CLINICAL STUDY PROTOCOL

Protocol Title: A PROSPECTIVE TRIAL OF IMMUNOTHERAPY AND STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR THE TREATMENT OF METASTATIC LUNG CANCER: SBRT SENSITIZATION OF THE PROGRAMMED DEATH-I (PD-I) EFFECT

VERSION 6.0, 06/18/2018

Clinical Phase: Pilot/Phase II

Hypothesis: The addition of Stereotactic Body Radiation Therapy sequenced prior to PD-I/PDL1 blockade leads to increased immunogenicity and immune system response. Increased response should translate to increased progression free survival and improved survival relative to PD-I blockade monotherapy in metastatic lung cancer.

Principal Investigator

Rachelle M. Lanciano MD

Department of Radiation Oncology

Crozer Keystone Health System/Philadelphia CyberKnife Center

2010 West Chester Pike, Havettown, PA 19083

1. INTRODUCTION

Enhancement of the anti-tumor immune response with immunotherapy agents has emerged as a highly effective and complementary approach to the therapeutic mainstays of surgery, cytotoxic chemotherapy, targeted drugs and radiation therapy. More recently, the induction of lasting responses and dramatic tumor regression suggests that immunotherapy may convert previously fatal diseases into chronic manageable situations.

The theory of immune surveillance and immunoediting is a dynamic process involving immune recognition and elimination of cancer, an equilibrium state and at times evasion of cancer from immune system control (1-3). Immune system avoidance and escape is now a recognized hallmark feature of cancer progression and carcinogenesis and the increased rates of lymphoma, sarcoma, and cervical cancer in immunocompromised individuals support the notion that immunoediting is essential for cancer suppression in humans (2), (4).

Under chronic stimulation, T cells lose proliferative and effector function capacity, often due to signal down-modulation via the increased expression of proteins such as PD-1, an inhibitory checkpoint receptor of the CD28 receptor family (5). The ligand for the PD-1 receptor, PD-L1, is expressed in a variety of human malignancies, and its high level of expression has been previously correlated with poor patient prognosis and resistance to treatment in non-small-cell lung cancer, glioblastoma multiforme, and squamous-cell carcinoma of head and neck (6-8)]. Binding of ligand (PD-L1 or PD-L2), often expressed on tumor cells, to PD-1 imparts an inhibitory signal to the T cell, thus down-modulating the anti-tumor T-cell response (9).

Blockade of the PD-1/PD-L1 T-cell checkpoint pathway is an effective and well tolerated approach to stimulating the immune response, and has achieved significant objective responses in advanced, melanoma, renal cell cancer (RCC), and NSCLC (10). However, optimal therapy will likely require combining anti-PD-1 monoclonal antibody (mAb) treatment with conventional therapies and novel immunotherapy approaches. Combination approaches to stimulate convergent aspects of host immunity by employing complementary immunomodulators as well as immune-stimulatory aspects of conventional modalities such as radiation and chemotherapy may result in the development of more effective cancer therapies.

1.1 RADIATION THERAPY AND IMMUNOGENICITY

The abscopal effect is a well described phenomenon in which tumor regression is observed outside of a radiation treatment field after radiation therapy. It is thought to be immune mediated and has sparked interested in multi-modal therapies (11-13). Radiotherapy is known to induce immunogenic cell death in cancer cells, marked by the expression of molecules that elicit "damage-associated molecular patterns" (DAMP's) (14). Chemokines and cytokines such as IL-1B and TNF-A, as well as heat shock protein 70 (HSP70), high mobility group box 1 protein (HMGB1) and adenosine triphosphate (ATP) serve to recruit dendritic cells. Also, DAMP's

induce maturation of dendritic cells enabling antigen presentation, and subsequently the development of an appropriate adaptive immune response (15, 16). Likewise, radiotherapy has been shown to induce the expression of the antigen-presenting molecule MHC-1 as well as *de novo* transcription and up-regulation of tumor antigen proteins in lung cancer cell lines. These cells show increased expression of tumor specific antigen and antigen-presenting complexes and demonstrate increased susceptibility to cytotoxic T-cell killing (17).

Radiation therapy may sensitize tumor cells to immune-mediated attack by releasing soluble tumor antigens from killed cells and increasing tumor cell surface expression of antigens and receptors mediating T-cell recognition and killing (18). Pre-clinical studies have demonstrated that ablative radiotherapy delivered in a hypofractionated regimen more frequently produces an abscopal effect, especially when combined with immunotherapy compared to conventionally fractionated radiation therapy (19). Researchers have speculated whether conventionally fractionated radiation therapy impairs immune response due to increased killing of circulating lymphocytes and reducing immune mediated cancer killing (20). In a pre-clinical mouse model of metastatic breast carcinoma, three doses of 8Gy was superior to a single dose of 20Gy or 5 doses of 6Gy of irradiation in inducing an abscopal effect in mice treated with a CTLA-4 blocking monoclonal antibody (19). Lee et al. showed that ablative doses of radiation correspond to greater levels of dendritic cell maturation and T-cell priming in draining lymph nodes in a mouse model of melanoma (21). Taken together, there is increasing evidence that ablative radiation treatment can produce an individualized "in situ vaccine" against the tumor cells that could work in concert with immunotherapy (22-24).

"Antigen cascade" is a term used to describe the process in which vaccination against a particular tumor antigen results in the acquisition of novel tumor antigens and activity of the immune system toward these newly discovered antigens (25). Antigenic cascade has been observed in preclinical mouse models as well as in human studies (26, 27). Antigenic cascade has been suggested as an essential component of abscopal tumor regression and that radiation therapy, by inducing an immunogenic cell death, when coupled with immunotherapy, can potentially cause polyclonal T-cell responses to a variety of tumor antigens through antigenic cascade leading to a robust immune response against tumor tissues that harbor these antigens (27).

T-regulatory (T-reg) cell representation in the tumor microenvironment after radiation therapy is a known phenomenon (20). Following sublethal irradiation of antigen-primed mice, antigen-specific immune suppression mediated primarily by T-regs develops over several weeks (18). The influx of T-reg cells into an irradiated tumor microenvironment therefore may counteract any benefit obtained from increased antigen release, enhanced antigen presentation, or influx of T effector cells. This observation is often used to suggest that radiation therapy impedes a vigorous immune response since T-reg cells promote tolerance of the immune system toward tumor cells (24),(28, 29). However, the increased presence of T-reg cells following SBRT in the

tumor microenvironment does not correlate with increased immunosuppression. In fact, functional analysis of these T-reg cells reveal impairment and inability to prevent T cell proliferation (30).

These studies suggest high dose hypofractionated radiation abrogates immune system suppressive responses to conventional fractionated radiation therapy creating a prime opportunity for enhanced tumor response when combining SBRT with immune modulating agents. Given the improved outcomes with immunotherapy relative to cytotoxic chemotherapy, it is plausible that enhanced response with combined modality approaches could yield further improvements in clinical outcomes.

1.2 RATIONALE FOR ANTI-PD1 BLOCKADE.

PD-1 is a cell surface molecule frequently expressed on the surface T-cells. It functions as an immune checkpoint and down regulates the immune system by preventing activation and proliferation of T-cells by increasing programmed cell death in cytotoxic T-cells and upregulating T-reg cells (31). Tumor cells have been shown to upregulate PD-1 ligand (PD-L1) expression as a mechanism of immune system evasion. Hence, PD-L1 expression by tumor cells contributes to immune system evasion by tumors (32). As such, PD-1 blockade is an obvious immunotherapy target and has been demonstrated as an effective approach to overcome cancer mediated immunosuppression.

Within the past several years, several groups have employed the use of radiotherapy with PD-1/PD-L1 signaling inhibition in mouse models with remarkable results. Ablative radiotherapy combined with PD-1 inhibition promoted tumor-associated antigen / MHC complex formation and subsequent antigen cross-presentation within lymph nodes followed by cytotoxic T-cell infiltration into tumors in a mouse model of melanoma (33). In a mouse model of intracranial glioma, combination radiation therapy and anti-PD-1 blockade resulted in increased number of killer T-cells and decreased T-reg cell infiltration in tumors when compared to either therapy alone (34). Moreover, up to 40% of mice treated with combination therapy survived longer than 90 days compared to ~ 30-day survival for either treatment alone and these "cured" mice also developed long-term immunity and were resistant to re-inoculation with tumor cells.

PD-1 expression by tumor cells prevents immune system recognition of distant metastases (35). In this mouse mouse model study of metastatic melanoma, PD-1 inhibition resulted in a 66% reduction in secondary non-irradiated tumors 20 days after a single ablative dose radiation. A single dose of 15Gy was chosen since this therapy is representative of SBRT aimed at controlling oligometastatic disease in humans.

2.0 PROPOSED TRIAL RATIONALE

Anti-PD-1 antibodies have demonstrated activity in the treatment of lung cancer. Opdivo was approved in February of 2015 by the FDA for patients with metastatic squamous NSCLC with progression on or after platinum based therapy. In the open-label trial, patients were randomized to receive OPDIVO (n=135) administered at 3mg/kg every 2 weeks. Median survival was improved to 9.2 months compared to 6 months in patients receiving docetaxel (n=137) 75mg/m^2 every 3 weeks, p=0.00025. Median progression free survival was slightly improved to 3.5 months compared to 2.8 months but 1 year overall survival was improved to 42% compared to 24% (36).

