Randomized Phase II Study of Checkpoint Blockade Immunotherapy combined with Stereotactic Body Radiation Therapy in Advanced Metastatic Disease

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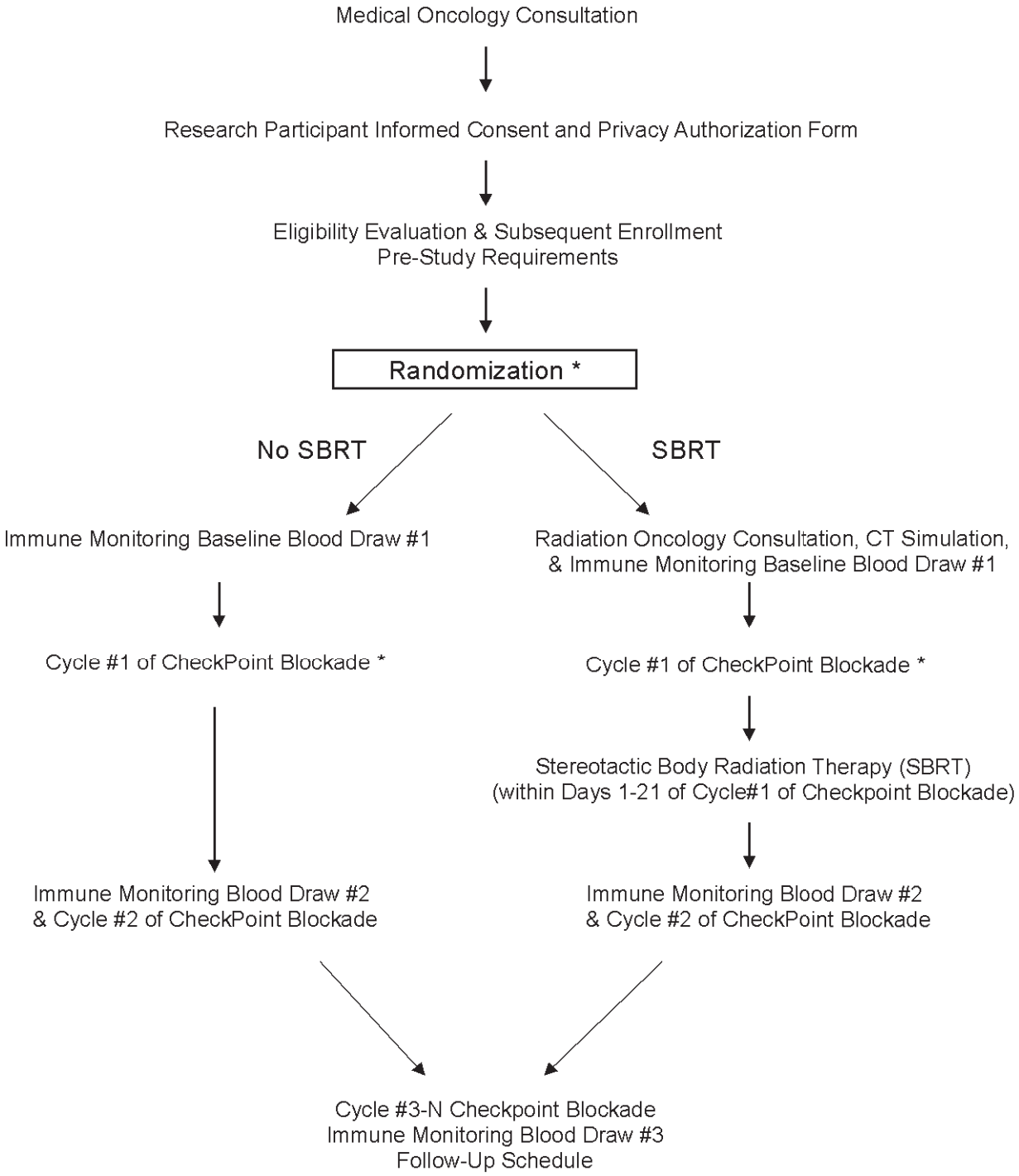
Table of Contents

SCHEMA



* Patient may have started cycle #1 of Checkpoint Blockade up to 5 days prior and still be enrolled and randomized as long as SBRT occurs with Days 1-21 of Cycle #1 of checkpoint blockade.

1. PROTOCOL SYNOPSIS

TITLE	Randomized Phase II Study of Checkpoint Blockade Immunotherapy combined with Stereotactic Body Radiation Therapy in Advanced Metastatic Disease.
STUDY PHASE	Phase II
INDICATION	Patients who will receive CBI immunotherapy with at least 1 site of measurable metastatic disease which will not be irradiated.
PRIMARY OBJECTIVE	• To determine whether SBRT combined with concurrent CBI improves the relative objective response rate (CR+PR) compared to CBI alone in patients with metastatic disease.
SECONDARY OBJECTIVES	• To assess the safety and toxicity of CBI used concurrently with SBRT delivered in 3 fractions in patients with metastatic disease • To determine the progression free survival, overall survival, and rate of stable disease greater than or equal to 6 months in patients after completion of SBRT in combination with CBI • To assess whether SBRT combined with concurrent CBI results in improvements in anti-tumor immune responses compared to CBI alone
HYPOTHESIS	Concurrent SBRT and CBI will increase the relative objective response (CR+PR) rate by at least 33% compared to CBI alone.
STUDY DESIGN	Patients who will receive CBI and have at least 1 site of measurable metastatic disease which will not be irradiated will be candidates for study. Patients will be randomized (1:1) to CBI combined with SBRT or CBI alone. SBRT at 9.5Gy x3 fractions will be delivered within 1-21 days of the start of Cycle #1 of CBI. The first six patients will be treated and observed for toxicity in the safety run-in phase for 30 days after radiation before continuing with further accrual. Radiation dose reduction is allowed if necessary to meet tissue constraints (6Gyx3 Minimum Dose). Response rates will be determined from the ***non-irradiated*** lesion/lesions and three blood draws will be obtained to analyze anti-tumor immune responses.
SAMPLE SIZE BY TREATMENT GROUP	73 patients per group (146 patients total)

SUMMARY OF SUBJECT ELIGIBILITY CRITERIA	1. At least 1 site of measurable metastatic disease which will not be irradiated. 2. Plan to treat patient with CBI 3. Age ≥ 3 years. 4. Lansky scale score of ≥70 (ages ≥ 3 or < 16 years) OR Karnofsky scale score of ≥70 (ages ≥ 16 or < 18 years) OR ECOG performance status ≤ 2 (18 years or older). 5. Histologic confirmation of malignancy (primary or metastatic tumor).
CBI PRODUCT DOSAGE AND ADMINISTRATION	Commercially available checkpoint blockade immunotherapy will be administered intravenously as clinically indicated.
CONTROL GROUP	CBI Alone
PROCEDURES	1. Physical exam 2. Three Research Blood draws 3. CT or MRI of Involved Site 4. PET-CT (optional) 5. SBRT 6. IV CBI administration

2. ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADL	Activities of daily living
AE	Adverse event
BID	Twice daily
BSA	Body surface area
BMP	Basic Metabolic Panel
CBI	Checkpoint Blockade Immunotherapy
CBC	Complete blood count
CI	Confidence interval
CMAX	Maximum concentration of drug
CNS	Central nervous system
CRF	Case report/Record form
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
GI	Gastrointestinal

Hgb	Hemoglobin
HPF	High-power field
HTN	Hypertension
IRB	Institutional Review Board
IV	Intravenous
LLN	Lower limit of normal
LFT	Liver Function Tests
MTD	Maximum tolerated dose
OS	Overall survival
PLT	Platelet
PD	Progressive disease
PFS	Progression free survival
PR	Partial response
QD	Once daily
RECIST	Response evaluation criteria in solid tumors
RR	Response rate
SAE	Serious adverse event
SBRT	Stereotactic body radiation therapy
SD	Stable disease
TTP	Time to progression
ULN	Upper limit of normal
UNK	Unknown
WBC	White blood cell
WHO	World Health Organization

3. OBJECTIVES

3.1 Primary Objective

3.1.1 To determine whether SBRT combined with concurrent CBI improves the relative objective response rate compared to CBI alone in patients with metastatic disease.

3.2 Secondary Objectives

3.2.1 To assess the safety and toxicity of CBI used concurrently with SBRT delivered in 3 fractions in patients with metastatic disease

3.2.2 To assess progression free survival, overall survival, and rates of stable disease greater than or equal to 6 months in patients after completion of SBRT in combination with CBI

3.2.3 To determine whether SBRT combined with concurrent CBI results in improvements in anti-tumor immune responses compared to CBI alone

4. BACKGROUND

4.1 Cancer Immunotherapy and Immune System

The primary modalities of cancer treatment are Surgery, Chemotherapy, and Radiation therapy. Unfortunately, cancer continues to rise as a primary cause of death in the United States because these current modalities are unable to cure most patients once cancer has metastasized[1]. Recently the field of immunotherapy has gained significant interest as basic science discoveries have been translated to FDA approved clinical therapies, including checkpoint blockade immunotherapy[2, 3]. Checkpoint Blockade Immunotherapy (CBI), including anti-CTLA-4 and anti-PD-1/PD-L1 antibodies, has received mainstream attention due to the potential for dramatic and durable clinical responses in certain patients with metastatic disease[4-6]. CBI is now FDA approved for melanoma and lung cancers and is helping to establish immunotherapy as a new fourth modality of cancer care. Unfortunately, not all patients respond to single agent or dual agent CBI and the activity of current agents appears to be limited to certain disease types. Thus the next logical step is combining CBI with surgery, chemotherapy or radiation therapy and understanding how to best incorporate immunotherapy into palliative and definitive treatment regimens[7, 8].

