ablative radiation to chemo-immunotherapy in de novo metastatic NSCLC

4.2.2 Secondary Study Endpoints

1. **Progression free survival**, PFS is defined as the time from initiation of study drug post-radiation, until the first documented, confirmed progression of disease or death. PFS will also be measured and reported from the initiation of study drug, pre-radiation.
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** radiation**:** The target lesion(s) selected for radiation will be followed for local control using RECIST criteria guidelines (version 1.1). 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 completion of radiotherapy.
5. **Safety and toxicity**: Incidence of adverse events with the combination of radiation and chemo-pembrolizumab

4.2.3 Exploratory Endpoints

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

4.2.4 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] v.5.0), timing, seriousness and relationship to study treatments
2. For patients receiving radiation to lung lesions, the development of grade 3 or greater pneumonitis that is probably or definitely attributable to either radiation or pembrolizumab within the follow-up period will be monitored

4.2.5 Biomarker Research

Pre-treatment archival and post treatment biopsy specimens and peripheral blood specimens on the study will be banked in the Wong Lab for exploratory analysis after completion of the study; In addition, pretreatment and on treatment imaging will be collected and archived for exploratory imaging biomarkers using imaging-derived quantitative measurements of responses.

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5 Study Enrollment and Withdrawal

5.1 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. Pathologically documented, metastatic NSCLC with no previous systemic therapy
3. At least 2 distinct measurable metastatic sites, which are 1 cm or larger; 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 response assessment.
4. Agreeable to provide archival tissue for correlative studies (1 cell block or 20 slides recommended); if no archival tissue or inadequate number of slides are available , exemption may be granted by the study team. Note: Cytology samples are acceptable.
5. Be ≥ 18 years of age on day of signing informed consent.
6. Have measurable disease based on RECIST 1.1.
7. Have a performance status of ≤2 ECOG Performance Scale.
8. Demonstrate adequate organ function as defined in Table 2, all screening labs should be performed within 14 days of treatment initiation
9. Have one measurable lesion of at least 1 cm outside the planned radiation field (defined as not receiving direct beam from any of the treatment portals).
10. 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.
11. Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section – Contraception, 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.
12. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section- Contraception, 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.

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

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 prior chemotherapy, immunotherapy or targeted small molecule therapy within 6 months prior to study Day 1.
6. Patient who have previously received radiation overlapping, as determined by the treating radiation oncologist, with the current planned radiation treatment fields are ineligible.
7. Patient's treated with whole brain radiation therapy are ineligible.
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 (with SRS and/or neurosurgery) may participate provided they are clinically stable and, have no evidence of new or enlarging brain metastases and also are off steroids 3 days prior to dosing with study medication.
10. Patients who have not recovered (i.e., ≤ Grade 2 or at baseline) from adverse events due to a previously administered agent. *Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy. Has active autoimmune

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

11. Has history of autoimmune disorders, (non-infectious) pneumonitis that required steroids, evidence of interstitial lung disease or active, non-infectious pneumonitis.
12. Has an active infection requiring systemic therapy.
13. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
14. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
15. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
16. Patients with prior history of chemoradiation for lung cancer
17. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
18. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected) and with abnormal liver function tests.
19. 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.

Table 2: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥7.5 g/dL without transfusion or EPO dependency (within 7 days of assessment)
Renal	
creatinine clearance **OR** eGFR	≤ 3 X upper limit of normal (ULN) **OR** ≥40 mL/min for subject with creatinine levels > 2 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 2 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	>1.5 g/dL
[a]Creatinine clearance should be calculated per institutional standard.	

5.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

5.4 Strategies for Recruitment and Retention

The inclusion and exclusion criteria in this study should not have a negative effect on the enrollment of the desired populations.

Target enrollment for this study is 40 patients over two years. The target accrual goal is 20 patients per year. Patients will be recruited from physicians participating in this study. Consenting, screening, and treatment will take place at the NYU Langone Health PCC or participating sub-sites under the supervision of the Site PI. Recruitment will end when approximately 40 participants are enrolled and receive at least radiation treatment. It is expected that approximately 40 participants will be enrolled from two participating sites.

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Prospective subjects will receive detailed information regarding this study; its investigational nature, required study procedures, alternative treatments, risks and potential benefits of the study. They will also receive the informed consent document to read. All questions are answered by the PI and qualified research personnel.

The Principal Investigator will:

1. Obtain signed and dated informed consent from the potential subject before any study specific procedures are performed.
2. Determine patient eligibility; see Section 5.1
3. Submit registration to NYU Langone Health Perlmutter Cancer Center CTO
4. Receive registration confirmation from the NYU Langone Health Perlmutter Cancer Center CTO, including a unique study identification number assigned to the patient that will be distributed to the study team upon registration of the patient.

Recruitment and consenting will take place in a private area such as an exam room to protect the patient's privacy. The informed consent process and documentation follows that established procedures of the NYU Langone Health Perlmutter Cancer Center Clinical Trials Office.

Recruited subjects will be from the clinical practices of the principal investigator, sub-investigator or co-investigator. All genders are eligible. There are no racial or ethnic restrictions. All participates must be older than 18 years of age. All women that have with the potential to become pregnant will undergo a urine pregnancy test for confirmation.