We expect that improvements in local control, increased immunogenic response and abscopal effect seen with combined modality treatment will result in improved local control, progression free survival and resultant significant increases in overall survival beyond 3 months. We propose a pilot/phase II study to assess the safety and efficacy of combination immunotherapy and stereotactic ablative radiation therapy (I-SABR).

Treatment will be a sequential combination treatment of SABR/SBRT and immunotherapy to assess the safety and feasibility of treatment. SABR/SBRT will be administered in 3-5 daily treatments followed by immunotherapy following the conclusion of SABR/SBRT. This approach will take advantage of the transient increase in antigen availability, increased antigen presentation and upregulation of PD-1 by tumor cells following ablative radiation therapy. After an interim safety analysis, the study will continue to the phase II portion where overall survival, progression free survival and response rate will be the primary and secondary end points. For reference, outcomes will be compared to the immunotherapy arms of checkmate 057 and Keynote 042 trials.

Several trials examining combination I-SABR are currently underway. A table of selected studies is included in **Table 1.**

Study (Institution)	SABR Target	Dose (Gy/Fractionation)	Immunotherapy Agent	Sequence
NCT02239900 (MD Anderson Cancer Center)	Liver Lung Adrenal	50/4 60/10	Ipilimumab	Concurrent/Sequential
NCT01862900 (Chiles Research Institute)	Lung Liver	15/1 201/1	Anti-OX40	Concurrent
NCT01769222 (Stanford University)	Any	20/2	Ipilimumab	Concurrent
NCT02298946 (NIH/NCI)	Liver	8/1 24/3	PD-1 Inhibitor	Sequential

Table 1. List of selected ongoing I-SABR studies

2.1 RATIONALE FOR DOSE SELECTION

A. Radiation Therapy: All patients in this trial will be treated with fractionated Stereotactic body radiation therapy. Treatment of oligometastatic lung cancer in this fashion has been explored in multiple studies with encouraging long term survival data (37-39). In a recent mult-institutional randomized trial from MD Anderson cancer center, patients with oligmetastatic lung cancer where randomized to systemic therapy plus SBRT to all metastatic sites versus systemic therapy alone (40). The study was terminated early after a planned interim safety analysis showed significantly improved in progression free survival in the SBRT group (11.9 vs 3.9 months) at median follow up of 12 months. Patients in the SBRT group were less likely to develop new lesions compared to patients on systemic therapy alone suggesting SBRT acted similarly to systemic therapy.

In a series of mouse tumor models treated with an anti-CTLA-4 antibody combined with 3 different radiation regimens, enhanced tumor responses were observed when treated with fractionated radiation regimens of 8 Gy × 3 or 6 Gy × 5 administered on consecutive days, but not with 20 Gy × 1 (19). The fractionated regimens, but not the single radiation dose, also resulted in abscopal effects. For uniformity, we will adhere to the radiation dose guidelines as prescribed in the NRG-BR001 protocol examining the role of SBRT for oligo-metastatic disease (41). Dose reductions are allowed to pre-specified doses at the treating physician's discretion if dosimetric criteria are not achievable. Dose schedules and prescriptions are described under radiation treatment.

B. Immunotherapy: All patients in this trial will be treated with either Nivolumab or Pembrolizumab at FDA approved dosing and indications (1, 36). If new FDA approved anti-PD-1 therapies emerge during the study duration, the study will be modified with IRB approval to allow addition of newly approved therapies to the protocol. (36). These FDA approved dosing schedules are established and have a favorable toxicity profile and will allow direct comparison of outcomes to immunotherapy alone trials vs immunotherapy plus SBRT.

3. STUDY OBJECTIVES

3.1 Primary Objectives

The primary objective of the pilot phase of the study is to characterize the safety, feasibility and tolerability of sequential combination I-SABR in patients with metastatic NSCLC. The first 20 patients will be evaluated for 15 weeks following treatments with I-SABR prior to continuing enrollment. In the Brahmer trial, 5% of patients in the Nivolumab arm developed pneumonitis with a median time to onset of treatment related pulmonary events of 15 weeks. All but one patient with pulmonary events were treated with glucocorticoids and all cases resolved with a median time to resolution of 5 weeks (range 0.6-12.1 weeks).

If more than 5% of patients develop grade ≥ 3 pneumonitis during the initial evaluation phase, no lung directed therapy will be permitted during the phase II portion.

The primary objective of the phase II portion of the study will be overall survival.

3.2 Secondary Objectives

The secondary objectives of the study are

1. To determine the progression free survival measured from time of enrollment to first evidence of progressive disease and evaluated 3 months after treatment initiation.
2. To determine the local control measured from time of enrollment to first evidence of progressive disease at the treatment site and evaluated 3 months after treatment initiation
3. To determine the incidence of grade ≥ 3 , pneumonitis 6 months of completing SBRT
4. To determine the influence of number of metastatic sites on OS, and PFS.

4. STUDY DESIGN

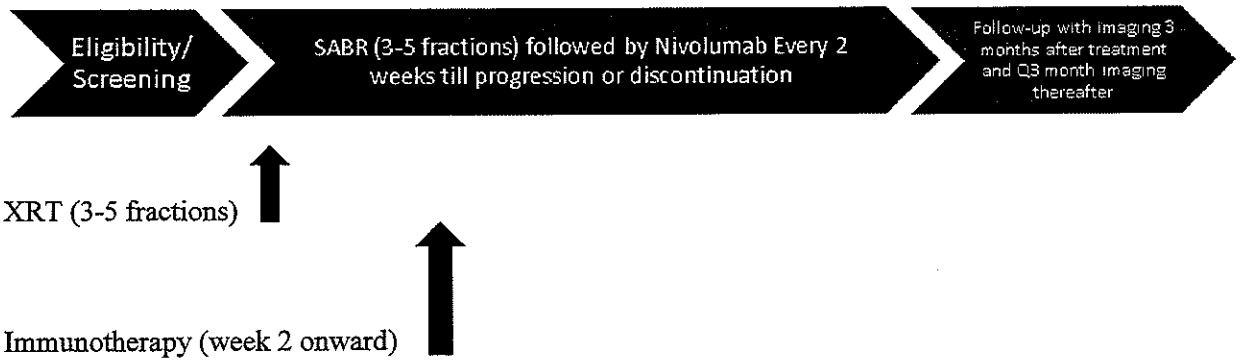
4.1 STUDY DESIGN AND DURATION

This is a combination single arm pilot/Phase II study of combination I-SABR for metastatic NSCLC. Treatment safety and feasibility will be assessed in the initial pilot phase and oncologic outcomes will be assessed in the second phase.

After screening, patients will receive 3-5 fractions of SBRT/SABR to up to 3 metastatic sites in addition to the primary tumor. Following the conclusion of SBRT/SABR, patients will receive Immunotherapy therapy at standard dosing until disease progression or discontinuation of treatment due to toxicity or patient choice (Figure 1).

Tumor assessment will be performed prior to SABR initiation and every 3 months or for clinical disease progression.

Figure 1: Sample Patient Treatment and Follow-Up Timeline



4.2 Radiation Therapy

Radiation therapy will be delivered using SABR or SBRT using the CyberKnife radiosurgery system. Treatment will be delivered in 3-5 fractions as specified in **Table 2**. SBRT can be directed to up to three separate metastatic sites in addition to the primary tumor. Symptomatic or at risk disease sites should be prioritized. Strict adherence to dosimetric criteria is required. If dosimetric criteria cannot be met with stipulated doses, a default dose of 30-40 Gy in 5 fractions will be prescribed. In all cases, a minimum dose of 95% of the prescribed dose is must be delivered to the PTV to satisfy protocol constraints. 90% will be considered an acceptable minimal deviation.

4.3 Immunotherapy

Immunotherapy will be delivered in the form of PD-1/PD-L1 blockade using approved anti PD-1/PD-L1 agents. Dose reductions are appropriate for toxicity as specified or at the discretion of the treating medical oncologist. Prior immunotherapy as part of multi-drug therapy or monotherapy is acceptable prior to initiation of SBRT.

The DLT observation period for continuation or discontinuation of therapy is defined as 14 days starting with cycle 1, day 1. To be evaluable for DLT, a patient must have received at least the first 2 administrations and be monitored for at least 14 days following the first administration. Any of the below outlined events occurring during each DLT observation period and considered to be at least possibly related to Nivolumab will qualify as a DLT.

Non-Hematologic Toxicity

1. Grade ≥2 uveitis
2. Any Grade ≥3 non-hematologic toxicity except
    a. Nausea, vomiting or diarrhea
    b. Clinically insignificant laboratory abnormalities
    c. Grade 3 infusion reactions that respond to medical management
    d. Grade 3 immune related effects other than uveitis that improve within 7-14 days with steroid treatment **(Appendix 1).**

Hematologic Toxicity

1. Grade 4 neutropenia lasting more than 1 week
2. Grade 4 thrombocytopenia
3. Grade 3 thrombocytopenia with bleeding
4. Grade ≥3 febrile neutropenia

Special

1. Grade ≥ 2 pneumonitis

4.4 Duration of Study

The study will conclude 24 months after the last patient is accrued. Given the poor prognosis and short overall survival in patients with metastatic NSCLC, all end-points should be realized within 24 months. At the conclusion of the study, patients and investigators may decide to continue with Immunotherapy treatment. We expect to enroll 100 patients over 2 years.