It is now widely accepted that the immune system plays a critical role in tumor biology, as described by the three E's of cancer immunoediting, elimination, equilibrium, and escape[9]. The term elimination represents the classical paradigm of immuno-surveillance, where the immune system is seeking and eradicating cells which have undergone malignant transformation. Equilibrium represents a dynamic state potentially lasting years where malignant cells under internal and external stress adapt and respond to survive while interacting and modulating the immune system. Tumor escape denotes a phase where select cancer cells have overcome barriers to continued growth and can proliferate and spread in an immunocompetent host. As these interactions between the immune system and cancer cells becomes better understood additional targets and strategies for immuno-modulation have been discovered and translated for clinical benefit. Immunotherapy aims to provide a highly specific, efficacious, and well tolerated anti-cancer therapy. However, until very recently most immunotherapy approaches have not proven to be very potent. Methods which enhance the induction and potency of the immune response are needed in order to continue the progress of immunotherapy in the clinic.

Development of an immune response is a complex and highly regulated process which involves interaction of multiple different cell types. In a simplified example, an antigen presenting cell (APC) such as a macrophage or dendritic cell (DC) captures an antigen which it then presents via MHC on the cell surface[10]. The APC then migrates back to a lymph node where it interacts with CD4 T-helper cells. The T-cell receptor binds to the antigen presented on MHC and in the presence of proper co-stimulation, a T- or B-cell is then signaled to propagate an immune response resulting in development of cytotoxic effector T-cells or tumor specific antibodies, respectively. There are classically two signals which are needed in order to induce a specific immune response: Signal 1 is the antigen; Signal 2 is the co-stimulatory

surface molecule. Professional APCs including DCs are the most potent antigen presenting cells capable of inducing immune responses due to their high antigen presentation capacity, high expression of co-stimulatory molecules and ability to secrete significant levels of co-stimulatory cytokines. The presence of these co-stimulatory molecules cannot be understated as DCs, which do not express co-stimulatory molecules, can cause T-cell anergy and actively suppress development of a specific immune response[10]. Unfortunately the tumor microenvironment is highly immunosuppressive and tumor cells use sophisticated mechanisms to inhibit immune responses. Indeed, there are a variety of different mechanisms used by tumors to suppress the immune response including physical barriers, loss of antigen or MHC, increasing expression of inhibitory cell surface molecules, secretion of inhibitory cytokines, and recruitment of suppressor cell populations such as T-regulatory cells (Tregs) or Myeloid derived suppressor cells (MDSC)[11-13]. The presence of these powerful inhibitory mechanisms highlights the need for combinatorial immunotherapy strategies to unlock the full potential of the immune system to fight cancer.

While immunotherapy is establishing itself as a novel and effective modality of cancer treatment, the current use FDA approved indication for CBI is in patients with metastatic disease. The ability for cancers to metastasize depends on a number of factors including histology, location, time, as well as the genetics or biology of the cancer. Interestingly, some aggressive tumors metastasize early in the course of disease while other cancers behave more indolently and may never metastasize. Along these lines there is a term called oligometastatic disease in which metastases are limited in number and location (for example only 3 lung metastasis, or only 2 liver metastasis). Although there is no strict definition of oligometastases, it is commonly interpreted to be no more than 5 or 6 metastatic sites. The presence of an oligometastatic state was originally coined by Hellman et al., who hypothesized that patients with olgiometastatic disease might derive benefit from effective local therapy applied to all sites of disease[14]. Clinical data has supported this hypothesis and the aggressive treatment of metastatic disease with surgery and chemotherapy in patients with isolated pulmonary metastases or liver metastases has resulted in long term survival[15-17]. The optimal type of treatment for metastases depends on a number of factors including histology, location, size, and number of sites. However, options for definitive local therapy include surgery (metastectomy), other ablative therapies such as radiofrequency ablation (RFA) or cryotherapy, specific targeted systemic therapies including hormonal therapy, or ablative radiation therapy (Stereotactic Body Radiation Therapy (SBRT). In this trial we are investigating combining checkpoint blockade immunotherapy with focused radiation therapy (SBRT) in attempt to enhance response rates and improve clinical outcomes for these patients.

4.2 Stereotactic Body Radiation Therapy (SBRT)

Radiation therapy has a long and established history in the field of oncology[18]. Recently, technological advances have allowed radiation oncologists to effectively treat tumors anywhere in the body using SBRT[19]. This ability to deliver high tumoricidal doses while limiting dose to surrounding normal structures has been a major advance and fundamental shift in the field of radiation oncology. The term stereotactic radiation or stereotaxy refers to the use of a referenced three-dimensional coordinate system to locate targets inside the body and deliver highly focused beams of radiation to that site with millimeter accuracy. Stereotactic delivery of radiation is usually termed stereotactic body radiation therapy (SBRT) for extracranial tumors, and referred to as Stereotactic Radiosurgery (SRS) for intracranial tumors. Because of the accuracy and ability to precisely modify the radiation dose distribution to minimize radiation to normal tissue, stereotactic radiation allows for "hypofractionation" or delivery of very high doses of radiation during each fraction of treatment. In the United States, clinical stereotactic radiation courses are currently completed in 1 to 5 fractions total. This is a dramatic shortening of total treatment time compared to conventionally fractionated radiation which can range from between 2-8 weeks or 10-40 fractions to complete. Clinically, stereotactic radiation achieves excellent local control rates, for example SRS for AVMs[20], trigeminal neuralgia[21], pituitary adenoma[22], brain metastases[23]. SBRT for early stage lung cancer has local control rates rivaling those of surgery[24].

SBRT is also being increasingly used as an effective local therapy for metastatic lesions or in patients with oligometastatic disease. Local control rates greater than 75% have been reported for metastatic tumors of the lung, liver, and spine, which is significantly higher than standard conventional moderate dose radiation[25-27]. Given these response rates, SBRT is being used in place of surgery for oligometastatic disease to target pulmonary metastasis, especially in patients who are not optimal surgical candidates. A number of institutions have reported favorable outcomes using either single or multi-fraction SBRT for oligometastatic sites within the lung. For example, a 90% control rate at 9 months was reported with SBRT was prescribed to 26 Gy in a single fraction[28]. Hof et al, reported a 63% progression free survival at 3 years when SBRT was prescribed to 12-30Gy[29]. Le et al, treated early stage and metastatic lung tumors with SBRT using doses of 15-30 Gy and report a local control of 91% for doses greater than 20 Gy and 54% for doses less than 20 Gy[26]. However, toxicity was rare when doses of less than 25 Gy were given[26]. Thus a dose of 9.5 Gy x 3 will allow for safe targeting of pulmonary metastases. Radiosensitizing effects of checkpoint blockade may result in synergistic effects and may improve the local control rates radiation while providing acceptable toxicity. There have been reports of high grade pneumonitis in patients receiving anti-PD-1/PD-L1 checkpoint blockade, although there has been no definitive evidence of supra-additive toxicity when radiation is combined with CBI[30, 31].

Regarding liver metastases, systemic chemotherapy or molecular-targeted agents rarely achieve long term control. On the other hand, surgical removal of colorectal liver metastases has resulted in reported 5-year survival rates approaching 50%, demonstrating that local therapy has a potential curative role in patients with oligometastatic disease[17, 25, 32]. In inoperable patients, the benefit of local therapy is

less clear, however long-term survival has been reported after the resection of liver metastases from sarcoma, breast cancer, and other histologies [33]. Classically the dose limiting toxicity with radiation therapy to the liver has been radiation-induced liver disease (RILD). However, with the technological advances in radiation therapy and image guidance SBRT can now be delivered safely resulting in high tumor doses to portions of the liver while sparing other portions of the liver. For example, no cases of RILD after radiation for colorectal liver metastases were seen when the mean liver dose was <31 Gy at the University of Michigan[34]. A phase I dose-escalation trial of single fraction treatment for liver metastases reported even high doses up to 30Gy in 1 fraction with no dose-limiting toxicity and a 2 year actuarial survival rate of 50% at a medial followup of 17 months[35].

In summary, SBRT has been well tolerated and efficacious with minimal toxicity in national and international trials. This significant advancement in radiation technology and capability calls for a re-evaluation of the effects of focused radiation on the immune system and in combination with immunotherapy. Based on data above, in this study we will evaluate whether CBI plus 28.5Gy of SBRT (9.5Gy x 3 fractions) improves objective response rates and local as well as distant control.