All adult individuals with untreated stage IV non-small cell lung cancer, able to tolerate a combination of immunotherapy (Pembrolizumab) and chemotherapy who are recommended by the principal investigator, sub-investigator or co-investigator will be offered trial participation unless one or more exclusion criteria's are met as detailed above. Prior to study entry, the patient's TP will give clearance for the subject to enroll in the study. The patient will be approached in a private setting such as the PI's or qualified research personnel office or exam room to protect the confidentiality and privacy of the patient. Subjects will be given a reasonable amount of time to review the study and determine their involvement. In the ICF SOP HSR-301: Informed Consent Process and Documentation it states, "The subject should be provided as much time as necessary to have his/her questions answered, consider the ramifications of participation, and be comfortable agreeing to participate".

During recruitment identifiable data will be maintained, stored and access by qualified research personnel in the patients file. Any identifiable data of screen failures will be destroyed immediately after the recruitment period has ended.

5.4.1 Use of DataCore/Epic Information for Recruitment Purposes

This study will utilize EPIC to identify patients that meet the inclusion criteria.

The data collected to recruit patients will be used for subject identification, contacting subjects, informing subjects, and review of a subjects eligibility. The data will be stored in compliance with IRB and FDA regulations. Medical record data will included demographics, medical history, surgery, pathology, labs, imaging, treatments, initial and current lung cancer stages, prior lung cancer treatments, last treatment received, and date/type of biological sample. The study team will search EPIC until the study is no longer open to recruitment.

Any recruitment information sent by email will utilize Send Safe email.

Once potential subjects have been identified, the study team will notify the treating physician (TP) that they have patients eligible to participate as follow:

- TP and Research PI send letter to all potential subjects (letter must have both TP and Research PI's name)
- TP agrees to permit study team to directly contact potential subjects on behalf of TP.
- TP has been notified that the study team will contact potential subjects directly, by phone or email.

Once contact is made, subjects will be told the reason they are being contacted and subjects will be asked if they are interested in participating in this specific study. Should the potential subjects agree, the study team will provide the subjects with information regarding the next steps for participation.

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If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact research-contact-optout@nyulangone.org or 1-855-777-7858.

5.5 Registration Procedures

5.5.1 General Guidelines

Each patient must sign and date an informed consent form before undergoing any study specific procedure unless a procedure is being performed as part of the patient's standard of care.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYULH PCC Clinical Trials Office. The following materials must be submitted to the CTO for subject registration:

1. Complete signed and dated informed consent form
2. Complete signed and dated eligibility checklist
3. All supporting documentation verifying each eligibility criterion has been met

Registration will occur within 48 hours of research coordinator receipt of all of the above documents. A written confirmation of enrollment including a unique study identification number assigned by the research coordinator will be disbursed to the study team upon registration.

Once eligibility is verified, a unique patient study number will be issued within 24 hours of receiving all required registration material. The patient will not be identified by name. This is the point, at which, the patient is considered accrued on study.

5.6 Duration of Study Participation

Patients will be followed 1 year after completion of the core 6 cycles of treatment until progression or death. Patients can continue treatment until disease progression or toxicity per standard of care.

5.7 Participant Withdrawal or Termination

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided.
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
- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab *Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements*
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in the Schedule of Events and Section 7 (Visit Requirements). After the end of treatment, each subject will be followed every 12 weeks post study for survival status and record of anti-cancer treatments for up to 1 year in follow-up or until death. withdrawal of consent, or the end of the study, whichever occurs firstSubjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be

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followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.7.1 Handling of Participant Withdrawals, Termination, or Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 18 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation.

5.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the participating sites, and funding sponsor. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6 Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

6.1 Study Agent(s) and Control Description

Pembrolizumab and chemotherapy are standard of care and will be administered per standard institutional protocol; Refer to the IB/approved label for detailed background information on pembrolizumab

6.1.1 Formulation, Appearance, Packaging, and Labeling

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

6.1.2 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.

6.1.3 Product Storage and Stability

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.

6.1.4 Preparation

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

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

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6.1.5 Dose Adjustments/Modifications/Delays

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below.

Table 3: 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 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
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Toxicity resolves to Grade 0-1	Withhold*
	Confirmed SJS, TEN, or DRESS	Permanently discontinue	Permanently discontinue
Myocarditis	2-4	Permanently discontinue	Permanently discontinue
Neurological Toxicities	2	Toxicity resolves to Grade 0-1	Withhold*
	3-4	Permanently discontinue	Permanently discontinue
Hemolytic Anemia	3-4	Permanently discontinue	Permanently discontinue

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Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
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.; Patients with Grade 3 elevation of AST/ALT without elevated T Bilirubin may continue after resolution of AST/ALT to Grade 1

[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; Refer to **Table 4.** – Infusion Reaction Treatment Guidelines for further management details.

[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.

[*]Resume in patients with complete or partial resolutions (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids.

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.

6.1.6 Duration of Therapy/Timing of Dose Administration

6.1.6.1 Core Study Period

The core study period will end at 6 cycles. Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Schedule of Events. Trial treatment may be administered up to 5 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis per standard institutional protocol.

6.1.6.2 Radiation Planning

We propose utilizing standardized 4 Gy x 5 dose fractionation schedule delivered in the upfront treatment of de novo stage IV NSCLC in up to five distinct subsites of metastatic NSCLC. All patients included will have de novo stage IV non-small cell lung cancer, and those who previously had overlapping radiation therapy in any form, including for a prior metachronous malignancy or otherwise, will be ineligible. Patients with symptomatic lesions will also be eligible for palliative radiotherapy and these lesions may be included within the treated quota, assuming palliation is delivered in the sanctioned dose fractionation schedule. Radiation modality and technique will be determined at the discretion of the treating radiation oncologist. Radiation will be delivered using electrons for superficial lesions, and photons using 3D conformal planning or IMRT (intensity modulated radiation treatment) for deeper tumors. Stereotactic body radiation therapy will not be permitted in the present study. 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.