5. PATIENT ELIGIBILITY AND CRITERIA

The target study population comprises patients with metastatic lung cancer who are eligible for an immunotherapy agent as monotherapy or combination therapy.

5.1 Inclusion Criteria

1. Histologically or cytologically confirmed Stage IV NSCLC according to the 7th AJCC staging manual. Patients with recurrent disease after definitive treatment with surgery or concurrent chemoradiation are eligible.

2. Patients must be eligible for an immunotherapy agent as determined by treating medical oncologist. Patients who progress after drug therapy (3 months) for ALK, EGFR or ROS mutation positive lung cancer are eligible. Patients who received prior combination immunotherapy or single agent monotherapy are eligible. Patients who progress on maintenance immunotherapy are eligible if sites of progression are amenable to local therapy for control.

3. At least 2 lesions that are safely amenable to SBRT/SABR.

4. ECOG $\geq$2.

5. At least 1 measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria for response assessment or at least 1 lesion with FDG avidity and CT correlate that can be monitored for PET-CT response by SUV Max increase or decrease.

6. $\geq$18 years old.

7. Normal Hepatic and renal function.

8. Bone marrow reserve:

   a. ANC $\geq 1.5 \times 10^9$/L

   b. Hemoglobin $\geq$9.0 g/dL

   c. Platelet count $\geq 75 \times 10^9$/L

9. Ability to comply with follow-up visits and evaluations, treatment planning and studies and other study related procedures and visits.

10. Ability to sign informed consent.

5.2 Exclusion Criteria

1. Patients with active CNS metastases. If metastases are treated and patients return to baseline and no steroids are required, patients are eligible.

2. Active, known or suspected auto-immune disease.

3. Patients with medical conditions that require systemic immunosuppression.

4. Patients with a history of interstitial lung disease.

5. Other active malignancy requiring intervention.

6. Prior lung radiation, with the only metastatic targets in the lungs.

7. Unresolved toxicity from prior chemotherapy or anti-cancer treatment.

8. Current or prior enrollment in clinical trial with an investigational drug within 4 weeks.

9. Pregnancy or positive pregnancy test.

5.3 Sample Size

More than 350 patients with metastatic lung cancer present to the Crozer-Keystone health system for treatment annually. If 50% of patients are eligible for this study, we expect approximately 100 patients will enroll and be treated on this study. Patients will be followed for 2 years on the study. The study will conclude 2 years after the last patient is enrolled. An interim safety and feasibility analysis will be performed on the first 20 patients in the pilot phase. Overall survival, progression free survival, local control and subgroup analysis will be performed on the entire patient cohort at the conclusion of the study.

5.4 Discontinuation of Study Treatment

Patients who discontinue study treatment will be asked to return to the clinic for all remaining study visits per the visit schedule, and will be expected to continue with relevant study assessments.

5.5 Withdrawal from Study

During the treatment period and follow-up period, a patient who withdraws consent to continue participation in the study will be removed from follow-up requirements. Routine clinical care will continue but no data will be collected for study purposes.

6. RADIATION THERAPY

6.1 Specifications for Radiation Therapy

SBRT/SABR will be delivered to up to three separate metastatic sites in 3-5 fractions. The primary lung tumor may be treated as well. Patients will receive the radiation therapy dose specified in **Table 2** for a given treatment site. Treatment at the protocol defined dosing regimen is only permitted if the normal tissue criteria are met. As a default dosing scheme, if dosimetric criteria are not achieved, then a dose of 30 Gy in 5 fractions will be delivered. A minimum of 95% of the prescribed dose must be delivered to the treatment planning volume (PTV). 90% will be considered an acceptable minor deviation.

The lesions selected for treatment should be lesions that can be safely irradiated with focal irradiation while sparing normal tissue in accordance with standard radiation oncology practice. If symptomatic or at risk lesions are present, these lesions should be prioritized for the target selection. No more than one lung lesion may be treated.

Table 2. Specified SBRT/SABR Prescription Doses

Lesion Location	Dose/Fractionation	Acceptable Variation
Lung-Peripheral Lesion	45 Gy/3 fractions	40 Gy/5 fractions
Lung-Central Lesion	50 Gy/5 fractions	40 Gy/5 fractions
Mediastinal/Cervical Node	50 Gy/5 fractions	40 Gy/5 fractions
Liver	45 Gy/3 fractions	40 Gy/5 fractions
Spine/Para-spinal	30 Gy/3 fractions	30 Gy/5 fractions
Bone (Other than spine)	30 Gy/3 fractions	30 Gy/5 fractions
Adrenal Gland/Pelvic Metastases	45 Gy/ 3 fractions	40 Gy/5 fractions

6.2 Radiation Therapy Simulation

All patients will undergo immobilized 1mm CT scans for treatment planning. IV contrast is required for central lung lesions and liver metastases. For other sites, the use of IV contrast is encouraged and left to the discretion of the treating radiation oncologist. Fiducials may be required for tumor tracking. Respiratory motion management (RMM) is required for all lesions for the potential for respiratory motion. Daily IGRT with CBCT is required for all treatment sites when an approved non-CyberKnife treatment system is utilized.

6.3 Treatment Planning and Target Volumes

Location: Each lesion will be assigned to one of the 7 locations specified in **Table 2**.

Lung Peripheral Lesion: The lesion is outside the proximal bronchial tree as defined as within 2cm in all directions around the carina, right and left main bronchi, right and left upper lobe

bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus and right lower lobe bronchi. The lesion does not the mediastinal or pericardial pleura.

Lung Central: The lesion is within 2cm of the proximal bronchial tree.

Mediastinal/Cervical Node: The lesion arises in the anatomic mediastinum or cervical lymph node levels I-VI or retropharyngeal space.

Liver: Lesion is located inside or touches the liver parenchyma.

Spine or Paraspinal: Lesion is located within vertebral body or within 1cm of a vertebral body, pedicle or posterior elements.

Bone: Lesion is located within a bony structure (excluding spine).

Adrenal Gland/Pelvic Metastases: Lesion arises within the adrenal gland or within the true pelvis or inguinal nodes.

6.4 Target Delineation and Treatment Planning

The gross tumor volume (GTV) will be contoured in the appropriate CT window. Rigid PET-CT/MRI fusion is allowed to assist in target delineation when necessary.

No clinical target volume (CTV) expansion is allowed. GTV=CTV.

For non-fiducial based tracking treatments, an internal target volume (ITV) must be generated for motion susceptible targets. The expiratory and inspiratory phase scans (Phase 0 and 50) from a 4D-CT are suggested for defining the ITV. MIP reconstructed images should be used with caution because lung and MIP reconstructions may erroneously generate an ITV when breathing is irregular or when lesions abut soft tissue structures.

A 3-5mm uniform expansion will be added to generate the planning target volume (PTV).

95% of the prescribed dose should encompass 100% of the PTV.

6.5 Organs at Risk (OAR)

OAR must be contoured. The specific OAR to be contoured will depend on the location of lesion being treated.

Lung Central/Lung Peripheral/Mediastinal/Cervical Lymph Node metastases:

The proximal tracheobronchial tree, lungs, left/right/combined, heart, esophagus, spinal cord, chest wall, brachial plexus (when at risk), skin, liver, larynx, stomach will be contoured.

Abdominal-pelvic metastases (liver, adrenal, lymph nodes):

The stomach, duodenum, spinal cord, kidneys, large and small bowel, rectum, bladder, lungs, and cauda will be contoured.

Spinal Metastases:

All spine target volumes will be contoured per the international spine radiosurgery consensus guidelines for target delineation. A partial spinal cord volume 6mm above and below the target region will be contoured. Additional OAR will be based on the spine level.

6.6 Dose Limits and DVH Criteria

See **Appendix II**.

6.7 Evaluation of Targeted Lesions

Targeted lesions will be evaluated on 3 month interval scans or scans procured for clinical progression. Evaluated lesions will be described as follows:

Complete Response (CR): Disappearance of target lesion.

Partial Response (PR): At least 30% decrease in the sum of the diameters of the target lesions using the baseline sum of diameters.

Progressive Disease (PD): At least 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

6.8 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. It must be representative of overall disease status change, not a single lesion increase in size.

7. IMMUNOTHERAPY

Immunotherapy administration will commence or continue following the conclusion of SBRT/SABR.

Immunotherapy will be administered as an IV infusion as specified. It is not to be administered as an IV push or bolus injection. At the end of the infusion the administration line will be flushed with a sufficient quantity of normal saline per standard of care. Infusions will continue on a standard schedule for the specific immunotherapy agent with pre-treatment assessments for adverse effects using a standard questionnaire.

Immunotherapy administration will be delayed in the case of any of the following:

Any Grade $\geq$ 2 non-skin, drug-related adverse event, with the following exceptions:– Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay

Any Grade 3 skin, drug-related adverse event

Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, or total bilirubin:

– Grade 3 lymphopenia or leukopenia does not require dose delay

– If a subject has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for drug-related Grade $\geq$ 2 toxicity

– If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade $\geq$ 3 toxicity

Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying immnunotherapy administration.