4.3 Checkpoint Blockade Immunotherapy

Recently, there have been several significant and critical advancements in the immunotherapy field[37, 38] including adoptive T-cell transfer, dendritic cell vaccines, peptide vaccines, oncolytic viruses, cytokine therapy, agonist monoclonal antibodies, and small molecules. Of these new advancements, checkpoint blockade Immunotherapy (CBI) is perhaps one of the most exciting in recent years. The significant interest in checkpoint blockade immunotherapy (CBI) stems from the dramatic and durable responses observed in a subset of patients with metastatic disease who have been heavily pre-treated. At its core, CBI functions to inhibit negative regulators of immune responses, or in other words removing the brakes on the immune system. For decades immunotherapy approaches have focused on attempting to positively stimulate the immune responses without necessarily addressing the powerful negative regulatory systems that are in place which dampen or prevent excessive immune responses. It is now understood that disabling these negative regulators or checkpoints can result in robust and clinically efficacious immune responses which in some cases can control widely metastatic disease. CTLA-4 (Cytotoxic lymphocyte antigen 4) is a receptor present on the surface of T-cells which binds the co-stimulatory molecules B7-1 and B7-2 on APCs with a much higher affinity than CD28. Instead of transmitting a positive co-stimulatory signal to the T-cell, ligation of CTLA-4 transmits a powerful inhibitory signal to T cells which can block T-cell activation. Indeed, CTLA-4 is one of the most powerful negative regulatory molecules on the cell surface of T-cells[36]. Similarly, Programmed death receptor 1 (PD-1) is a receptor on T-cells which binds PD-L1 or PD-L2 and recruits SHP phosphatases to impose a powerful inhibitory signal on T-cell activation and proliferation. Inhibiting the CTLA-4 and PD-1 pathways is now FDA approved for metastatic melanoma, NSCLC cell lung cancer and Kidney Cancer.

In 2011 the FDA granted approval to the anti-CTLA-4 drug ipilimumab (Yervoy, Bristol-Myers Squibb) for the treatment of unresectable or metastatic melanoma. In Sept 2014 the FDA granted approval to the anti-PD-1 drug pembrolizumab (Keytruda, Merck Sharp & Dohme Corp.) for the treatment of patients with unresectable or metastatic melanoma.

In Dec 2014 the FDA granted accelerated approval for the anti-PD-1 drug nivolumab (Opdivo, Bristol-Myers Squibb) for patients with progressive unresectable or metastatic melanoma after treatment with ipilimumab or BRAF inhibitor. Nivolumab received FDA approval on March 4th 2015 for treatment of advanced squamous NSCLC that has progressed after treatment with platinum-based chemotherapy. In the phase II clinical trial CheckMate-063, tumors shrank in 15% of patients who took Opdivo, and 26% had stable disease. Additionally the phase III CheckMate-017 trial in which NSCLC patients received either docetaxel chemotherapy or Opdivo was stopped early after it became evident that nivolumab outperformed docetaxel. In Sept 2015 the FDA granted accelerated approval to nivolumab in combination with ipilimumab for the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma. Along the same lines, the anti-PD-1 drug Keytruda

(Pembrolizumab) received FDA approval on Oct 2nd, 2015 for advanced (metastatic) non-small cell lung cancer (NSCLC) whose disease has progressed after other treatments and with tumors that express a protein called PD-L1. In the KEYNOTE-001 trial Keytruda resulted in an overall response rate of 41% (n=25/61) in patients who had PD-L1 positive tumors (Tumor proportion score ≥ 50%). In Nov 2015 the FDA approved Nivolumab to treat patients with advanced (metastatic) renal cell carcinoma. Additionally CBI has demonstrated clinical activity in a variety of tumor types including bladder cancer, Hodgkin's lymphoma, and prostate cancer among many others [4-6, 30, 37-42]. The body of clinical data evaluating the activity of CBI is established and remarkable[39-46] with additional FDA approved indications for different disease sites anticipated.

Immunotherapies and CBI can have unique profile of side effect termed termed immune-related adverse events (irAEs). Examples of irAE include dermatologic (rash), gastrointestinal (colitis), hepatic (hepatitis), endocrine (hypophysitis), pulmonary (pneumonitis) and are thought to relate to general increased activity of the immune system and inflammation. CBI has been studied in Phase III clinical trials with large numbers of patients evaluated and the general frequencies of irAE have been reported. These reported frequencies serve as reference values for estimating any increased toxicity with combinatorial therapies.

4.4 Rationale for SBRT combined with CBI

There is now an established body of pre-clinical literature demonstrating that radiation can modify anti-tumor immune responses. Radiation has been demonstrated to cause upregulation of Major Histocompatibility Complex (MHC) and increase presentation of antigens on surface of tumor cells [43-48]. The DNA damage and reactive oxygen species induced by radiation have been shown to result in inflammatory tumor cell death and release of damage associated molecular patterns (DAMPs), including high mobility group box chromosomal protein 1 (HMGB1), which can activate antigen presenting cells[49-51]. Radiation induced activation of antigen presenting cells has also been demonstrated in animal models to enhance tumor antigen cross-presentation in the draining lymph node and result in activation and proliferation of tumor specific cytotoxic T-cells[47, 52-57]. Radiation has also been shown to influence expression of cytokines and chemokines, such as IL-1, IL-2, L-6, TNF-alpha, TGF-beta, CXCL-16, as well as Type I and Type II Interferons which may play a critical role in modulating immune responses[58-65]. Undoubtedly due to the culmination of these effects, multiple groups have demonstrated that radiation can cause tumor cells to become more susceptible to immune mediated attack[44, 45, 66]. Indeed some authors have suggested that the therapeutic effects of radiation alone may depend on the status of the host immune system and anti-tumor immune responses in the radiation field[54, 63, 67-69]. Given these effects using radiation alone there has been a significant effort to combine radiation with various immunotherapies with sometimes striking results within the radiation field (radiosensitizing immunotherapy), as well as distantly outside the radiation field (abscopal responses)[44, 47, 53, 65, 66, 69-78]. A number of excellent

reviews have also highlighted the potential benefits and ongoing clinical trials of radiation combined with immunotherapy[61, 79-83].

Along these lines, recent evidence has demonstrated that focused radiation can in fact stimulate an anti-tumor immune response outside of the radiation field, termed the abscopal effect. This phenomenon was originally coined by Dr. R.H. Mole in 1953 as an effect of radiation away from the primary target, or in other words, an action at a distance (49). Work by Silvia Formenti and colleagues from New York University has further characterized the abscopal effect (50) (51). Demaria et al. found that growth of a non-irradiated mammary carcinoma was impaired with the use of Flt3-ligand and radiation to a contralateral tumor (50). The authors also provided evidence that this effect was T-cell dependent as it was not observed in T-cell deficient hosts. Given that radiation is capable of inducing inflammation, apoptosis, cell death, and release of tumor antigens (53), this would create an ideal local environment for induction of a potent immune response (50) (54) (55) (56). Thus the preponderance of pre-clinical data would suggest that adding SBRT to CBI has the potential to enhance systemic anti-tumor immune responses which could help to control *systemic* metastatic disease and improve objective response rates. Indeed, a number of ongoing clinical trials are evaluating radiation therapy combined with CBI.

On the basis of this preclinical and clinical evidence, we propose a phase II study of CBI combined with SBRT in patients with metastatic disease. With published data establishing the relative safety of multi-fraction SBRT to the brain, lungs, liver, prostate, and pancreas, we have decided to proceed with 28.5 Gy of SBRT (9.5Gy x3 fractions) concurrently with CBI. However, the use of a three fractions concurrent with CBI is not of proven benefit. This investigation aims to confirm the safety and efficacy for SBRT used concurrently with a CBI in the setting of metastatic disease. The dose selected has been carefully chosen with the belief that it is safe and effective based on prior experience with SBRT. All patients will be treated with three fractions, targeted to the lesion concurrently with CBI.

Patient's with metastatic disease have a poor prognosis. Current treatment modalities are generally palliative and patients are rarely cured, thus additional treatment modalities are certainly needed. This proposed study represents a logical extension of the current understanding of immunotherapy and radiation therapy and potential for synergy between these two modalities. This study will refine the current understanding of radiation tolerance for normal tissues in 3 fractions, thereby making it possible to treat future patients more safely and aggressively. Additionally, this study could identify a new indication for SBRT in specifically for enhancing the systemic effects of immunotherapy. Finally, this study has the potential to translate into improved local as well as distant control ultimately improved overall survival.

5. PARTICIPANT SELECTION AND ENROLLEMENT CRITERION

5.1 Inclusion Criteria

5.1.1 The PI or Co-Investigator Radiation Oncologist states that one of the lesions can be treated with SBRT.

5.1.2 Patient must have at least 1 site of measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria on computed tomography (CT) or Magnetic resonance imaging (MRI) which will not be irradiated.

5.1.3 Histological confirmation of malignancy (primary or metastatic tumor).

5.1.4 Patient may have any prior therapy allowed aside from having had prior radiotherapy to the treatment site (see exclusion criteria 5.2.3).

5.1.5 Patient must be ≥ 3 years of age.

5.1.6 Lansky scale score of ≥70 (ages ≥ 3 or < 16 years) - OR - Karnofsky scale score of ≥70 (ages ≥ 16 or < 18 years) – OR - ECOG performance status ≤ 2 (18 years or older).