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Definition of "distinct subsites":
Patients diagnosed with metastatic NSCLC will be eligible for the trial and upfront non-ablative radiation therapy will be delivered to up to a maximum of five "distinct metastatic subsites," with the location of treatment at the discretion of the treating radiation oncologist. Distinct metastatic subsites are defined as follows:

- Lung
- Axial skeleton
- Appendicular skeleton
- Adrenal
- Liver
- Non-regional lymph nodes
- Soft tissue

No patient will receive radiation to more than two sites of metastatic disease within the *same* metastatic subsite with the exception of skeletal disease. For those patients who undergo radiotherapy to multiple sites of metastatic disease within the same subsite, standard TG 101 dose constraints will be utilized to ensure safe radiation delivery to the adjacent organs at risk. Brain disease is not included within the "distinct subsite" designation given intracranial disease will require treatment prior to enrollment. Patients with intracranial disease treated with stereotactic radiosurgery and/or neurosurgical resection will be candidates for enrollment. However, patient's treated with whole brain radiation therapy will be excluded from eligibility.

Number of lesions irradiated:

- The number of treated lesions will ultimately be dictated by the attending radiation oncologist and will not exceed five lesions.
- We encourage irradiation of the maximal number of distinct subsites that can safely be treated while respecting the geographical distribution of involved sites at presentation, not exceeding a total of five metastatic lesions.
- No patient will receive radiation to more than two sites of metastatic disease within the same metastatic subsite (not applicable to bone lesions). That is, for a patient diagnosed with one bone metastasis and one adrenal metastasis, we encourage treatment of both the bone and adrenal metastases with non-ablative radiotherapy.
- Patients with symptomatic disease requiring palliative radiotherapy will also be eligible, withstanding the dose fractionation schedule is in accordance with the present trial.
- At least one lesion, metastatic or locoregional disease, must remain untreated.

Example patient #1: Patient with two metastases in the same subsite, we encourage non-ablative radiation to both lesions in the same subsite at the discretion of the treating radiation oncologist.
Example patient #2: Patient with two metastases within two different subsites, we encourage non-ablative radiation to both lesions in each distinct subsite at the discretion of the treating radiation oncologist.

Example patient #3: Patient with innumerable asymptomatic metastases in a single subsite. We encourage non-ablative radiation to up to two lesions within this subsite. However, if this subsite is axial or appendicular skeletal disease, a two lesion limit does not apply and up to five lesions within the skeleton may be treated at the discretion of the treating radiation oncologist.

Example patient #4: Patient with innumerable asymptomatic metastases in every aforementioned subsite. We encourage non-ablative radiation to five distinct subsites targeting five distinct metastatic lesions at the discretion of the treating radiation oncologist.

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 4 Gy x 5 in a non-previously irradiated

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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. Tumor measurements will be performed according to RECIST criteria.

Non-Ablative radiation administration
Radiation should be delivered as soon as feasible after planning and simulation. Patients will be treated +/- 5 days of administration of pembrolizumab. See study schema and calendar.

Radiation Dose Modification and Supportive Care
Radiation dose of 4 Gy x 5 is considered low dose and routinely used in clinical practice 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.

Definition of Dose Limiting Toxicity
For the purpose of determining the safety of upfront radiation and pembrolizumab combination, a DLT will be considered to be any of the following adverse events which are probably or definitely attributable to radiation, and which occur between the radiation and within 60 days of the last fraction of radiation.

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

Planned subgroup analyses
Preplanned subgroup analysis will be performed based on 1) histology (non-squamous and Squamous) 2) PD-L1 status (TPS <1, 1-49 and TPS ≥ 50) pre-treatment; 3) Radiation dose/Fractionation schedule (4 Gy x 5) 4) Number of lesions treated (≤2 vs. >2).

6.1.7 Concomitant Medications/Vaccinations (allowed & prohibited)

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 study team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

6.1.7.1 Acceptable Concomitant Medications

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

6.1.7.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol

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- Investigational agents other than pembrolizumab
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

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

6.1.8 Rescue Medications & Supportive Care

6.1.9 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 6.1.5 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. This will be performed per clinical standard of care (SOC)

- **Pneumonitis**:
  - Subjects will be closely monitored with pulse ox readings on every visit and instructed about what to do regarding side effects experienced due to 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)**

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

Table 4: Treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

NCI CTCAE Grade	Severity	Dosage Modification
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue pembrolizumab

For reference, see the product label for pembrolizumab at:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125514s133lbl.pdf.

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6.2 Diet/Activity/Other Considerations

Diet

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

6.3 Contraception

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

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

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

1. postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);
   -OR-
2. have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;
   -OR-
3. has a congenital or acquired condition that prevents childbearing.

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

1. practice abstinence† from heterosexual activity
   -OR-
2. use (or have their partner use) acceptable contraception during heterosexual activity

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

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

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

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

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

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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. Women of childbearing potential will receive routine pregnancy testing at each study visit.

6.3.1 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.

6.3.2 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.

7 Study Procedures and Schedule

The Schedule of Events summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

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

7.1 Study Procedures/Evaluations

7.1.1 Screening

Approximately 28 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.

7.1.2 Enrollment/Baseline

Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

- Laboratory tests are to be performed within 14 days prior to the first dose of trial treatment
- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to 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.
- 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.