7.1 Dose reductions and modifications

There will be no dose reduction or modifications in Immunotherapy administration.

7.2 Treatment Compliance

Treatment compliance will be monitored by the site P.I and documented in the medical record.

8.0 PATIENT ASSESSMENTS

8.1 Study Parameters

See Appendix III

8.2 Data Collection

Patients will be stratified by number of metastatic lesions. ≤3 lesions, 4-5 lesions and ≥5 lesions.

All study data will be coded and de-identified. Codes and patient data will be stored separately in a password protected file. Any hard copies will be stored in a locked file cabinet. All other data will be stored on a password secured and encrypted computer only accessible to study staff.

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial by the study investigator.

For pre-specified time points and required reporting please see Appendix IV.

APPENDIX I. RECOMMENDED DOSE MODIFICATION OR DISCONTINUATION AND SUPPORTIVE CARE GUIDELINES FOR SPECIFIC DRUG-RELATED ADVERSE EVENTS

Event(s)	CTCAE v4.03 Grade	Management	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Colitis events • Bowel obstruction • Colitis • Colitis microscopic	≤ Grade 1	No change in dose	For diarrhea, treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet). Endoscopy is recommended if symptoms persist. • Grade 1 diarrhea that persist for >1 week should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily.	Symptoms may include (but are not limited to): • Abdominal pain, cramping and/or bloating • Blood and/or mucus in stool with or without fever • Constipation • Diarrhea • Ileus Nausea • and/or vomiting • Peritoneal signs consistent with bowel perforation Rectal • bleeding • With or without fever Patients with diarrhea should be	All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a *Clostridium difficile* titer.
• Enterocolitis hemorrhagic • Gastrointestinal (GI) perforation • Necrotizing colitis	Grade 2	Hold until ≤Grade 1. Resume at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.	GI consultation and endoscopy is recommended to confirm or rule out colitis for grade 2 diarrhea that persists >1 week or grade 1-2 diarrhea with rectal bleeding (additional guidelines for the treatment of persistent colitis are provided below). Grade 2 diarrhea should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily. Grade 2 diarrhea with diffuse ulceration and bleeding seen on endoscopy may require oral steroids with prolonged taper and represent an increased risk for the development of bowel perforation. Consider prophylactic antibiotics for opportunistic infections. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • In patients with Grade 2 enterocolitis, IMMUNOTHERAPY should be withheld and antidiarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (eg, 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.		
Diarrhea: *...atients who experience diarrhea 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.*					

Event(s)	CTCAE v4.03 Grade	Management	Action/Supportive Care Guidelines
Colitis events **(continued)**	Grade 3–4	Withhold IMMUNOTHERAPY Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity	• In patients with Grade 3 enterocolitis, OPDIVO will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1–2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Consider prophylactic antibiotics for opportunistic infections. For Grade 3–4 diarrhea (or Grade 2 diarrhea that persists after initial steroid treatment), • Rule out bowel perforation. Imaging with plain films or computed tomography (CT) can be useful. • Consider consultation with gastroenterologist and confirmation biopsy with endoscopy. • Treat with intravenous (IV) steroids (methylprednisolone 125 mg) followed by high-dose oral steroids (prednisone 1–2 mg/kg once per day or dexamethasone 4 mg every 4 hours). When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6–8 weeks in patients with diffuse and severe ulceration and/or bleeding. • If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48–72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45–60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. CAUTION: infliximab is contraindicated in patients with bowel perforation or sepsis[b]. • If symptoms persist despite the above treatment a surgical consult should be obtained.

Event(s)	CTCAE v4.03 Grade	Management	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Endocrine events • Hyperthyroidism • Hypophysitis • Hypopituitarism	Grade 1-2	No change in dose	• Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.	Symptoms may include (but not limited to): • Abdominal pain • Abnormal thyroid function tests and/or serum chemistries (Thyroid-stimulating hormone increased [decreased], Free thyroxine increased, Tri-iodothyronine increased.) • Arrhythmias[c] • Cold or heat intolerance • Fatigue • Fever • Headache • Hypotension[c] • Loss of appetite • Mental status and/or behavior changes Nausea • and/or vomiting Unusual • bowel habits • Vision disturbances	All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection. An endocrinology consultation is recommended.
Endocrine events • Hypothyroidism • Thyroid disorder • Thyroiditis	Grade 3-4	Hold until on stable replacement dose	• Consider endocrine consultation. • Rule out infection and sepsis with appropriate cultures and imaging. • Replacement of appropriate hormones as required.		
Endocrine events • Adrenal insufficiency • Hypophysitis • Pan-hypopituitarism	Grade 1-4	Hold until on stable replacement dose	• Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency. • If Grade 1–2 hypophysitis is considered, pituitary gland imaging should be considered (magnetic resonance imaging [MRIs] with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis). • Grade 3–4 hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. Hospitalization and IV methylprednisolone should be initiated.		

Event(s)	CTCAE v4.03 Grade	Management	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Eye event: **Uveitis** **(iritis, iridocyclitis)**	Grade 1	Discontinue IMMUNOTHERAPY if symptoms persist despite treatment with topical immunosuppressive therapy	• Evaluation by an ophthalmologist is strongly recommended. • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.	Symptoms may include (but are not limited to): • Blurred vision • Diffuse erythema and a prominent blush on the sclerae • Dryness of the eyes • Pain • Photophobia	All attempts should be made to rule out other causes such as metastatic disease, infection, or other ocular disease (*e.g.*, glaucoma or cataracts).
	Grade 2	Discontinue IMMUNOTHERAPY if symptoms persist despite treatment with topical immunosuppressive therapy and do not improve to Grade 1 within the retreatment period OR requires systemic treatment.	• Evaluation by an ophthalmologist is strongly recommended. • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.		
	Grade 3–4	Discontinue IMMUNOTHERAPY.	• Treat with systemic corticosteroids such as prednisone at a dose of 1-2 mg/kg per day. When symptoms improve to ≤Grade 1, steroid taper should be started and continued over no less than 4 weeks.		

Event(s)	CTCAE v4.03 Grade	Management	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Hepatic events • Hepatitis • Hepatitis, Autoimmune	Grade 1–2	Withhold IMMUNOTHERAPY if there is a treatment-emergent concurrent elevation of ALT and bilirubin that corresponds to an upward shift of 2 or more grades in both parameters.	• Monitor liver function tests more frequently until returned to baseline values.	Symptoms may include (but are not limited to): Elevations • in: o AST >2.5 × ULN o ALT >2.5 × ULN o Total bilirubin >1.5 × ULN • Fever • Malaise Upper • quadrant abdominal pain	All attempts should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug toxicity, infectious causes and/or myositis.
	Grade 3–4	Discontinue IMMUNOTHERAPY when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.	• Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary. • Treat with high-dose IV glucocorticosteroids for 24–48 hours. When symptoms improve to grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1–2 mg/kg should be started and continued over no less than 4 weeks. • If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity[b]. • Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.		

	CTCAE	Management		Symptoms[a]	Differential

Event(s)	v4.03 Grade		Action/Supportive Care Guidelines		Diagnosis
Neutropenia	≤Grade 1	No change in dose			
	Grade 2	No change in dose			
	Grade 3	No change in dose			
	Grade 4	Hold until resolves to ≤Grade 1. May increase the dosing interval by 1 week. Discontinue if toxicities do not resolve within 12 weeks.			

Event(s)	CTCAE v4.03 Grade	Management	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Pneumonitis events • Pneumonitis Interstitial lung disease • Acute interstitial pneumonitis	Grade 1	Consider hold of therapy. IMMUNOTHERAPY may be continued with close monitoring.	• Radiologic findings should be followed on serial imaging studies at least every 3 weeks. • Monitor for symptoms every 2–3 days. • Consider pulmonary consultation and/or bronchoscopy if clinically indicated.	Symptoms may include (but are not limited to): • Abnormal breath sounds • Chest pain and/or tightness[c] • Dyspnea[c] • Dry cough • Fatigue	All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.
	Grade 2	Hold IMMUNOTHERAPY	**To rule out other causes such as infection:** • Consider pulmonary consultation with bronchoscopy and biopsy/bronchoalveolar lavage (BAL). • Consider pulmonary function tests. • Follow radiologic findings on serial imaging studies every 1–3 days		
			If the patient is determined to have study drug associated pneumonitis: • Monitor symptoms daily; consider hospitalization. • Treat with systemic corticosteroids at a dose of 1–2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Treatment with IMMUNOTHERAPY may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of methylprednisolone 10 mg by mouth daily or less. Repeat chest imaging monthly as clinically indicated. **For Grade 2 pneumonitis that improves to**	• Fever • Hemoptysis	

			≤Grade 1 within 12 weeks, the following rules should apply: • First episode of pneumonitis: May increase dosing interval by one week in subsequent cycles. • Second episode of pneumonitis: Discontinue IMMUNOTHERAPY if upon rechallenge the patient develops a second episode of ≥ Grade 2 pneumonitis.		
	Grade 3–4	Discontinue IMMUNOTHERAPY.	• Consider pulmonary function tests with pulmonary consult. • Bronchoscopy with biopsy and/or BAL is recommended. • Treat with IV steroids (2–4 mg/kg per day prednisone or equivalent). When symptoms improve to grade 1 or less, a high-dose oral steroid (1–2 mg/kg prednisone once per day or 4 mg dexamethasone every 4 hours) taper should be started and continued over no less than 4 weeks. • Add prophylactic antibiotics for opportunistic infections. • If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48–72 hours, treat with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45–60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab.		