5.1.7 Patient's screening laboratory values must meet the following criteria:

Leukocytes	≥2,000/μL
Absolute Neutrophil Count	≥1,000/μL
Platelets	≥50,000/μL
Total bilirubin	≤2x institutional upper limit of normal
AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal
Serum creatinine	≤ 1.5x ULN or creatinine clearance (CrCl) ≥ 40 mL/min (using the Cockcroft-Gault formula):

(1) Female CrCl = (140 - age in years) x weight in kg x 0.85 /72 x serum creatinine in mg/dL

(2) Male CrCl = (140 - age in years) x weight in kg x 1.00/72 x serum creatinine in mg/dL

Pulse Oximetry	≥92% on Room Air at Rest

5.1.8 Patient or parent/legal guardian must have the ability to understand and the willingness to sign a written informed consent document.

5.1.9 For Patients <18 years of age, enrollment on trial and potential for use of CBI or CBI combined with SBRT must be agreed upon by consensus opinion of a multidisciplinary pediatric tumor board.

5.2 Exclusion Criteria

5.2.1 Patient has had chemotherapy or radiotherapy within 4 weeks prior to entering the study or those who have not recovered from adverse events due to agents

administered more than 4 weeks earlier.

5.2.2 Patient receiving any investigational or experimental agents other than immunotherapy.

5.2.3 Patient who has had any prior radiotherapy to the treatment site(s).

5.2.4 Patient is a pregnant woman (pregnant women are excluded from this study because radiation treatment has known potential for teratogenic or abortifacient effects).

5.2.5 Patient refuses to sign informed consent.

6. TREATMENT PLAN

6.1 Diagnostic Procedures

A CT scan or MRI will be performed for tumor localization using rigid immobilization appropriate for stereotactic treatment. A separate PET-CT may be performed (optional) for diagnostic purposes and can be used for treatment planning with fusion – the identical study would be performed if the patient were having standard conventional dose radiation.

6.2 Therapeutic Procedures

Patients will be pre-screened for eligibility and should be enrolled and randomized prior to starting immunotherapy. However, patients who have started immunotherapy up to 5 days prior to enrollment will be still be eligible for screening, randomization, and enrollment.

Upon confirmation of eligibility and enrollment in the study, the following will be completed:

1) Demographics review, medical history and clinical exam
2) Review of concurrent medications
3) Vital signs, height and weight
4) Laboratory Bloodwork including: CBC, BMP, LFT.
5) Plasma and Peripheral blood mononuclear cells will be collected and subsequently frozen for immune monitoring assays.
6) Tumor measurements (Recist 1.1) within 4 weeks prior to start of CBI

Upon randomization into the SBRT arm of the protocol, patients will be seen by at least one of the Co-Investigator Radiation Oncologists. CT simulation will be performed with fabrication of a radiation therapy immobilization device (such as a Vac-Lok) which will be custom made for each patient. The treating radiation

oncologist will identify the location of the tumor. Gross tumor volume (GTV) delineation will be performed on sequential axial computed tomography images. An SBRT treatment plan will be developed based on tumor size and location. The dose will be prescribed to the minimal isodose line that completely covers the GTV plus a 5 mm margin. Adjacent normal structures including but not limited to the chest wall, spinal cord, heart, esophagus, aorta, kidneys, rectum, bowel, liver, and stomach within 5 cm of the GTV will be identified for the purpose of limiting incidental radiation to these structures.

In addition, prior to treatment delivery, a four-dimensional cone beam CT study will be performed on individual patients to assess respiration in these patients and to determine tumor targeting accuracy for those tumors that may be subject to respiratory motion such as those in the lung, abdomen, or liver. If tumor motion is greater than 5 mm, the planning target volume (PTV) will be expanded to account for respiration.

Within three weeks of the 1st cycle of checkpoint blockade, SBRT will be administered using image-guidance. An Vac-Lok (or equivalent immobilization device such as Alpha-Cradle) will be used to minimize movement of the chest, spine, and abdomen during treatment. During treatment, cone beam CT images of the patient's body site of interest will be obtained. Cone beam CT scan will be obtained immediately prior to treatment and will be repeated until the treatment shift, required to align the CT planning scan and the cone beam CT scan performed on the day of treatment cone beam CT, is within tolerance for the body site per standard clinical practice.

The patient will receive SBRT within 1-21 days of the start of Cycle#1 of CBI. Afterwards, the patient will continue to receive CBI as indicated and recommended by the treating medical oncologist. Patients will be evaluated for adverse events/toxicities during their treatment.

6.2.1 The dose limits for surrounding critical structures are as follows [Base in part from Stereotactic body radiation therapy: The report of AAPM Task Group 101, Med. Phys. 37(8), August 2010]:

- **Spinal Cord**: maximal allowable total point dose is 2190cGy (7.3Gy/fx)
- **Lung**: Combined mean lung dose < 400 cGy, V20<4%, and at least 1500cc < 1160 cGy
- **Heart**: Volume of heart receiving 24 Gy should be <15cc
- **Esophagus**: 50% of the esophagus volume should be kept under 1000 cGy and no single point dose in the esophagus should exceed 2700 cGy.
- **Brachial Plexus**: maximal allowable point dose is 2400 cGy
- **Liver**: Approx 2/3 of liver or at least 700cc < 1920c Gy
- **Kidneys:** 2/3 volume of each kidney <1060 cGy.
- **Small Bowel:** <5% of bowel limited to <2000 cGy.

6.3 Follow-Up Procedures

Subsequent to Cycle 1 Day 1, patients will be followed clinically, radiographically, and with bloodwork. A detailed medical and physical examination will be performed at 8 weeks and 16 weeks, 6 months, 12 months, 18 months and 24 months. A complete blood count (CBC) and comprehensive chemistry panel and CT scan including the treated site will be performed at the 8 week and 16 week follow-up and will continue at intervals of every 6 months until 2 years post SBRT treatment.

Tumor measurements (Recist 1.1) at 8 weeks (+/- 10 days) and 16 weeks (+/- 10 days) will be used to determine radiographic response.

6.4 Duration of Therapy

The patient will receive CBI as indicated and recommended by the treating medical oncologist.

6.5 Duration of Follow-Up

It is anticipated that this study will last 5 years. Routine follow-up appointments as clinically indicated after 2 years will be used to capture and determine overall survival endpoints.

6.6 Criteria for Patient Removal

Unacceptable adverse events grade IV or greater with an attribution of possibly related to CBI Monotherapy, Combination CBI, or CBI combined with SBRT.

Intercurrent illness that prevents further administration of treatment.

Extraordinary Medical Circumstance: If at any time the treating physician feels constraints of this protocol are detrimental to the patients's health the patient can be removed from protocol therapy.

Patient can elect to discontinue treatment at any time.

6.7 Alternatives

The study has been designed to minimize potential risks to participants. This is primarily through designation of a dose range shown to be safe in previous SBRT trials and careful patient monitoring. The risks of CBI are detailed in section 7 as well as in the manufacturer treatment guidelines. Risks to confidentiality will be minimized by having access to study records available only to the investigators with the exception of the standard clinical records (lab values, dictations, operative notes, etc) which are maintained through the UCSD Health System and Moores Cancer Center.

Standard therapies for metastatic disease include conventional radiotherapy, chemotherapy, or observation. Such treatment may or may not be applicable for patients enrolled in this study. Regardless, patients will be expected to forgo standard chemotherapy or radiotherapy until there is evidence of clinical or radiographic disease progression. The amount of radiation administered via protocol therapy will be considered in determining how much additional radiation can be given using conventional external beam fractionation.

6.8 Costs

Patients and/or their insurance companies will be responsible for the cost of all procedures and treatments under this protocol.

6.9 Compensation

Patients and/or their insurance companies will be responsible for the cost of all procedures and treatments under this protocol.

6.10 Withdrawal from Study

The reasons for withdrawal from the study include:

- Subject withdraws consent for follow-up.
- Subject is lost to follow-up.
- Study is terminated for any reason.

If participants withdraw from the study, they will be followed for survival data.

7. CHECKPOINT BLOCKADE IMMUNOTHERAPY DRUG INFORMATION

7.1 ANTI-CTLA-4 DRUG INFORMATION AND ADMINISTRATION

7.1.1 Relevant Prior Clinical Information

The results of a randomized, Phase 3 clinical trial published in 2010 showed a first-ever overall survival (OS) benefit for patients with previously treated stage III/stage IV metastatic melanoma who received ipilimumab compared with the controls. The patients in that trial (N=676) were randomized to receive either glycoprotein 100 (gp100) vaccine with Ipilimumab, gp100 alone, or Ipilimumab monotherapy in a 3:1:1 ratio. Patients receiving Ipilimumab monotherapy or with gp100 experienced a significantly longer median OS compared to those who received gp100 alone (approximately 10 vs. 6.4 months respectively). The risk of progression was reduced 19% with Ipilimumab plus gp100 and 36% with Ipilimumab alone compared to gp100 alone; subsequently, the FDA approved Ipilimumab alone in 2011. This OS advantage was observed while using a lower dose (3 mg/kg), than preceding studies (10 mg/kg) with a durable response demonstrated despite the lack of a maintenance phase.