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7.1.3 Intermediate Visits

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, results of directed physical examination
- Collect blood for the following:
  - CBC with differential
  - Comprehensive serum chemistry panel
  - T3, FT4, and TSH
  - Correlative studies
- Administer the study agent or provide additional medication to the participant.
- Record participant's adherence to treatment program.

7.1.4 Final Study Visit
Post-study follow up

Safety Follow-Up Visit
The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of core study (i.e. after 6 cycles) treatment or EOT visit, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first.

Survival Follow-up
Subjects will be followed every 12 weeks post study for survival status and record of anti-cancer treatments for up to 1 year in follow-up or until death, withdrawal of consent, or the end of the study, whichever occurs first. 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.

7.2 Study Specific Procedures

a) Patients will receive standard of care chemotherapy with 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 6 cycles. After cycle 6 (End of Treatment visits) patients will continue maintenance treatment as standard of care if they are tolerating and have no disease progression.
b) Patients will be monitored post study every 12 weeks for post-study treatment status, response assessment, and survival; these could be done by review of patient's medical records or contacting patient's medical provider or the subject.
c) Patient's disease will be monitored with CT scans of the chest, abdomen and pelvis after every 2 cycles (i.e. prior to every odd cycle +/- 7 days) or sooner if clinically indicated; Patients on study treatment beyond 6 cycles will have CT scans every 3 cycles, and sooner if clinically indicated at the discretion of the treating physician.
d) Patients should have archival tissue available for central testing and correlative studies. If tissue is unavailable for correlative studies an exemption should be requested from the study team.
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) If screening labs are within 14 days of C1D1, they do not need to be repeated.

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.

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.

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Prior and Concomitant Medications Review

Prior Medications

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

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.

Disease Details

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

Prior Treatment Details

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

Subsequent Anti-Cancer Therapy Status

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

Trial Compliance (Medication/Diet/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.

7.2.1Standard of Care Study Procedures

Clinical Procedures/Assessments

Full Physical Exam

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

Directed Physical Exam

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

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 Schedule of Events. Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 18) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Schedule of Events.

7.3 Laboratory Procedures/Evaluations

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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 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. Patients on study treatment beyond 6 cycles will have CT scans every 3 cycles.

Subjects who discontinue trial treatment for reasons other than disease progression should receive tumor imaging every 3 months 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 the sites for imaging correlative studies.

7.3.1 Clinical Laboratory Evaluations
Tumor Tissue Collection and Correlative Studies Blood Sampling

a) Correlatives in biopsy tissue
All the tissue based immunological correlatives and other exploratory correlatives will be performed in the Wong Lab and NYU core facilities. However, these will be banked in the Wong lab and the exploratory analysis will be done after the study completion.

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

7.3.2 Other Assays or Procedures

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

Table:5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin		Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase		(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)		
WBC (total and differential)	Aspartate aminotransferase (AST)		
Red Blood Cell Count	Lactate dehydrogenase (LDH)		Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡		Free thyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		

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Hematology	Chemistry	Urinalysis	Other
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
‡ If considered standard of care in your region.

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

Correlative Blood Draws *

Correlative studies Sample Type	**PBMC**	**Serum**	**Plasma**
Timepoints collected	Screening C1D1 C3D1 +/-7days C5D1 +/-7days C6D1 or Treatment Discontinuation	Screening C1D1 C3D1 +/-7days C5D1 +/-7days C6D1 or Treatment Discontinuation	Screening C1D1 C3D1 +/-7days C5D1 +/-7days C6D1 or Treatment Discontinuation
Draw tube/ Additive type	cfDNA	Red Top Serum	
Qty of tubes	1	1	
Volume per tube	10 mL	5 mL	

* Patients enrolled to the trial in NYU Brooklyn site are exempt from the correlative/research blood draws

8 Assessment of Safety

8.1 Specification of Safety Parameters

8.1.1 Definition of Adverse Events (AE)

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

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

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event

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

- fatal
- life-threatening
- requires or prolongs hospital stay

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- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

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

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

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

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

Adverse Event (AE) Monitoring
The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Schedule of Events 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 5.0. 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).

8.3 Reporting Procedures- notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULH IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

This section also specifies the NYULH IRB requirements for investigator reporting of unanticipated problems posing risk to subjects or others, including adverse events. The IRB requirements reflect the current guidance documents released by the Office of Human Research Protections (OHRP), and the Food and Drug Administration (FDA) and are respectively entitled “Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events” and “Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting – improving Human Subject Protection”.

The NYULH IRB address is:
NYULH School of Medicine IRB
1 Park Avenue, 6th Floor
New York, NY 10016

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Report promptly, but no later than 10 working days:
Researchers are required to submit reports of the following problems promptly but no later than 10 working days from the time the investigator becomes aware of the event:

- Unanticipated problems including adverse events that are unexpected and related
  - **Unexpected**: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.
  - **Related to the research procedures**: An event is related to the research procedures if in the opinion of the principal investigator, the event was more likely than not to be caused by the research procedures.
  - **Harmful**: either caused harm to subjects or others, or placed them at increased risk

Other Reportable events:
The following events also require prompt reporting to the IRB, though no later than10 working days:

- Complaint of a research subject when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol deviations or violations (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - one or more participants were placed at increased risk of harm
  - the event has the potential to occur again
  - the deviation was necessary to protect a subject from immediate harm
- Breach of confidentiality
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
  New Information indicating a change to the risks or potential benefits of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market).