	CTCAE	Management/		Symptoms[a]	Differential

Event(s)	v4.03 Grade		Action/Supportive Care Guidelines		Diagnosis
Renal events • Nephritis • Nephritis autoimmune	Grade 1	Consider withholding IMMUNOTHERAPY if event does not improve with symptomatic treatment	• Provide symptomatic treatment. Monitor creatinine weekly; when it returns to • baseline, resume routine creatinine monitoring per protocol.	Symptoms may include (but not limited to): • Fatigue • High blood pressure • Increased serum creatinine • Swelling	All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury to other chemotherapy agents. A renal consultation is recommended.
• Renal failure	Grade 2	Consider withholding IMMUNOTHERAPY.	Systemic corticosteroids at a dose of 1–2 • mg/kg/day of prednisone or equivalent may be indicated. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Consider prophylactic antibiotics for • opportunistic infections. • Consider renal biopsy. If elevations persist >7 days or worsen, treat as • Grade 4.		
• Renal failure, Acute	Grade 3-4	Discontinue IMMUNOTHERAPY.	Renal consultation with consideration of • ultrasound and/or biopsy as appropriate. • Monitor creatinine daily. • Treat with systemic corticosteroids at a dose of 1–2 mg/kg prednisone or equivalent once per day. • When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Discontinue IMMUNOTHERAPY if unable to reduce corticosteroid dose for irAEs to ≤10 mg. • IMMUNOTHERAPY treatment may be restarted and the dose modified as specified in the protocol.		

Event(s)	v4.03 Grade		Action/Supportive Care Guidelines		Diagnosis
Skin events • Dermatitis exfoliative • Erythema multiforme • Stevens-Johnson syndrome • Toxic epidermal necrolysis	Grade 1–2	No change in dose	• Symptomatic treatment should be given such as topical glucocorticosteroids (eg, betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral antipruritics (eg, diphenhydramine HCl or hydroxyzine HCl). Treatment with oral steroids is at investigator discretion for Grade 2 • events.		All attempts should be made to rule out other causes such as metastatic disease, infection, or allergic dermatitis.
If considered to be immune related, ≥ Grade 3 or result in dose modification or discontinuation:	Grade 3	Hold IMMUNOTHERAPY.	• Consider dermatology consultation and biopsy for confirmation of diagnosis. • Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.		
• Pruritus Rash • Rash generalized • Rash maculo-papular • Vitiligo	Grade 4	Permanently discontinue IMMUNOTHERAPY.	• Dermatology consultation and consideration of biopsy and clinical dermatology photograph. Initiate steroids at 1–2 mg/kg prednisone or equivalent. When • symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.		
Thrombocytopenia	≤ Grade 1	No change in dose			
	Grade 2	No change in dose			
	Grade 3	No change in dose	Grade 3 drug-related thrombocytopenia • >7 days or associated with bleeding requires discontinuation.		
	Grade 4	Hold IMMUNOTHERAPY until resolves to ≤ Grade 1. May increase the dosing interval by 1 week.	Grade 4 drug-related thrombocytopenia • >7 days or associated with bleeding requires discontinuation.		

[a] The signs and symptoms may be associated with any of the diagnoses in the associated "Event(s)" column.

[b] REMICADE (Infliximab) prescribing information

[c] If symptoms indicate possible new or worsening cardiac abnormalities, additional testing and/or a cardiology consultation should be considered.

APPENDIX II: DOSE LIMITS AND DVH CRITERIA

Table 3.0 OAR Dose Limits for 3 fraction SBRT

Serial Organ	Volume	Volume Dose (Gy)	Avoidance Endpoint
Spinal Cord	<0.03 cc	22.5	Myelitis
	<1.2 cc	13	Myelitis
Ipsilateral Brachial Plexus	< 0.03 cc	26	Brachial Plexopathy
	<3 cc	22	Brachial Plexopathy
Cauda Equina	<0.03 cc	25.5	Neuritis
	<5 cc	21.9	Neuritis
Sacral Plexus	<0.03 cc	24	Neuropathy
	<5 cc	22.5	Neuropathy
Trachea and Ipsilateral Bronchus*	<0.03 cc	30	Stenosis/Fistula
	<5cc	25.8	Stenosis/Fistula
Esophagus*	<0.03 cc	27	Stenosis/Fistula
	<5cc	17.7	Stenosis/Fistula
Heart/Pericardium	<0.03cc	30	Pericarditis
	<15 cc	24	Pericarditis
Great vessels*	<0.03cc	45	Aneurysm
	<10 cc	39	Aneurysm
Skin	<0.03cc	33	Ulceration
	<10cc	31	Ulceration
Stomach	<0.03cc	30	Ulceration/Fistula
	<10cc	22.5	Ulceration/Fistula
Duodenum*	<0.03cc	24	Ulceration

	<10cc	15	Ulceration
Bowel*	<0.03 cc	34.5	Ulceration
	<20cc	24	Colitis/Fistula
Rectum*	<0.03 cc	49.5	Ulceration
	<3.5 cc	45	Proctitis/Fistula
	< 20 cc	27.5	Proctitis/Fistula
Bladder	0.03cc	33	Cystitis/Fistula
	<15 cc	16.8	Cystitis/Fistula
Ureter	<0.03 cc	40	Stenosis
Penile bulb	< 3cc	25	Impotence
Femoral heads	<10 cc	24	Necrosis
Bile duct	< 0.03 cc	36	Stenosis
Renal hilum/vascular trunk	<15 cc	19.5	Malignant Hypertension
Rib	< 0.03 cc	50	Pain or Fracture
	<5 cc	40	Pain or Fracture
Parallel Organ	**Volume**	**Volume Dose (Gy)**	**Avoidance Endpoint**
Lung (total)	<15% lung volume	20	Pneumonitis/Lung Function
	< 37% lung volume	11	Pneumonitis
	1500 cc	10.5	Basic Lung Function
	1000 cc	11.4	Pneumonitis
Ipsilateral kidney	<130 cc	12.3	Nephritis
Total Kidney	<200cc	15	Basic Renal Function
Liver	<700 cc	17.1	Liver function

*NOTE: Avoid circumferential irradiation.

Table 4.0 OAR Dose Limits for 5 fraction SBRT

Serial Organ	Volume	Volume Dose (Gy)	Avoidance Endpoint
Spinal Cord	<0.03 cc	28	Myelitis
	<0.35 cc	22	Myelitis
	<1.2 cc	15.6	Myelitis
Ipsilateral Brachial Plexus	< 0.03 cc	32	Brachial Plexopathy
	<3 cc	30	Brachial Plexopathy
Cauda Equina	<0.03 cc	32	Neuritis
	<5 cc	30	Neuritis
Sacral Plexus	<0.03 cc	32	Neuropathy
	<5 cc	30	Neuropathy
Trachea and Ipsilateral Bronchus*	<0.03cc	40	Stenosis/Fistula
	<5cc	32	Stenosis/Fistula
Esophagus*	<0.03cc	35	Stenosis/Fistula
	<5 cc	27.5	Stenosis/Fistula
Heart/Pericardium	<0.03 cc	38	Pericarditis
	<15 cc	32	Pericarditis
Great vessels*	<0.03 cc	53	Aneurysm
	<10 cc	47	Aneurysm
Skin	< 0.03cc	38.5	Ulceration
	< 10cc	36.5	Ulceration
Stomach	< 0.5cc	35	Ulceration
	< 5cc	26.5	Ulceration
Duodenum*	< 0.5 cc	30	Ulceration

	< 5 cc	18.3	Ulceration
Bowel*	< 0.03 cc	40	Ulceration
	<20 cc	28.5	Colitis/Fistula
Rectum*	<0.03 cc	55	Ulceration
	<3.5 cc	50	Proctitis/Fistula
	<20 cc	32.5	Proctitis/Fistula
Bladder	< 0.03	38	Cystitis/Fistula
	<15 cc	20	Cystitis/Fistula
Ureter	< 0.03 cc	45	Stenosis
Penile Bulb	<3 cc	30	Impotence
Femoral head	<10 cc	30	Necrosis
Bile Duct	<0.03 cc	41	Stenosis
Renal hilum/Vascular Trunk	<15 cc	23	Malignant Hypertension
Rib	<0.03 cc	57	Pain or Fracture
	<5 cc	45	Pain or Fracture
Parallel Organ	**Volume**	**Volume Dose (Gy)**	**Avoidance Endpoint**
Lung (total)	< 37% lung volume	13.5	Pneumonitis
	< 1500 cc	12.5	Basic Lung Function
	< 1000 cc	13.5	Pneumonitis
Total Kidney	< 200cc	18	Basic Renal Function
Liver	<700 cc	21	Liver Function

*__NOTE__: Avoid circumferential irradiation.