In a Phase 1 trial testing ipilimumab in patients with stage III and IV melanoma, three doses were given: 0.3 mg/kg, 1 mg/kg, and 3 mg/kg. A dose-response was seen, with only the 3mg/kg dose achieving trough concentrations of 10 μg/mL. Steady state was achieved by the third dose at approximately 22 μg/mL. On average, the elimination half-life of Ipilimumab is 14.7 days. Volume of distribution and clearance increase with increasing body weight. The following mean (percent coefficient of variation) parameters have been generated through population pharmacokinetic analysis: terminal half-life of 15.4 days (34%); systemic clearance (CL) of 16.8 mL/h (38%) [17]. The volume of distribution at steady-state (Vss) is 7.21 L and the mean (±SD) Ipilimumab Cmin achieved at

steady state with the 3-mg/kg regimen is 21.8

The effects of various covariates on Ipilimumab pharmacokinetics have been assessed in population pharmacokinetic analyses. Ipilimumab CL increases with increasing body weight; however, no dose adjustment of ipilimumab is required for body weight after administration on a milligram per kilogram basis. The following factors have no clinically meaningful effect on the CL of Ipilimumab: age (range 26 to 86 years), gender, performance status, renal impairment, mild hepatic impairment, prior use of systemic anticancer therapy, or baseline lactate dehydrogenase (LDH) levels. [84].

Renal Impairment: Creatinine clearance at baseline does not have a clinically important effect on Ipilimumab pharmacokinetics in patients with calculated creatinine clearance values of 29 mL/min or greater[84].

Hepatic Impairment: Baseline AST, total bilirubin, and ALT levels does not have a clinically important effect on Ipilimumab pharmacokinetics in patients with various degrees of hepatic impairment[84].

7.1.2 Safety Profile

Ipilimumab has been reported to cause high levels of adverse events (AEs), the most common of which are immune related[84]. Blockade of CTLA-4 may cause an increase in self-reactive T cells and autoimmunity leading to rash, vitiligo, diarrhea, colitis, uveitis, episcleritis, hepatitis and hypophysitis.called immune related adverse events (irAEs).

The results of dose escalation studies have shown that increasing dosage correlates with increased efficacy as well as increased severity of irAEs. Roughly 60% of patients taking Ipilimumab experienced an irAE of any grade, with 10-15% of those grade 3 or 4 at the 3mg/kg dose. The most commonly reported adverse effects at the 3 mg/kg dose are grade I and II adverse events including rash, pruritus and diarrhea[84]. A cases series of 11 patients found an increased rate of transaminitis compared to the results from the Hodi et al trial[37]. Six of eleven patients had >Grade 1 elevations of liver enzymes compared to only 3 patients in the Hodi trial; four of eleven had grade 3 elevations compared to none in the Hodi trial[37].

irAEs can have a delayed onset and may be persistent. The reported median time to onset of an irAE depends on event type but ranges from 3.1 to 11 weeks. The median time to resolution of any grade II-IV event has been reported to be 4.9 weeks. Diarrhea, the most common irAE in clinical trials, has a median time to resolution of 1-2 weeks but it may be longer than 4 weeks for a grade III or IV event. The standard of care for treating irAEs is systemic administration of corticosteroids, as the majority of irAEs caused by ipilimumab can be resolved with steroids alone. Additional therapies that have been published include immune-suppressants, hormone replacement therapy for irAEs of the endocrine system, and intravenous immunoglobulin for immune-mediated blood disorders.

Ipilimumab has been attributed to the death of 14 patients in the Hodi et al trial, 7 of those due to immune related adverse events[37]. A boxed warning regarding the risk of enterocolitis, hepatitis, dermatitis, neuropathies, and endocrinopathies is included with ipilimumab. A Risk Evaluation and Mitigation Strategy (REMS) program for ipilimumab is mandated by the FDA to ensure that the benefits of ipilimumab outweigh the risk of these severe irAEs.

7.1.3 Ipilimumab Dosing

Ipilimumab will be dosed and scheduled according to FDA approved labels or per institutional guidelines at discretion of treating medical oncologist. For additional details regarding drug storage, preparation, and administration please refer to Ipilimumab package insert[84].

7.1.4 Treatment of Ipilimumab Related Infusion Reactions

Infusion reactions should be graded according to CTCAE Version 4.0 Allergic reaction/hypersensitivity criteria. Severe infusion reactions require the immediate interruption of ipilimumab therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms. In each case of an infusion reaction, the investigator should institute treatment measures according to the best available medical practice.

7.2 ANTI-PD-1/ ANTI-PD-L1 DRUG INFORMATION AND ADMINISTRATION

7.2.1 Relevant Prior Clinical Information

Nivolumab (Opdivo) is a fully human monoclonal immunoglobulin (Ig) G4 antibody that binds to the programmed death-1 (PD-1) cell surface membrane receptor, a negative regulatory molecule expressed by activated T and B lymphocytes[85].

Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T cell responses to both foreign antigens as well as self antigens. PD-1 receptor blockade by Nivolumab is an FDA approved approach for immunotherapy of advanced metastatic melanoma, lung cancer, and renal cell carcinoma[85]. Nivolumab received FDA approval on March 4th 2015 for treatment of advanced squamous NSCLC that has progressed after treatment with platinum-based chemotherapy. In the phase II clinical trial CheckMate-063, tumors shrank in 15% of patients who took Opdivo, and 26% had stable disease. Additionally the phase III CheckMate-017 trial in which NSCLC patients received either docetaxel chemotherapy or Opdivo was stopped early after it became evident that nivolumab outperformed docetaxel.

Pembrolizumab (Keytruda) is a human programmed death receptor-1 (PD-1)-blocking antibody and is an FDA approved approach for immunotherapy of advanced

metastatic melanoma and lung cancer[86]. Pembrolizumab received FDA approval on Oct 2nd, 2015 for advanced (metastatic) non-small cell lung cancer (NSCLC) whose disease has progressed after other treatments and with tumors that express PD-L1. The accelerated FDA approval was based on a multicenter, open-label multi-cohort, activity-estimating study (KEYNOTE-001), which evaluated Pembrolizumab in a cohort of 280 patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy and any evidence of PD-L1 expression by a clinical trial immunohistochemistry assay. In the KEYNOTE-001 trial Keytruda resulted in an overall response rate of 41% (n=25/61) in patients who had PD-L1 positive tumors (Tumor proportion score ≥ 50%).

Atezolizumab (Tecentriq) is a fully humanized, engineered monoclonal antibody of IgG1 isotype against the protein programmed cell death-ligand 1 (PD-L1). It has multiple FDA approved indications.

Avelumab (Bavencio) is a fully human monoclonal antibody targeting the protein programmed death-ligand 1 (PD-L1). It was FDA approved in March 2017 for Merkel-cell carcinoma.

Durvalumab (Imfinzi) is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that blocks the interaction of programmed cell death ligand 1 (PD-L1). It has multiple FDA approved indications.

7.2.2 Safety Profiles

7.2.2.1 Nivolumab

Patients have received nivolumab at doses of 0.1, 0.3, 1, 3, 10, or 20 mg/kg intravenously every 2 weeks with no maximal tolerated dose identified[85]. The incidence, severity and relationship of AEs are generally similar across dose levels and tumor types. Nivolumab related AEs of any grade occur in approximately 75% of subjects[85]. The most frequently reported AEs are fatigue (54.9%), decreased appetite (35.0%), diarrhea (34.3%), nausea (30.1%), and cough (29.4%). Most treatment-related AEs are low grade. Treatment-related high grade (Grade 3-4) AEs have been reported in approximately. 17.0% of subjects. The most common treatment-related high grade AEs are fatigue (2.3%) and diarrhea (1%). Drug-related SAEs have been reported to occur in approximately in 11% of subjects. Select AE categories include: GI AEs, pulmonary AEs, renal AEs, hepatic AEs, skin AEs, and endocrinopathies. Patients who receive 10 mg/kg have had a numerically greater frequency of high-grade select AEs including the subcategories of endocrinopathies, GI, pulmonary, and infusion reaction. High grade events have been reported to resolve following the treatment guidelines for the treatment of pulmonary events, GI events, hepatic events, renal events, and endocrine events, respectively. Treatment-related AEs leading to discontinuation have been reported in 10.5%, the most frequent of these were pneumonitis (2.6%) and colitis (1.0%)[85].