8.4 Reporting Procedures-Notifying the Study Sponsor and NYULH Clinical Trials Office

SAE reporting will begin in conjunction with the date of treatment administration. Any SAEs regardless of relationship or expectedness procedure must be reported immediately to the principal investigator, with a notification email sent to NYUPCCsafetyreports@nyulangone.org and recorded on the case report form.

The following describes events that must be reported to the study sponsor in an expedited fashion. Any member of the study team who becomes aware of an event informs the rest of the study team staff and the PI/Sub-I. The PI/Sub-I determines if the event is unexpected and related to the trial and if the event is harmful to the subject. If the Principal Investigator is not available at the time of the initial report, then the form can be submitted by a Sub-Investigator. This form should be reviewed by the Principal Investigator, whom sign and date initial report upon return.

Initial Report (within 24 hours):
The following events must be reported to the study sponsor within 24 hours of awareness of the event using the NYU CTO Medical Events Form:

- Unanticipated problems
- Serious adverse events, regardless of whether they are unexpected or relationship.

The investigator shall maintain a copy of the Medical Events Form on file at the study site. All report forms must be signed and dated by the Principal Investigator. If the Principal Investigator is not available at the time of the initial report, then the form can be submitted by a Sub-Investigator. This form should be reviewed by the Principal Investigator, whom sign/date initial report upon return.

Report to: NYUPCCsafetyreports@nyulangone.org

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Events of Clinical Interest (any medical event that is deemed significant via Principal Investigator's expertise, but does not apply to SAE categories) will be reported within 2-5 days, or as per study Sponsor specifications.

The study clinician or a study team member will complete a SAE Form within the following timelines: All fatal or life-threatening adverse events must be immediately reported to the Principal Investigator, via appropriate reporting mechanism (on the SAE Form) and submitted to the DSMC/study sponsor within 24 hours of the site awareness. The Serious Adverse Event Form (SAE Form) must be emailed to NYUPCCsafetyreports@nyulangone.org whether full information regarding the event is known or not. Additional follow-up by the investigator will be required if complete information is not known. De-identified source documentation of all examinations, diagnostic procedures, etc. which were completed with respect to the event should be included with the SAE form. For laboratory results, include the laboratory normal ranges.

The Serious Adverse Event Form must also be emailed to the principal investigator, DSMC and Clinical Trials Office within 24-hours (NYUPCCsafetyreports@nyulangone.org), this documentation will be forwarded to the DSMC's appointed medical monitor within 24 hours of the event whether full information regarding the event is known or not. Additional follow-up by the investigator will be required if complete information is not known.

The investigator shall maintain a copy of the Medical Events Form (SAE Form) on file at the study site. All report forms must be signed and dated by the Principal Investigator. If the Principal Investigator is not available at the time of the initial report, then the form can be submitted by a Sub-Investigator. This form should be reviewed by the Principal Investigator, whom sign/date initial report upon return.

Report to: NYUPCCsafetyreports@nyulangone.org

AND

Principal Investigator
Vamsidhar Velcheti, MD
160 East 34th Street, 8th Floor
New York, NY 10016
212-731-5662
Vamsidhar.Velcheti@nyulangone.org

AND

Nina D'Abreo, MD
Nina.D'Abreo@nyulangone.org

Follow-Up report: within 48 hours:
As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the DSMC and study sponsor and should be provided as soon as possible. Current contact information shall be maintained at the site within the regulatory binder.

All SAEs will be evaluated by the DSMC. The investigator is responsible for reporting all SAEs to the appropriate IRB and DSMC. Other AEs will be submitted to the DSMC/study sponsor within 72 hours of site awareness.

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9 Statistical Considerations

9.1 Statistical Hypotheses

The primary objective of this open label trial is to estimate BORR (best overall response (CR or PR) by 4 cycles in previously untreated stage IV NSCLC patients given non-ablative radiation followed by chemotherapy with pembrolizumab and safety and toxicity. Secondary objectives include PFS, assessment of toxicity, and other efficacy measures including response duration, overall control of disease within the radiation field, and exploratory objectives that evaluate immune response and biomarkers such as PD-L1 expression.

Sample size considerations- primary endpoint. The observed response rate Gandhi, etal, 2018 was 47.6% (95% CL: 42.6-52.5) in the metastatic NSCLC setting in the pembrolizumab-combination treatment arm of this completed randomized trial.

Table 6 below illustrates the exact 95% Clopper Pearson confidence intervals for BORR by 4 cycles as the BORR varies. Thus, we note that if the observed rate is greater than 60.5%, the lower edge of the confidence interval would exceed the observed lower edge from Gandhi, et al, 2018.

Table 6. Exact 95% Clopper Pearson Confidence Intervals; 40 Patients Single Arm Trial. Observed Response Rate (pembrolizumab-combination observed rate 47.6%; 95% CL: 42.6-52.5; Gandhi, et al, 2018).

	95% Clopper Pearson Exact Confidence Interval	
Observed Rate %	Lower Limit %	Upper Limit %
42.6	27.1	59.2
47.6	31.6	64.0
52.5	36.1	68.5
57.5	40.9	73.0
60.5	43.8	75.6
62.5	45.8	77.3
65.5	48.8	79.8
67.5	50.9	81.4
72.5	56.1	85.4

There will be no planned interim analysis.

No formal interim toxicity monitoring is planned for this study since standard of care low doses are employed.