APPENDIX III: STUDY PARAMETERS AND ASSESSMENTS

Table 5.0: Pre-treatment assessments

Assessment	Time Points
	≤ 30 days prior to registration
Evaluation by a radiation oncologist	X
Evaluation by a medical oncologist	X
History/physical examination	X
Performance Status (ECOG)	X
CBC w/ diff & ANC, platelets, ALT, AST	≤ 30 days prior to registration
Serum/urine pregnancy test (if applicable)	≤ 14 days prior to registration
CT Scans of the chest/abdomen/ pelvis with radionuclide bone scan OR whole body PET/CT	X
Histological confirmation from at least one metastasis	x
MRI of the vertebral column	If vertebral column metastases identified on staging and will be treated

Table 6.0: Post-Treatment Assessments

ASSESSMENTS IN FOLLOW-UP

Assessment	Time Points	
	30 days after completion of SBRT	**Every 3 months after completion of SBRT for a total of 2 years**
Physical examination	X	X
Evaluation by a radiation oncologist	X	X
Performance status	X	X
ALT, AST, Total and Direct Bilirubin	X (If SBRT delivered to the liver)	X (If SBRT delivered to the liver) Perform at 3 months then every 6 months
Hgb	Recommended if clinical symptoms of anemia on physical exam post-treatment	
Diagnostic Imaging		X Per protocol or if clinically warranted
Adverse event evaluation	X	X

LIST OF COMMON ABBREVIATIONS AND DEFINITIONS OF TERMS

ADL Activities of Daily Living

AE Adverse event

AESI Adverse event of special interest

ALP Alkaline phosphatase

ALT Alanine aminotransferase

ANA Antinuclear antibody

ANC Absolute neutrophil count

aPTT Activated partial thromboplastin time

ARGUS Pharmacovigilance and clinical safety software system

AST Aspartate aminotransferase

AUC Area under the concentration–time curve

BAL Bronchoalveolar lavage

BC Breast cancer

BUN Blood urea nitrogen

CPA Cyclophosphamide

CR Complete response

CRF; eCRF Case report form (electronic or paper); electronic case report form

CRO Contract research organization

CRP C-reactive protein

CT Computed tomography

CTLA-4 Cytotoxic T-lymphocyte antigen 4

CTV Clinical target volume

(NCI-) CTCAE (National Cancer Institute) Common Terminology Criteria for Adverse Events

DLT Dose-limiting toxicity

Dmax Maximum radiation dose

EC Ethics committee

ECG Electrocardiogram

EDC Electronic data capture

FDG-PET 18F-fluorodeoxyglucose positron emission tomography

FFPE Formalin-fixed, paraffin-embedded

FNA Fine-needle aspirate

fx Fraction(s)

GCP Good clinical practice

GBM Glioblastoma multiforme

GM-CSF Granulocyte-macrophage colony-stimulating factor

GTV Gross target volume

H&N Head and neck

HPV human papillomavirus

HLA Human leukocyte antigen

ICF Informed consent form

ICH International Conference on Harmonisation

IHC Immunohistochemistry

INR International Normalized Ratio

irRC Immune-related response criteria

IRB Institutional Review Board

irAE Immune-related adverse event

ITV. Internal target volume

IUD Intrauterine device

IV Intravenous

LC Local control

LD Longest diameter

LE Local enlargement

LDH Lactate dehydrogenase

LDL Low-density lipoprotein

LLOQ Lower limit of quantification

mAb Monoclonal antibody

Max Vol Maximum (tissue) volume

MedDRA Medical Dictionary for Regulatory Activities

monoRX Monotherapy

MRI Magnetic resonance imaging

MTD Maximum tolerated dose

NCI-CTCAE National Cancer Institute-Common Terminology Criteria for Adverse Events

NOAEL No-observed-adverse-effect level

NSCLC Non–small-cell lung cancer

PBMC Peripheral blood mononucleated cell

PD-1 Programmed death-1 (receptor)

PD-L1, PD-L2 Programmed death ligand 1, programmed death ligand 2

PET Positron-emission tomography

PK Pharmacokinetic

PR Partial response

PT Preferred term

PTV Planning target volume

RBC Red blood cell

RCC Renal cell cancer

RECIST Response Evaluation Criteria in Solid Tumors

Regeneron Regeneron Pharmaceuticals, Inc.

RF Rheumatoid factor

RILD Radiation-induced liver disease

RP2D Recommended phase 2 dose

SAE Serious adverse event

SAF Safety analysis set

SAP Statistical analysis plan

SAS Statistical Analysis Systems (software)

SABR Stereotactic Ablative Radiatiotherapy

SBRT Stereotactic Body Radiotherapy

SCHNC squamous-cell head and neck cancer

SOC System organ class

SSA Sjögren's syndrome A antigen

SSB Sjögren's syndrome B antigen

t½ Beta-phase terminal half life

TEAE Treatment-emergent adverse event

TSA a mouse mammary adenocarcinoma cell line

TSH Thyroid-stimulating hormone

WBC White blood cell

XRT Radiotherapy

REFERENCES

1. Mittal D, Gubin MM, Schreiber RD, et al.: New insights into cancer immunoediting and its three component phases--elimination, equilibrium and escape. Curr Opin Immunol 27:16-25, 2014

2. Schreiber RD, Old LJ, Smyth MJ: Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science 331:1565-1570, 2011

3. Vesely MD, Kershaw MH, Schreiber RD, et al.: Natural innate and adaptive immunity to cancer. Annu Rev Immunol 29:235-271, 2011

4. Hanahan D, Weinberg RA: Hallmarks of cancer: the next generation. Cell 144:646-674, 2011

5. Zou W, Chen L: Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol 8:467-477, 2008

6. Creelan BC: Update on immune checkpoint inhibitors in lung cancer. Cancer Control 21:80-89, 2014

7. Wei B, Wang L, Zhao X, et al.: The upregulation of programmed death 1 on peripheral blood T cells of glioma is correlated with disease progression. Tumour Biol 35:2923-2929, 2014

8. Zandberg DP, Strome SE: The role of the PD-L1:PD-1 pathway in squamous cell carcinoma of the head and neck. Oral Oncol 50:627-632, 2014

9. Francisco LM, Sage PT, Sharpe AH: The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 236:219-242, 2010

10. Topalian SL, Hodi FS, Brahmer JR, et al.: Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 366:2443-2454, 2012

11. Lock M, Muinuddin A, Kocha WI, et al.: Abscopal Effects: Case Report and Emerging Opportunities. Cureus 7:e344, 2015

12. Formenti SC, Demaria S: Combining radiotherapy and cancer immunotherapy: a paradigm shift. J Natl Cancer Inst 105:256-265, 2013

13. Tang C, Wang X, Soh H, et al.: Combining radiation and immunotherapy: a new systemic therapy for solid tumors? Cancer Immunol Res 2:831-838, 2014

14. Frey B, Rubner Y, Wunderlich R, et al.: Induction of abscopal anti-tumor immunity and immunogenic tumor cell death by ionizing irradiation - implications for cancer therapies. Curr Med Chem 19:1751-1764, 2012

15. Bezu L, Gomes-de-Silva LC, Dewitte H, et al.: Combinatorial strategies for the induction of immunogenic cell death. Front Immunol 6:187, 2015

16. Kwilas AR, Donahue RN, Bernstein MB, et al.: In the field: exploiting the untapped potential of immunogenic modulation by radiation in combination with immunotherapy for the treatment of cancer. Front Oncol 2:104, 2012

17. Garnett CT, Palena C, Chakraborty M, et al.: Sublethal irradiation of human tumor cells modulates phenotype resulting in enhanced killing by cytotoxic T lymphocytes. Cancer Res 64:7985-7994, 2004

18. McFarland HI, Puig M, Grajkowska LT, et al.: Regulatory T cells in gamma irradiation-induced immune suppression. PLoS One 7:e39092, 2012

19. Dewan MZ, Galloway AE, Kawashima N, et al.: Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. Clin Cancer Res 15:5379-5388, 2009

20. Derer A, Deloch L, Rubner Y, et al.: Radio-Immunotherapy-Induced Immunogenic Cancer Cells as Basis for Induction of Systemic Anti-Tumor Immune Responses - Pre-Clinical Evidence and Ongoing Clinical Applications. Front Immunol 6:505, 2015

21. Lee Y, Auh SL, Wang Y, et al.: Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. Blood 114:589-595, 2009

22. Pilones KA, Vanpouille-Box C, Demaria S: Combination of radiotherapy and immune checkpoint inhibitors. Semin Radiat Oncol 25:28-33, 2015

23. Kalbasi A, June CH, Haas N, et al.: Radiation and immunotherapy: a synergistic combination. J Clin Invest 123:2756-2763, 2013

24. Demaria S, Pilones KA, Vanpouille-Box C, et al.: The optimal partnership of radiation and immunotherapy: from preclinical studies to clinical translation. Radiat Res 182:170-181, 2014

25. Wattenberg MM, Fahim A, Ahmed MM, et al.: Unlocking the combination: potentiation of radiation-induced antitumor responses with immunotherapy. Radiat Res 182:126-138, 2014