7.2.2.2 Pembrolizumab

The most common adverse reactions with Pembrolizumab include fatigue, pruritus, rash, constipation, diarrhea, nausea, and decreased appetite (Reported in >20% of patients) [86]. Pneumonitis has been reported to occur in approximately 2.9% of melanoma patients, including Grade 2 or 3 cases in 1.9% and 0.2% of patients, respectively [86]. The median time to development of pneumonitis was 5 months (range 0.3 weeks-9.9 months). The median duration was 4.9 months (range1 week-14.4 months). Five of eight patients with Grade 2 and one patient with Grade 3 pneumonitis required initial treatment with high-dose systemic corticosteroids followed by a corticosteroid taper. The median initial dose of high-dose corticosteroid treatment was 63.4 mg/day of prednisone or equivalent with a median duration of treatment of 3 days (range 1-34) followed by a corticosteroid taper. Pneumonitis led to discontinuation of Pembrolizumab in 3 (0.7%) patients. Pneumonitis completely resolved in seven of the nine patients with Grade 2-3 pneumonitis[86]. Colitis has been reported to occur in approximately 1% of patients, including Grade 2 or 3 cases in 0.2% and 0.5% of patients, respectively. The median time to onset of colitis was 6.5 months (range 2.3-9.8). The median duration was 2.6 months (range 0.6 weeks-3.6 months). All three patients with Grade 2 or 3 colitis were treated with high-dose corticosteroids with a median initial dose of 70 mg/day of prednisone or equivalent; the median duration of initial treatment was 7 days (range 4-41), followed by a corticosteroid taper. Hepatitis (including autoimmune hepatitis) has been reported to occur in approximately 0.5% of patients, including Grade 4 in 0.2% of patients. The time to onset was 22 days for the case of Grade 4 hepatitis which lasted 1.1 months. Hypophysitis has been reported to occur in approximately 0.5% of patients including Grade 2 and Grade 4 at at 0.2% each in patients. The time to onset was 1.7 months for the patient with Grade 4 hypophysitis and 1.3 months for the patient with Grade 2 hypophysitis. Hypophysitis may require permanent hormone replacement therapy. Nephritis has been reported to occur in approximately 0.7% of patients, including Grade 2 autoimmune nephritis (0.2%), and Grade 3 and Grade 4 interstitial nephritis with renal failure (0.5%). All patients fully recovered renal function with treatment with high-dose corticosteroids followed by a corticosteroid taper. Hyperthyroidism has been reported to occur in approximately 1.2% of patients, including Grade 2 or Grade 3 cases at 0.5% and 0.2% respectively. The median time to onset was 1.5 months (range 0.5-2.1). The median duration was 2.8 months (range 0.9 to 6.1). The following clinically significant, immune-mediated adverse reactions have been reported to occur in less than 1% of patients treated with Pembrolizumab: exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures arising in a patient with inflammatory foci in brain parenchyma, adrenal insufficiency,

myasthenic syndrome, optic neuritis, and rhabdomyolysis.

7.2.3 Nivolumab Dosing

Nivolumab will be dosed and scheduled according to FDA approved labels or per institutional guidelines at discretion of treating medical oncologist. For additional details regarding drug storage, preparation, and administration please refer to Nivolumab package insert[85]

7.2.4 Nivolumab combined with Ipilimumab Dosing

Nivolumab combined with Ipilimumab will be dosed and scheduled according to FDA approved labels or per institutional guidelines at discretion of treating medical oncologist. For additional details regarding drug storage, preparation, and combination administration please refer to Nivolumab package insert[85]

7.2.5 Pembrolizumab Dosing:

Pembrolizumab will be dosed and scheduled according to FDA approved labels or per institutional guidelines at discretion of treating medical oncologist For additional details regarding drug storage, preparation, and combination administration please refer to Pembrolizumab package insert[86].

7.2.6 Atezolizumab Dosing

Atezolizumab will be dosed and scheduled according to FDA approved labels or per institutional guidelines at discretion of treating medical oncologist. For additional details regarding drug storage, preparation, and administration please refer to Atezolizumab package insert [87]

7.2.7 Avelumab Dosing

Avelumab will be dosed and scheduled according to FDA approved labels or per institutional guidelines at discretion of treating medical oncologist. For additional details regarding drug storage, preparation, and administration please refer to Avelumab package insert [88]

7.2.8 Durvalumab Dosing

Durvalumab will be dosed and scheduled according to FDA approved labels or per institutional guidelines at discretion of treating medical oncologist. For additional details regarding drug storage, preparation, and administration please refer to Durvalumab package insert [89]

7.2.9 Treatment of anti-PD-1/PD-L1 Related Infusion Reactions

Infusion reactions should be graded according to CTCAE Version 4.0 Allergic reaction/hypersensitivity criteria. Severe infusion reactions require the immediate interruption of anti-PD-1/PD-L1 therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the

complete resolution of all signs and symptoms. In each case of an infusion reaction, the investigator should institute treatment measures according to the best available medical practice.

8 DOSING DELAYS/DOSE MODIFICATIONS AND DISCONTINUATION CRITERION

8.1) Dose Delay Criterion for CBI or CBI combined with SBRT

Dose delay criteria specified below apply for all checkpoint blockade immunotherapies or any combination of checkpoint blockade immunotherapies with SBRT (regardless of whether or not the event is attributed to CBI, SBRT or both)

CBI and SBRT administration should be delayed for the following:

- Any Grade ≥ 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 asymptomatic amylase or lipase, AST, ALT, or total bilirubin:
  - − Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay.
  - − If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
  - − If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity
- Any adverse event, laboratory abnormality, or concurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

8.2) Discontinuation Criterion for CBI or CBI combined with SBRT:

Discontinuation criteria apply for all drug-related adverse events attributed to checkpoint blockade immunotherapies or any combination of checkpoint blockade immunotherapies with SBRT (regardless of whether or not the event is attributed to CBI, SBRT or both)

Treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, and infusion reactions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation

- Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except: ☐Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation

Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:

- AST or ALT > 8 x ULN
- Total bilirubin > 5 x ULN
- Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations, or radiographic signs of pancreatitis.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.

If a subject discontinues combination CBI treatment for example with nivolumab + ipilimumab due to a drug-related adverse event prior to completing four doses of the combination therapy, the subject may continue treatment with nivolumab 3mg/kg every 2 weeks as long as the AE leading to discontinuation was clearly attributed to ipilimumab and not nivolumab. In such circumstances, the subject may re-start nivolumab therapy when the subject fully recovers from the drug-related adverse event that led to discontinuation.

8.3) Dose Modification for SBRT:

Dose modifications to SBRT due to safety or toxicity concerns will be performed by the treating radiation oncologist as clinically indicated. This includes dose reduction below 9.5Gy x3 fractions in order to meet tolerances listed above for critical normal structures when deemed necessary by the treating radiation oncologist. The minimum dose of SBRT delivered will be 6Gy x3 fractions.

9 CORRELATIVE/SPECIAL STUDIES

9.1) Blood Sample Transport, Processing, and Storage.

9.1.1 A peripheral blood draw (80cc maximum for adults and 20 cc maximum for participants <18 years old or those under a specific weight criteria) will be obtained by venipuncture in BD Vacutainer® CPT™ (Franklin Lakes, NJ) tubes or an appropriate substitute cell preparation tube at baseline prior to treatment, prior to cycle #2 of CBI, and at 2 month post-SBRT follow-up visit.

9.1.2 The study coordinator or research staff from the laboratory of Dr. Andrew Sharabi will transport the specimen to the laboratory of Andrew B. Sharabi, M.D., PhD for storage and processing. Samples will be stored indefinitely.

9.1.3 Blood for serum should be collected in standard 10 ml red top polypropylene tubes and allowed to clot for 30 minutes at room temperature in a vertical position. The

samples should be separated in a centrifuge for 30 minutes at 3500 rpm. Without delay, 1.5 ml serum aliquots should be pipetted into a 2.0 ml snap cap cryovials. After removing the serum, the red top tube will be discarded and each cryovial will be labled with the date and patient case ID to protect patient privacy. Cyrovials will be frozen immediately at -70°C in a dedicated freezer in the laboratory of Dr. Andrew Sharabi. If a -70°C freezer is not available serum samples may be stored at -20°C..

9.1.4 Blood for plasma should be collected in standard 10 ml Heparin coated tubes. The samples should be immediately separated in a centrifuge for 10 minutes at 1500 +/- 150g (=1500RCF). Without delay, transfer the resulting supernatant plasma to a fresh 15 ml conical centrifuge tube. After removing the plasma, use the same transfer pipet to carefully aspirate the exposed WBC layer (buffy coat) in a volume of 1 ml or less. Aspirate slowly, using a circular motion, to pull all the visible buffy coat material into the pipet. Expel the buffy coat into one cryovial. Discard the lavender top tubes and the transfer pipet tip. Label each buffy coat cryovial with the with the date and patient case ID to protect patient privacy. Run the 15 ml conical centrifuge tube containing the supernatant plasma in a centrifuge for a second time for 10 minutes at 1500 +/- 150g (=1500RCF). Without delay and using a fresh transfer pipet tip, 1.5 ml plasma aliquots of the resulting supernatant should be pipetted into a 2.0 ml snap cap cryovials. Leave a residual volume of about 0.3 ml (~7 mm) on the bottom of the 15 ml conical centrifuge tube to avoid cellular contamination. Cyrovials will be frozen immediately at -70°C in a dedicated freezer in the laboratory of Dr. Andrew Sharabi. If a -70°C freezer is not available serum samples may be stored at -20°C.

9.2) Assessment of Immune Reponses

9.2.9 Multiparametic Flow cytometery will be used to analyze Immune subset proportions (%CD4+ T-cells, %CD8+ T-cells, %T_{reg} T-cells, %Myeloid Derived Suppressor Cells, %Natural Killer cells, etc.) will be determined by flow cytometry analysis performed in the UCSD Moores Cancer Center Flow Cytometry Core.

9.2.10 T-cell Receptor Repertoire analysis will be performed on Baseline and post-treatment PBMC. DNA will be extracted and assessed for quality control utilizing standard manufacturer DNA extraction kits and per manufacturer instructions (i.e. DNeasy, Qiagen, N.V.) and per standard spectrophotometric 260nm/280nm methods. Extracted DNA from each sample will be analyzed for T-cell and B-cell receptor mutations by next generation sequencing on the Adaptive Biotechnologies Immunoseq platform. This work will be outsourced and performed in collaboration with Adaptive Biotechnologies (Seattle, WA).