9.2 *Statistical Analysis Plan*

Distributions of patient and baseline disease characteristics will be summarized using frequency distributions for qualitative characteristics and summary statistics and graphical displays (including boxplots) for quantitative characteristics. The primary endpoint, BORR by 4 cycles, based on response of the radiated lesions, will be estimated using exact 95% Clopper Pearson confidence intervals and will include only patients who receive radiation. In addition, response rates will be presented within the prespecified subgroups. Defined by PL1+ levels (<1%, 1-49%, ≥50%), by performance status, and by levels of other key patient and disease characteristics.

Additional descriptive analyses will examine the effects of PDL1+ levels, performance status, and other key characteristics jointly in exploratory analyses.

9.3 Safety Review

Safety / Toxicity will be graded using CTCAE version 5.0 criteria, categorized by organ system, and summarized as frequency counts and percentages.

9.4 Secondary endpoints.

Progression free survival will be summarized descriptively using Kaplan Meier methods including time to PFS curves.

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Other secondary efficacy endpoints including response duration, and overall survival will be summarized using Kaplan-Meier methods.

Local control will be defined using RECIST v1.1 criteria for each irradiated lesion, individually. Lesional control will be reported both for the individual patient and in the aggregate for the entire cohort.

All genomic, transcriptomic, and proteomic molecular analyses will be exploratory.

9.5 *Safety Oversight*

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

Review of Serious Adverse Events (SAEs)

All Internal SAEs reported by the CTO, occurring to patients on clinical trials that are not monitored by any other institution or agency, are reported via email to the DSMC list-serv(NYUPCCsafetyreports@nyulangone.org) and to the PCC Medical Monitor listed in the study protocol reviewed within 24 hours by the DSMC. Based on the review, one of three determinations will be made:

- SAE report is considered to be adequate
- Queries for clarification to PI regarding treatment attribution and/or resolution of SAE or completeness of other information. The committee may request a cumulative review of all SAEs on the study to date.
- Request for full DSMC committee review of protocol at the next scheduled meeting.

The DSMC Coordinator will record the committee's decision and incorporate it into the study summary for the next protocol review.

10 Clinical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan detailed below. Adverse events are evaluated regularly by the principal investigator in conjugation with the research team, the DSMC and PCC medical monitor are notified of adverse events via email initially, and then reviewed at the next DSMC monthly meeting. The NYU Perlmutter Cancer Center Data and Safety Monitoring Committee (DSMC) reviews all data collected for patient safety and protocol compliance quarterly Medical monitoring will include a regular assessment of the number and type of serious adverse events.

10.1 Data Monitoring Committee

This investigator-initiated study will be monitored by the Data and Safety Monitoring Committee (DSMC) of the New York University (NYU) Perlmutter Cancer Center (PCC). The DSMC operates based on the National Cancer Institute approved Charter. It is an existing and multidisciplinary committee (consisting of clinical investigators/oncologists, biostatisticians, nurses, and research administration staff knowledgeable of research methodology and design and in proper conduct of clinical trials) that is responsible for monitoring safety, conduct and compliance in accordance with protocol data monitoring plans for interventional clinical trials conducted in the NYULH Perlmutter Cancer Center that are not monitored by another institution or agency. The DSMC reports to the Director of the NYULH PCC.

Per the NYU PCC Institutional Data Safety Monitoring Plan, this phase II trial will be monitored by DSMC at least quarterly (from the date the first patient is enrolled), at protocol-specified interim time points, and at the completion of the study prior to study closure. This review includes accrual data, subject demographics and adverse events. Principal Investigators are required to attend the review of their studies. Additional reviews can be scheduled based on SAE reports, investigator identified issues, external information, etc. The NYU Perlmutter Cancer Center Data and Safety Monitoring Committee (DSMC) reviews all data collected for patient safety and protocol compliance quarterly."

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The study will be monitored every 4 to 6 weeks by Nina D'Abreo, MD to abide to the compliance of protocol procedures, specimen collection and data quality in the study.

The data and safety of the study will undergo monthly review by the CTO's Quality Assurance unit to ensure that all consent procedures were performed per protocol and all records are completed, stored and retained.

Study Halting Rules
Study will be halted when three grade 3 AEs determined to be "probably related" are reported to the DSMC. The investigator will notify the study sponsor and investigators immediately when the third grade 3 event is reported and enrollment screens will stop accepting new study participants. The study sponsor will inform the DSMC members within 24 hours of this occurrence and will provide the DSMC with AE listing reports. After DSMC evaluation a determination will be made on whether the study can continue.

11 Quality Assurance and Quality Control
This study will be monitored according to the monitoring plan outlined in Section 10.1.The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all noted study-related documents (Section 12) and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit. A risk-based, data-driven monitoring approach will be used to verify data for this trial which will also include a centralized review of data for quality, trends, consistency and general safety review. A quality assurance specialist will review the progress of the trial, study data and site processes, remotely, unless source documentation is not available electronically. At each visit, the monitor will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and study manual and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff.

During scheduled monitoring visits, the investigator and the investigational site staff must be available to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor. Any queries identified through this review will be managed within the systems established for query resolution and tracking. Inquiries related to study conduct, which require further information or action will be discussed within the study team for appropriate and documented escalation plans. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database.

External Sites:
The quality assurance specialist will confirm an upcoming monitoring visit with a Subsite Investigator and staff. If remote EMR access is not available, then the Subsite Coordinator will ensure that all source documents for subjects are de-identified and labeled only with the subject ID number(s), and emails all requested documents to the quality assurance specialist by the specified visit date. All documents are reviewed and a monitoring report is submitted within 5 business days from the date of the visit. Any outstanding documents will be listed in the report as a high-priority request for the next monitoring visit. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database. Continued non-compliance and failure to submit documentation will result in the suspension of subject enrollment at the site, until the documents have been received.