26. Gulley JL, Arlen PM, Bastian A, et al.: Combining a recombinant cancer vaccine with standard definitive radiotherapy in patients with localized prostate cancer. Clin Cancer Res 11:3353-3362, 2005

27. Hodge JW, Sharp HJ, Gameiro SR: Abscopal regression of antigen disparate tumors by antigen cascade after systemic tumor vaccination in combination with local tumor radiation. Cancer Biother Radiopharm 27:12-22, 2012

28. Anestakis D, Petanidis S, Kalyvas S, et al.: Mechanisms and applications of interleukins in cancer immunotherapy. Int J Mol Sci 16:1691-1710, 2015

29. Kachikwu EL, Iwamoto KS, Liao YP, et al.: Radiation enhances regulatory T cell representation. Int J Radiat Oncol Biol Phys 81:1128-1135, 2011

30. Wei S, Egenti MU, Teitz-Tennenbaum S, et al.: Effects of tumor irradiation on host T-regulatory cells and systemic immunity in the context of adoptive T-cell therapy in mice. J Immunother 36:124-132, 2013

31. McDermott DF, Atkins MB: PD-1 as a potential target in cancer therapy. Cancer Med 2:662-673, 2013

32. Deng L, Liang H, Burnette B, et al.: Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Invest 124:687-695, 2014

33. Sharabi AB, Nirschl CJ, Kochel CM, et al.: Stereotactic Radiation Therapy Augments Antigen-Specific PD-1-Mediated Antitumor Immune Responses via Cross-Presentation of Tumor Antigen. Cancer Immunol Res 3:345-355, 2015

34. Zeng J, See AP, Phallen J, et al.: Anti-PD-1 blockade and stereotactic radiation produce long-term survival in mice with intracranial gliomas. Int J Radiat Oncol Biol Phys 86:343-349, 2013

35. Park SS, Dong H, Liu X, et al.: PD-1 Restrains Radiotherapy-Induced Abscopal Effect. Cancer Immunol Res 3:610-619, 2015

36. Brahmer J, Reckamp KL, Baas P, et al.: Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 373:123-135, 2015

37. Rusthoven KE, Hammerman SF, Kavanagh BD, et al.: Is there a role for consolidative stereotactic body radiation therapy following first-line systemic therapy for metastatic lung cancer? A patterns-of-failure analysis. Acta Oncol 48:578-583, 2009

38. Salama JK, Chmura SJ, Mehta N, et al.: An initial report of a radiation dose-escalation trial in patients with one to five sites of metastatic disease. Clin Cancer Res 14:5255-5259, 2008

39. Sheu T, Heymach JV, Swisher SG, et al.: Propensity score-matched analysis of comprehensive local therapy for oligometastatic non-small cell lung cancer that did not progress after front-line chemotherapy. Int J Radiat Oncol Biol Phys 90:850-857, 2014

40. Gomez DR, Blumenschein GR, Jr., Lee JJ, et al.: Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol, 2016

41. Steven Chmura: Stereotactic Body Radiation Therapy in Treating Patients With Metastatic Breast Cancer, Non-small Cell Lung Cancer, or Prostate Cancer, in , 2016

STUDY ADDENDUM 1.

Since the development of this study, additional data regarding immunotherapy has emerged. Additional immunotherapy agents have shown efficacy in the treatment of metastatic NSCLC in the first line setting. Pembrolizumab is a humanized monoclonal antibody against the PD-1 with antitumor activity in advanced NSCLC expressing PD-L1. The Keynote-024 trial compared previously untreated advanced NSCLC with PD-L1 expression on at least 50% of tumor cells and no sensitizing mutation of the epidermal growth factor receptor gene or translocation of the anaplastic lymphoma kinase gene to receive either Pembrolizumab (at a fixed dose of 200 mg every 3 weeks) or the investigator's choice of platinum-based chemotherapy (1). Median progression free survival, 6 month overall survival and response rate were significantly improved in the Pembrolizumab arm. Pembrolizumab has now redefined initial systemic therapy for PD-L1 expressing tumors in the metastatic setting.

We hereby propose that immunotherapy in this trial now include Nivolumab or Pembrolizumab as long as patients are eligible.

References

1. Reck M et al. N Engl J Med. 2016 Nov 10;375(19):1823-1833. Epub 2016 Oct 8.

STUDY ADDENDUM 2.

Since the last re-authorization of the study, there have been several changes in the immunotherapy landscape from randomized phase III trials. These changes affect our proposed utilization of stereotactic body radiation therapy (SBRT) and immunotherapy in 17-009.

First line systemic therapy for metastatic lung adenocarcinoma now includes combination chemotherapy and immunotherapy. Keynote-189 showed an improved overall survival with pembrolizumab/alimta and carboplatin vs carboplatin/alimta alone (1). This survival benefit was higher with increasing PD-L1 expression but was maintained regardless of PD-L1 expression. Similarly, Key-407 showed an improved overall survival in patients with metastatic squamous cell lung carcinoma with combination carboplatin/taxol/pembrolizumab vs carboplatin/taxol alone (2) with PD-L1 expression ≥1%. Additionally, the PACIFIC trial showed an significant increase in overall survival in patients with stage III non-small cell carcinoma when Darvalumab was added following concurrent chemoradiation vs observation (3).

With these changes in the immunotherapy landscape, it is highly likely that patients with lung cancer will be increasingly exposed to immunotherapy agents earlier in the treatment course making them ineligible for our study since we currently exclude patients with prior immunotherapy treatments.

Early data with sequential or combination SBRT suggest increased immunotherapy efficacy with similar rates or minimal changes in the toxicity profile of immunotherapy agents (4-5). Since our initial eligibility criteria was designed to limit excess patient toxicity and current available data suggests a combination/sequential regimen is safe, it is prudent that we revise our inclusion/exclusion criteria.

We hereby propose that patients with prior/ongoing immunotherapy treatment be eligible for participation in this study. The eligibility criterion has been modified as such to reflect this change.

References

1. Ghandi L. et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. N Engl J Med May 2018; 378:2078-2092
2. Lopes G. et al. Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥ 1%: Open-label, phase 3 KEYNOTE-042 study. J Clin Oncol 36, 2018 (suppl; abstr LBA4).
3. AstraZeneca Press Release 05/2018: https://www.astrazeneca.com/media-centre/press-releases/2018/imfinzi-significantly-improves-overall-survival-in-the-phase-iii-pacific-trial-for-unresectable-stage-iii-non-small-cell-lung-cancer-25052018.html

4. Theelen W. et al. Randomized phase II study of pembrolizumab after stereotactic body radiotherapy (SBRT) versus pembrolizumab alone in patients with advanced non-small cell lung cancer: The PEMBRO-RT study. J Clin Oncol 36, 2018 (suppl; abstr 9023)
5. McArthur H. et al. A phase II, single arm study assessing the e□cacy of pembrolizumab (Pembro) plusradiotherapy (RT) in metastatic triple negative breast cancer (mTNBC). J Clin Oncol 36, 2018 (suppl; abstr 9023)

CLINICAL STUDY PROTOCOL

Protocol Title: A PROSPECTIVE TRIAL OF IMMUNOTHERAPY AND STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR THE TREATMENT OF METASTATIC LUNG CANCER: SBRT SENSITIZATION OF THE PROGRAMMED DEATH-1 (PD-1) EFFECT

VERSION 6.0, 06/18/2018

Clinical Phase: Pilot/Phase II

Hypothesis: The addition of Stereotactic Body Radiation Therapy sequenced prior to PD-1/PD-L1 blockade leads to increased immunogenicity and immune system response. Increased response should translate to increased progression free survival and improved survival relative to PD-1 blockade monotherapy in metastatic lung cancer.

Principal Investigator

Olusola Obayomi-Davies MD

Department of Radiation Oncology

Crozer Keystone Health System/Philadelphia CyberKnife Center

2010 West Chester Pike, Havertown, PA 19083

STUDY ADDENDUM 2.

Since the last re-authorization of the study, there have been several changes in the immunotherapy landscape from randomized phase III trials. These changes affect our proposed utilization of stereotactic body radiation therapy (SBRT) and immunotherapy in 17-009.

First line systemic therapy for metastatic lung adenocarcinoma now includes combination chemotherapy and immunotherapy. Keynote-189 showed an improved overall survival with pembrolizumab/alimta and carboplatin vs carboplatin/alimta alone (1). This survival benefit was higher with increasing PD-L1 expression but was maintained regardless of PD-L1 expression. Similarly, Key-407 showed an improved overall survival in patients with metastatic squamous cell lung carcinoma with combination carboplatin/taxol/pembrolizumab vs carboplatin/taxol alone (2) with PD-L1 expression $\geq$1%. Additionally, the PACIFIC trial showed an significant increase in overall survival in patients with stage III non-small cell carcinoma when Darvalumab was added following concurrent chemoradiation vs observation (3).

With these changes in the immunotherapy landscape, it is highly likely that patients with lung cancer will be increasingly exposed to immunotherapy agents earlier in the treatment course making them ineligible for our study since we currently exclude patients with prior immunotherapy treatments.