9.2.11 Sequencing Analysis. DNA will be extracted and assessed for quality control utilizing standard manufacturer DNA extraction kits and per manufacturer instructions (i.e. DNeasy, Qiagen, N.V.) and per standard spectrophotometric 260nm/280nm methods. Extracted DNA from each sample will be analyzed for overall mutation burden, individual gene mutations, and individual gene fusions on the Illumina HiSeq Next Generation Sequencing platform.

9.2.12 Serum markers and cytokine of interest (i.e. IFN-□ TGF-□ IL-10, IL-4, IL-5, IL-

13, IFN-□) will be analyzed will be selected based on assay methodology optimization and validation testing.

9.2.13 Additional exploratory analysis of the relationship between circulating free tumor DNA/RNA, micro-RNA, and other novel platforms will be pursued as resources and specimen availability permit.

10 STUDY CALENDAR

Parameter	Pre-TX	CBI Cycle#1	SBRT 3 Fx	CBI Cycle #2	CBI Cycle#3+	Post C1D1 8 weeks @	Post C1D1 16 weeks @	Post C1D1 6mo @	Post C1D1 12mo @	Post C1D1 18mo @	Post C1D1 24mo @
Informed Consent	X										
Demographics	X										
Med HX & Medication Rev	X					X	X	X	X	X	X
Physical Exam	X					X	X	X	X	X	X
Standard of Care Labs	X	X		X	X	X	X	X	X	X	X
Research Blood Draw	X*			X*		X*					
Imaging Assessment	X					X	X		X	X	X
AE Evaluation	X	X		X	X	X	X	X	X	X	X

~ SBRT: to be administered in three fractions.
* indicates optional
@ +/- 10 days

11 MEASUREMENT OF EFFECT

11.1 Antitumor Effect-Solid Tumors

For the purposes of this study, patients should be re-evaluated for response 8 weeks after the initial treatment, 16 weeks after treatment, and at 6 month intervals thereafter.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) Committee (30). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

The RECIST read at 16 weeks will be used to determine the objective response rate for the primary endpoint of this study.

11.2 Definitions

Evaluable Population: will consist of all patients who have received at least 1 cycle of CBI with or without SBRT.

Safety Population: Will consist of all subjects who were enrolled and have received at least 1 cycle of CBI with or without SBRT. This will be used to assess the clinical safety and tolerability of the study.

Evaluable for Objective Response: Patients who have measurable disease present at baseline and have received at least 1 cycle of CBI , and have had their disease re- evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

11.3 Disease Parameters

Measurable Disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$0.5 cm with diagnostic techniques (CT, PET/CT (all are optional), or MRI). All tumor measurements must be recorded in centimeters.

Non-Measurable Disease: All other lesions (or sites of disease), including small lesions (longest diameter <0.5 cm with diagnostic techniques), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis, inflammatory breast disease, and cystic lesions are all non-measurable.

Target Lesions: Target lesion in this study will be considered metastatic sites up to a maximum of 3 lesions per patient. They should be recorded and measured at baseline. Target lesions should be equal to or larger than 1.0 cm in the smallest

cross-sectional diameter on CT or MRI and/or any lesion that shows increase metabolic uptake on PET/CT scans.

Non-Target Lesions: Non-Target lesion in this study will be considered metastatic sites up to a maximum of 10 lesions per patient. They should be recorded and measured at baseline. Non-target lesions should be equal to or larger than 0.5 cm in the smallest cross-sectional diameter on CT or MRI and/or any lesion that shows increase metabolic uptake on PET/CT scans. Importantly, a sum of the longest diameter (LD) for all ***non-target*** lesions will be calculated and reported as the baseline sum LD. The baseline sum LD of the ***non-target*** lesions will be used as reference by which to characterize the objective tumor response.

11.4 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 6 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Conventional CT, PET/CT (all are optional), and MRI These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis.

11.5 Response Criteria (via RECIST 1.1)

11.5.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all targeted and ***Non-Targeted*** lesions

Objective Response (OR): At least a 30% decrease in the sum of the longest diameter (LD) of targeted and ***Non-targeted*** lesions, taking as reference the baseline sum LD

Progressive Disease (PD): At least a 20% increase in the sum of the LD of Targeted or Non- Targeted lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the

smallest sum LD since the treatment started

11.5.2 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Best overall response will be based on the overall response of the ***Non-targeted*** lesions.

11.5.3 Duration of Response

Response will be defined as evidence of CR, PR, or stable disease. The duration of response will be measured from the start of treatment until the criteria for progression are met.

Duration of CR or PR: The duration of CR or PR will be recorded from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that current or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

Duration of Stable Disease: Stable disease is measured from the start of the treatment and must be at least 6 months in duration or until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

11.5.4 Clinical Response Parameters

Time to Local Progression (TTLP) is defined as the elapsed time from the start of treatment to the date of documented local progression or death, whichever happens earliest.

Progression-Free Survival (PFS) is defined is the time from starting treatment to the time of first documented tumor progression or death due to any cause, whichever occurs first. Death is considered as an event here. For subjects whose disease does not progress or who do not die, PFS will be censored at the time of the last visit.

Time to Progression (TTP) is defined as the time from starting treatment to the time of first documented tumor progression. Subjects who do not progress will be censored at the time of the last contact. In addition, death from any cause will also be censored.

Overall Survival (OS) is defined as the time from starting treatment until death due to any cause. For subjects who do not die, time to death will be censored at the time of last contact.

Locoregional Control (LRC) is defined as the time from starting treatment until local and/or regional relapse is documented

11.5.5 Response Review

All responses will be reviewed by the study co-investigator radiologist.

12 ADVERSE EVENT REPORTING REQUIREMENTS

12.1 General

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v 4.0) that is available at http://ctep.cancer.gov/reporting//ctc.html.

Information on all Grade 3 or greater adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections. In addition, grade 1 and 2 adverse events treated with concomitant medicine/procedure or deemed to be of clinical significance by a study investigator will be collected, recorded, followed and reported as described in the following sections.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12.2 Definitions

12.2.1 Adverse Event (AE)

An adverse event is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

For this Phase II study only Grade 3 or higher adverse events, or grade 1 and 2 adverse events treated with concomitant medicine/procedure, or grade 1 and 2 adverse events deemed to be of clinical significance by a study investigator will be collected.

12.2.2 Serious adverse event (SAE)

A serious adverse event is an undesirable sign, symptom, or medical condition which:

- is fatal or life-threatening;
- requires or prolongs inpatient hospitalization;
- results in persistent or significant disability/incapacity;
- constitutes a congenital anomaly or birth defect; or
- jeopardizes the participant and requires medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

12.2.3 Expectedness

- Expected: Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

- Unexpected: An adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk

12.2.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

12.3 Potential Adverse Events

Signs and symptoms of disease progression are not considered AEs. The development of a new cancer should be regarded as an AE. New cancers are those that are not the primary reason for administration of study treatment and have been

identified after inclusion of the patient into the clinical study.

Because patients are receiving standard treatments, which are not part of this study, their treating physician will be counseling them on the risk of their treatments, including the risk of surgery, radiation therapy, and/or chemotherapy, whichever is appropriate for the type and the stage of their cancer. The procedures related to the study are phlebotomy, PET imaging (all are optional), SBRT, and CBI administration.

Phlebotomy can cause pain, bleeding, and rare needle site infection. PET imaging results in low dose radiation exposure (see Investigator's Brochure for details of dosimetry), which has an extremely small risk of causing a secondary cancer.

12.4 Stereotactic Body Radiation Treatment

It is difficult at this time to predict with confidence the complication rate from the proposed SBRT; however, it is reasonable to extrapolate from the current experience and reported literature with SBRT. One significant toxicity is radiation pneumonitis, which can be manifested as fever, increased excertional dypsnea, pleuritic chest pain, and peritumoral infiltrate on chest imaging. It generally occurs between 1 to 3 months of completion of radiotherapy. The risk of grade 2-4 radiation pneumonitis is aproximately 10-15% in patients treated with standard fractionated large field radiotherapy and higher in patients treated with combined chemoradiotherapy. It is highly dependent on the volume of the lung treated to high dose and the mean lung dose. At this point, the incidence of RT pneumonitis from SBRT combined with immunotherapy for small pulmonary tumors is unknown. However, if the treated tumor volume is kept $\leq$ 65 cc, the risk should be <10-15% with the proposed dose level.

Other toxicities commonly associated with such treatment includes colitis, diarrhea, hypophysitis, rash, arthritis, fatigue, nausea, vomiting, anorexia, and weight loss. Some of these symptoms can also be due to tumor progression. Clinical and radiographic assessments will be performed as indicated to identify all adverse effects, ascertain their etiology, and provide the most appropriate palliative measures. Complications orther than radiation pneumonitis, if any, will be graded according to the Common Toxicity Criteria, National Cancer Institute, version 4.0.