At any time during the course of the study, representatives of the FDA and/or local regulatory agencies may review the conduct or results of the study at the investigational site. The investigator must promptly inform NYU PCC CTO of any audit requests by health authorities, and will provide NYU PCC CTO with the results of any such audits and with copies of any regulatory documents related to such audits.

In accordance with HIPAA and associated privacy regulations, a patient's authorization to use personal identifiable health information may be required from each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

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At the NYU Perlmutter Cancer Center, all investigator-initiated protocols are subject to a standardized data and safety monitoring, which includes scientific peer review, IRB review and DSMC review as well as internal auditing.

The review of AEs and trial conduct for this trial occurs at several levels:

1. Principal Investigator: Adverse events are evaluated monthly by the principal investigator in conjunction with the research nurses, data manager and research team.
2. DSMC, at least quarterly.
3. Institutional Review Board (IRB): An annual report to the IRB is submitted by the trial PI for continuation of the protocol. It includes a summary of all AEs, total enrollment with demographics, protocol violations, and current status of subjects as well as available research data.
4. In addition, the quality assurance unit will monitor this trial at least with quarterly interim monitoring to verify adherence to the protocol; the completeness, accuracy and consistency of the data; and adherence to ICH Good Clinical Practice guidelines.

12 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

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

An electronic database capture system will be created to record the data for this trial. Research coordinators will input clinical trial data into the database. This database is password protected and only the PI, assigned study team members, and CTO staff will have access to the database. DataCore, a core resource of the institution, will provide the primary data collection instrument for the study. All data requested in the system must be reported. All missing data must be explained. The quality assurance specialists will monitor this trial at least quarterly for data entry accuracy.

Source documentation should be consistent with data entered into any electronic medical record or the ***electronic data capture system***. Relevant source documentation to be reviewed by the DSMC throughout the study includes:

1. Baseline measures to assess pre-protocol disease status
2. Concurrent medications
3. Treatment records
4. Adverse events

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the

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changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The following consent materials are submitted with this protocol.

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

The consenting process and documentation will follow Standard Operating Procedures (Obtaining Informed Consent for Clinical Trials) of the NYULMC PCC CTO.

13.3.3 Informed Consent

A participating investigator who has completed requisite training for human subject research and has been instructed by the Principal Investigator about the potential participant; also must address any questions/concerns prior to obtaining written informed consent for participation and HIPAA authorization can also obtain consent.

Patients will be given adequate time to read the consent form. They will be given time to ask questions about the study in private exam rooms. Questions will be answered by a participating physician, or qualified research study team member all of whom have completed requisite training for human subject research. Investigators will review the informed consent form with patients and address any questions or concerns prior to obtaining written informed consent for participation. Investigators will stress that participation in the study is completely voluntary and will not affect the care patients receive or result in any loss of benefits to which patients are otherwise entitled.

The Investigator will explain to each potential participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, potential compensation and or costs incurred by the patient and any discomfort this trial may entail. This informed consent should be given by means of standard written statement, written in non-technical language. All patients will be required to sign a written informed consent prior to being registered on this study. No patient can enter the study before his/her informed consent has been obtained. Every effort will be made to answer questions raised by patients and their families or advocates regarding the protocol and alternative therapies prior to asking a patient to sign the consent form.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB approval.

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For non-English speaking patients, institutional translation services will be utilized. All procedures for consenting non-English speaking patients will be in accordance with NYU Langone Health PCC CTO guidelines and policies.

For patients who cannot read. A witness, not related to the research study will be present. The consent will be read to the patient. The patient will also be allowed to ask any questions s/he may have. The investigator will ask the patient questions to ensure s/he understands the study. If the investigator determines the subject understands the study, the patient will mark an X where his/her name would go and the witness will sign the consent form.

13.3.4 Documentation of Consent

The Principal Investigator or IRB approved sub-investigator will be responsible for documentation in the medical record that consent has been obtained from all participants. A signed copy of the consent form will be given to each participant. Original consent forms will be stored in the subject's medical chart.

13.4 Posting of Clinical Consent Form

The informed consent form will be posted on the Federal website after the clinical trial is closed to recruitment and no later than 60 days after the last study visit by any subject, as required by the protocol. Per institutional guidelines, SOP#: HSR-601, instructs the principal investigator on registration and results reporting on clinicaltrials.gov.

13.5 Participant and Data Confidentiality

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

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

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

13.5.1 Research Use of Stored Human Samples, Specimens, or Data

- Intended Use: Samples and data collected under this protocol may be used to study immunotherapy with non-ablative radiation, in previously untreated patients with stage IV NSCLC. No genetic testing will be performed.
- Storage: De-identified data will be stored and maintained in accordance to NYULH institutional policies, in password protected HIPAA-compliant NYULH database TrialMaster, using codes assigned by the investigators. De-identified data will be kept in password-protected EDC. Only investigators and key study personnel will have access to the de-identified data, using unique username and password. There will be no protected health information from the stored de-identified data themselves. Only the PI and key personnel will have the linking key code to associate PHI and study unique identification number. The linking key code is stored separately from the de-identified data on a password-protected NYU Langone Health server. Study data including the linking key will be maintained for in accordance to NYULH institutional policies. The principal investigator will oversee all activities related to the database.
- Tracking: Data will be tracked using TrialMaster.
    - Disposition at the completion of the study: All stored samples will be sent to the Wong Lab. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

13.5.1.1 Future Use of Stored Specimens

Data collected for this study will be analyzed and stored at NYULH. After the study is completed, the de-identified, archived data will be transmitted to and stored at the designated data repository under the supervision of Dr. Velcheti for use by other researchers including those outside of the study. Samples will be stored indefinitely.