Early data with sequential or combination SBRT suggest increased immunotherapy efficacy with similar rates or minimal changes in the toxicity profile of immunotherapy agents (4-5). Since our initial eligibility criteria was designed to limit excess patient toxicity and current available data suggests a combination/sequential regimen is safe, it is prudent that we revise our inclusion/exclusion criteria.

We hereby propose that patients with prior/ongoing immunotherapy treatment be eligible for participation in this study. The eligibility criterion has been modified as such to reflect this change.

1. REVISED PATIENT ELIGIBILITY AND CRITERIA

The target study population comprises patients with metastatic lung cancer who are eligible for an immunotherapy agent as monotherapy or combination therapy.

1.1 Inclusion Criteria

1. Histologically or cytologically confirmed Stage IV NSCLC according to the 7th AJCC staging manual. Patients with recurrent disease after definitive treatment with surgery or concurrent chemoradiation are eligible.

2. Patients must be eligible for an immunotherapy agent as determined by treating medical oncologist. Patients who progress after drug therapy (3 months) for ALK, EGFR or ROS

mutation positive lung cancer are eligible. Patients who received prior combination immunotherapy or single agent monotherapy are eligible. Patients who progress on immunotherapy are eligible if sites of progression are amenable to local therapy for control.

3. At least 2 lesions that are safely amenable to SBRT/SABR.

4. ECOG ≥2.

5. At least 1 measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria for response assessment or at least 1 lesion with FDG avidity and CT correlate that can be monitored for PET-CT response by SUV Max increase or decrease.

6. ≥18 years old.

7. Normal Hepatic and renal function.

8. Bone marrow reserve:

   a. ANC ≥ 1.5 x 10^9/L

   b. Hemoglobin ≥9.0 g/dL

   c. Platelet count ≥75 x 10^9/L

9. Ability to comply with follow-up visits and evaluations, treatment planning and studies and other study related procedures and visits.

10. Ability to sign informed consent.

1.2 Exclusion Criteria

1. Patients with active CNS metastases. If metastases are treated and patients return to baseline and no steroids are required, patients are eligible.

2. Active, known or suspected auto-immune disease.

3. Patients with medical conditions that require systemic immunosuppression.

4. Patients with a history of interstitial lung disease.

5. Other active malignancy requiring intervention.

6. Prior lung radiation, with the only metastatic targets in the lungs.

7. Unresolved toxicity from prior chemotherapy or anti-cancer treatment.

8. Current or prior enrollment in clinical trial with an investigational drug within 4 weeks.

9. Pregnancy or positive pregnancy test.

References

1. Ghandi L. et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. N Engl J Med May 2018; 378:2078-2092
2. Lopes G. et al. Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥ 1%: Open-label, phase 3 KEYNOTE-042 study. J Clin Oncol 36, 2018 (suppl; abstr LBA4).
3. AstraZeneca Press Release 05/2018: https://www.astrazeneca.com/media-centre/press-releases/2018/imfinzi-significantly-improves-overall-survival-in-the-phase-iii-pacific-trial-for-unresectable-stage-iii-non-small-cell-lung-cancer-25052018.html
4. Theelen W. et al. Randomized phase II study of pembrolizumab after stereotactic body radiotherapy (SBRT) versus pembrolizumab alone in patients with advanced non-small cell lung cancer: The PEMBRO-RT study. J Clin Oncol 36, 2018 (suppl; abstr 9023)
5. McArthur H. et al. A phase II, single arm study assessing the e□cacy of pembrolizumab (Pembro) plusradiotherapy (RT) in metastatic triple negative breast cancer (mTNBC). J Clin Oncol 36, 2018 (suppl; abstr 9023)

CLINICAL STUDY PROTOCOL

Protocol Title: A PROSPECTIVE TRIAL OF IMMUNOTHERAPY AND STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR THE TREATMENT OF METASTATIC LUNG CANCER: SBRT SENSITIZATION OF THE PROGRAMMED DEATH-1 (PD-1) EFFECT

VERSION 6.0, 06/18/2018

Clinical Phase: Pilot/Phase II

Hypothesis: The addition of Stereotactic Body Radiation Therapy sequenced prior to PD-1/PD-L1 blockade leads to increased immunogenicity and immune system response. Increased response should translate to increased progression free survival and improved survival relative to PD-1 blockade monotherapy in metastatic lung cancer.

Principal Investigator

Olusola Obayomi-Davies MD

Department of Radiation Oncology

Crozer Keystone Health System/Philadelphia CyberKnife Center

2010 West Chester Pike, Havertown, PA 19083

STUDY ADDENDUM 2.

Since the last re-authorization of the study, there have been several changes in the immunotherapy landscape from randomized phase III trials. These changes affect our proposed utilization of stereotactic body radiation therapy (SBRT) and immunotherapy in 17-009.

First line systemic therapy for metastatic lung adenocarcinoma now includes combination chemotherapy and immunotherapy. Keynote-189 showed an improved overall survival with pembrolizumab/alimta and carboplatin vs carboplatin/alimta alone (1). This survival benefit was higher with increasing PD-L1 expression but was maintained regardless of PD-L1 expression. Similarly, Key-407 showed an improved overall survival in patients with metastatic squamous cell lung carcinoma with combination carboplatin/taxol/pembrolizumab vs carboplatin/taxol alone (2) with PD-L1 expression $\geq$1%. Additionally, the PACIFIC trial showed an significant increase in overall survival in patients with stage III non-small cell carcinoma when Darvalumab was added following concurrent chemoradiation vs observation (3).

With these changes in the immunotherapy landscape, it is highly likely that patients with lung cancer will be increasingly exposed to immunotherapy agents earlier in the treatment course making them ineligible for our study since we currently exclude patients with prior immunotherapy treatments.

Early data with sequential or combination SBRT suggest increased immunotherapy efficacy with similar rates or minimal changes in the toxicity profile of immunotherapy agents (4-5). Since our initial eligibility criteria was designed to limit excess patient toxicity and current available data suggests a combination/sequential regimen is safe, it is prudent that we revise our inclusion/exclusion criteria.

We hereby propose that patients with prior/ongoing immunotherapy treatment be eligible for participation in this study. The eligibility criterion has been modified as such to reflect this change.

1. REVISED PATIENT ELIGIBILITY AND CRITERIA

The target study population comprises patients with metastatic lung cancer who are eligible for an immunotherapy agent as monotherapy or combination therapy.

1.1 Inclusion Criteria

1. Histologically or cytologically confirmed Stage IV NSCLC according to the 7th AJCC staging manual. Patients with recurrent disease after definitive treatment with surgery or concurrent chemoradiation are eligible.

2. Patients must be eligible for an immunotherapy agent as determined by treating medical oncologist. Patients who progress after drug therapy (3 months) for ALK, EGFR or ROS

mutation positive lung cancer are eligible. Patients who received prior combination immunotherapy or single agent monotherapy are eligible. Patients who progress on immunotherapy are eligible if sites of progression are amenable to local therapy for control.

3. At least 2 lesions that are safely amenable to SBRT/SABR.

4. ECOG ≥2.

5. At least 1 measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria for response assessment or at least 1 lesion with FDG avidity and CT correlate that can be monitored for PET-CT response by SUV Max increase or decrease.

6. ≥18 years old.

7. Normal Hepatic and renal function.

8. Bone marrow reserve:

   a. ANC ≥ 1.5 x 10^9/L

   b. Hemoglobin ≥9.0 g/dL

   c. Platelet count ≥75 x 10^9/L

9. Ability to comply with follow-up visits and evaluations, treatment planning and studies and other study related procedures and visits.

10. Ability to sign informed consent.

1.2 Exclusion Criteria

1. Patients with active CNS metastases. If metastases are treated and patients return to baseline and no steroids are required, patients are eligible.

2. Active, known or suspected auto-immune disease.

3. Patients with medical conditions that require systemic immunosuppression.

4. Patients with a history of interstitial lung disease.

5. Other active malignancy requiring intervention.

6. Prior lung radiation, with the only metastatic targets in the lungs.

7. Unresolved toxicity from prior chemotherapy or anti-cancer treatment.

8. Current or prior enrollment in clinical trial with an investigational drug within 4 weeks.

9. Pregnancy or positive pregnancy test.

References

1. Ghandi L. et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. N Engl J Med May 2018; 378:2078-2092
2. Lopes G. et al. Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥ 1%: Open-label, phase 3 KEYNOTE-042 study. J Clin Oncol 36, 2018 (suppl; abstr LBA4).
3. AstraZeneca Press Release 05/2018: https://www.astrazeneca.com/media-centre/press-releases/2018/imfinzi-significantly-improves-overall-survival-in-the-phase-iii-pacific-trial-for-unresectable-stage-iii-non-small-cell-lung-cancer-25052018.html
4. Theelen W. et al. Randomized phase II study of pembrolizumab after stereotactic body radiotherapy (SBRT) versus pembrolizumab alone in patients with advanced non-small cell lung cancer: The PEMBRO-RT study. J Clin Oncol 36, 2018 (suppl; abstr 9023)
5. McArthur H. et al. A phase II, single arm study assessing the e□cacy of pembrolizumab (Pembro) plusradiotherapy (RT) in metastatic triple negative breast cancer (mTNBC). J Clin Oncol 36, 2018 (suppl; abstr 9023)