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With the participant's approval, de-identified biological samples will be stored at the Wong Lab with the same goal as the sharing of data: to study immunotherapy with non-ablative radiation, in previously untreated patients with stage IV NSCLC. These samples could be used for research into the causes of stage IV NSCLC, its complications and other conditions for which individuals with this disease are at increased risk, and to improve treatment. The data will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage will not be possible after the study is completed As the samples will have already been fully anonymized.

Only the study team will have access to the samples. Samples will be coded with freezer safe labels and will be stored in freezers with emergency backup power. Samples will be coded and only the NYU PI will have access to the linking key between subject ID and subject identity. Genetic testing in a certified lab to diagnose subjects' predisposition to conditions they don't currently know they have will not be done. Subjects can withdraw their samples from banking by contacting the site PI.

When the study is completed, access to study data and/or samples will be provided through the institution's guidelines and under the supervision of the PI.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into TrialMaster, a 21 CFR Part 11-compliant data capture system provided by DataCore. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.2 Study Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.
These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3

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- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity.

All protocol deviations must be addressed in study source documents and reported to IRB Program Official at the time of annual continuing review. If a protocol deviation is determined to be reportable new information, the IRB will be notified immediately.

14.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric post market surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

15 Study Finances

15.1 Funding Source

All study elements are standard of care and will be billed to third parties. The regulatory, data management and clinical responsibilities cost will be covered by the Perlmutter Cancer Center.

15.2 Costs to the Participant

This immunotherapy and radiation is considered standard of care and will be billed to the insurance company or subject.

15.3 Participant Reimbursements or Payments

No subject will receive payments or stipends for participation in this research study.

16 Study Administration

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16.1 Study Leadership

The Steering Committee will govern the conduct of the study. The Steering Committee will be composed of the principal investigator, the PI of the clinical sites, and the PI of the Central Biochemistry Laboratory. The Steering Committee will meet in person at least annually.

17 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the appropriate conflict of interest review committee that has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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

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18 APPENDICES

Table 6*: ECOG Performance Status*

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

18.1 Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

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

18.2 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

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APPENDIX I

Table 7: 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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20 Schedule of Events

Trial Period:	Screening Phase	Treatment Cycles[a]						Post-Treatment	
Treatment Cycle/Title:	Main Study Screening Visit	1	2	3	4	5	End of study treatment will be cycle 6/EOS visit	Safety follow-up visit	Survival Follow Up[b] Every 12 weeks post Discon
Scheduling Window (Days):	-28 to -1		± 7	± 7	±7	± 7	± 7 At time of Discon	+30	
Informed Consent/ Inclusion/Exclusion Criteria	X								
Prior and Concomitant Medication Review	X								
Pembrolizumab		X	X	X	X	X	X*		
RADIATION		X							
Survival Status/ Post-study anticancer therapy status								X	X
Review Adverse Events	X	X	X	X	X	X	X	X	
Full Physical Examination	X[e]								
Directed Physical Examination	X	X	X	X	X	X	X		
ECOG Performance Status	X	X	X	X	X	X	X		
Pregnancy Test – Urine or Serum β-HCG	X	X	X	X	X	X	X		
CBC with Differential	X	X[f]	X	X	X	X	X		
Comprehensive Serum Chemistry Panel	X	X[f]	X	X	X	X	X		
T3, FT4 and TSH	X	X[f]		X		X			
Tumor Imaging (standard of care)	X[c]			X		X			
Archival or Newly Obtained Tissue Collection	x[d]								
Correlative Studies Blood Collection	X	X		X		X	X		

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a) Patients will receive pembrolizumab every 3 weeks (± 7 days per protocol) until progression or unacceptable toxicity. A treatment break for up to 6 weeks for will be allowed upon discussion with study PI. The core study period will end at 6 cycles. After cycle 6, patients are followed for standard of care, seen and monitored; there is continuous treatment monitoring and/ or monitoring in case of side effects.
*After cycle 6 (End of Treatment visit) patients will continue pembrolizumab as standard of care if they are tolerating and have no disease progression. If patients progress prior to cycle 6, there will be an EOT visit, at least 90 days after the last dose of radiation.
b) Patients will be monitored post study every 12 weeks (+/- 3 weeks) for post-study treatment status, clinical safety updates and survival; these could be done by review of patient's medical records or contacting patient's medical provider or the subject.
c) Patient's disease will be monitored with CT scans of the chest, abdomen and pelvis after every 2 cycles (i.e. prior to every odd cycle +/- 7 days) or sooner if clinically indicated; Patients on study treatment beyond 6 cycles will have CT scans every 3 cycles, and sooner if clinically indicated.
d) Patients who have recent (<12 weeks from start of study treatment) tissue biopsy or patients who have had recurrence after surgery within 6 months of surgical resection may be eligible without a fresh biopsy; If the archival tissue is not available, an exception may be made upon discussing with the PI.
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) If screening labs are within 14 days of C1D1, they do not need to be repeated.
g) *For Blood draws, patients who refuse or do not complete the blood draw will not create protocol deviation.
h) For survival follow-up, chart review or phone call will be used to monitor subjects.

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