12.5 Reporting Procedures

12.5.1 General

Adverse events will be recorded at each visit. If an adverse event requiring medical attention occurs between visits, this will be recorded as well. The variables to be recorded for each adverse event include, but are not limited to, onset, resolution, intensity, action taken, outcome, causality rating and whether it constitutes an SAE or not. The intensity of the adverse event should be captured using CTCAE criteria, version 4.0, when possible.

Pregnancy in itself is not reported as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

All adverse events will be captured on the appropriate study-specific case report forms (CRFs).

12.5.2 Institutional Review Board

All adverse events and serious adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse event. If an adverse event requires modification to the study protocol, these modifications will be provided to the IRB as soon as is possible.

13 DATA AND SAFETY MONITORING PLAN

Data and safety monitoring oversight will be conducted by the UCSD Moores Cancer Center Safety Monitoring Committee at the University of California at San Diego. All reportable anticipated and unanticipated protocol events/problems and amendments that are submitted to the IRB will also be reviewed by the Safety Monitoring Committee Chair (or designee) and QA manager.

14 REGULATORY CONSIDERATIONS

14.1 Protocol Review and Amendments

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per the current institutional standards.

Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB prior to implementation.

14.2 Informed Consent

The investigator (or his/her designee) will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary, that she may withdraw from the study at any time, and that withdrawal of consent will not affect her subsequent medical treatment or relationship with the treating physician(s) or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The

subject should read and consider the statement before signing and dating it, and will be given a copy of the document. No subject will enter the study or have study-specific procedures done before his/her informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

14.3 Ethics and GCP

This study will be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigators agree to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

15 STATISTICAL CONSIDERATIONS

15.1 Endpoints

15.1.1 Primary Objectives

To determine whether SBRT combined with concurrent CBI improves the objective response rate compared to CBI alone in patients with metastatic disease.

15.1.2 Secondary Objectives

- To assess the safety and toxicity of CBI used concurrently with SBRT delivered in the population enrolled using grading with CTCAE v. 4.0
- To assess progression free survival and overall survival in patients after completion of SBRT in combination with CBI. Progression-free survival will be measured from time of enrollment to date of disease progression or death. Patients who are lost to follow-up will be censored for determination of progression-free survival on the date of their last evaluation. Overall survival is defined as time from enrollment to death

due to any cause.
- To assess the rates of stable disease great than or equal to 6 months during and after SBRT in combination with CBI compared to CBI alone
- To determine whether SBRT combined with concurrent CBI results improvements in anti-tumor immune responses compared to CBI alone

15.2 Sample Size/Accrual Rate

The primary endpoint will be objective response rate at 16 weeks. The treatment regimen would be considered of insufficient activity for further study in this population if the 16 week objective response is 10% less than historical controls.

The objective response rate to CBI monotherapy depends on disease type and is reported to be approximately 40% in melanoma and 20-25% in NSCLC. Dual agent checkpoint blockade has recently been shown to have a response rate of 61% in Metastatic melanoma. In order to detect a cumulative relative 33% increase in objective response rate [i.e. from 61% to 81% (for dual agent), 40% to 53% for single agent in melanoma, and 25% to 33% in NSCLC] with a one tailed p value <0.05% with 80% power incorporating the respective frequencies of tumor types this would require 146 patients total.

15.3 Safety Run-In Phase

There is no significant published experience with SBRT used concurrently with CBI in this study population. Therefore, to ensure that the combination is safe, the first six patients will be treated and observed for toxicity for 30 days after radiation before continuing with further accrual. 6 patients will be enrolled at the proposed dose of CBI and SBRT. If $\leq$ 3 toxicity events occur in the first 6 patients within 30 days of therapy, we proceed with additional accrual with this regimen to complete a total of 146 patients. If $\geq$ 4 toxicity events occur among the first 6 patients, we will suspend the study pending data review.

Toxicity Event: $\geq$grade 3 adverse event (CTCAE v 4.0) with an attribution of possible, probable, or definite.

15.4 Early Stopping Guidelines:

This study will monitor site-specific grade 4/5 toxicity. If it becomes evident that the proportion of grade 4/5 toxicity at specific sites convincingly exceeds 30%, the study will be halted for a safety consultation. Specifically, we will apply a Bayesian toxicity monitoring rule that suspends the enrollment if the posterior probability of toxicity being larger than 30% threshold is 75% or higher.

15.5 Analysis of Primary Objectives

The primary efficacy analysis will be the objective response rate of SBRT combined with concurrent CBI compared to CBI alone in patients with metastatic disease. Objective response is defined as at least a 30% decrease in the sum of the longest diameter (LD) of ***Non-Targeted*** lesion/lesions, taking as reference the

baseline sum LD. The analysis population includes all registered subjects who have received the three fractions of SBRT.

15.6 Analysis of Secondary Objectives

- For safety analysis, adverse events will be summarized by type and grade.
- To determine whether SBRT combined with concurrent CBI results in statistically significant improvements in anti-tumor immune responses compared to CBI alone we will perform immunologic assays quantifying lymphocyte specificity and activation, including Immune cell Sequencing, ProtoArrays, Immunoassays, and multiparametric flow cytometry.
- Hazard rate estimates and 95% confidence intervals as well as Kaplan-Meier (KM) estimates will be used to summarize survival (OS), progression free survival (PFS), time to locoregional progression (TTLP) and time to distant progression (TTDP), duration of response functions over time, and stable disease (SD). The median OS, PFS, TTLP, TTDP, and SD will be reported.

15.7 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment of CBI.

15.8 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 8) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-8 should be considered to have a treatment failure (disease progression).

All conclusions should be based on all eligible patients. Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub-analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The reason for performing subset analyses would be to generate hypotheses for future prospective clinical trials.

REFERENCES:

1. ACS. *Cancer Facts & Figures*. 2015; Available from: http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2015/index.
2. Drake, C.G., E.J. Lipson, and J.R. Brahmer, *Breathing new life into immunotherapy: review of melanoma, lung and kidney cancer.* Nat Rev Clin Oncol, 2014. **11**(1): p. 24-37.
3. Couzin-Frankel, J., *Breakthrough of the year 2013. Cancer immunotherapy.* Science, 2013. **342**(6165): p. 1432-3.
4. Hamid, O., et al., *Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma.* N Engl J Med, 2013. **369**(2): p. 134-44.
5. Topalian, S.L., et al., *Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab.* J Clin Oncol, 2014. **32**(10): p. 1020-30.
6. Wolchok, J.D., et al., *Nivolumab plus ipilimumab in advanced melanoma.* N Engl J Med, 2013. **369**(2): p. 122-33.
7. Sharabi, A.B., et al., *Stereotactic radiation therapy combined with immunotherapy: augmenting the role of radiation in local and systemic treatment.* Oncology (Williston Park), 2015. **29**(5): p. 331-40.
8. Tang, C., et al., *Combining radiation and immunotherapy: a new systemic therapy for solid tumors?* Cancer Immunol Res, 2014. **2**(9): p. 831-8.
9. Dunn, G.P., L.J. Old, and R.D. Schreiber, *The immunobiology of cancer immunosurveillance and immunoediting.* Immunity, 2004. **21**(2): p. 137-48.
10. Gause, W.C., et al., *The development of CD4+ T effector cells during the type 2 immune response.* Immunol Res, 1999. **20**(1): p. 55-65.
11. Joyce, J.A. and D.T. Fearon, *T cell exclusion, immune privilege, and the tumor microenvironment.* Science, 2015. **348**(6230): p. 74-80.
12. Lampen, M.H. and T. van Hall, *Strategies to counteract MHC-I defects in tumors.* Curr Opin Immunol, 2011. **23**(2): p. 293-8.
13. Kao, J., et al., *Targeting immune suppressing myeloid-derived suppressor cells in oncology.* Crit Rev Oncol Hematol, 2011. **77**(1): p. 12-9.
14. Hellman, S. and R.R. Weichselbaum, *Oligometastases.* J Clin Oncol, 1995. **13**(1): p. 8-10.
15. Fong, Y., et al., *Liver resection for colorectal metastases.* J Clin Oncol, 1997. **15**(3): p. 938-46.
16. Bacci, G., et al., *High grade osteosarcoma of the extremities with lung metastases at presentation: treatment with neoadjuvant chemotherapy and simultaneous resection of primary and metastatic lesions.* J Surg Oncol, 2008. **98**(6): p. 415-20.
17. Simmonds, P.C., et al., *Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies.* Br J Cancer, 2006. **94**(7): p. 982-99.
18. Gunderson&Tepper, *Clinical Radiation Oncology*. Third Edition. 2012, Philadelphia, PA: Elsevier.
19. Timmerman, R.D., J. Herman, and L.C. Cho, *Emergence of stereotactic body radiation therapy and its impact on current and future clinical practice.* J Clin Oncol, 2014. **32**(26): p. 2847-54.
20. Flickinger, J.C., et al., *A dose-response analysis of arteriovenous malformation obliteration after radiosurgery.* Int J Radiat Oncol Biol Phys, 1996. **36**(4): p. 873-9.

21. Cheng, J.S., et al., *Management of medically refractory trigeminal neuralgia in patients with multiple sclerosis.* Neurosurg Focus, 2005. **18**(5): p. e13.
22. Sheehan, J.P., et al., *Stereotactic radiosurgery for pituitary adenomas: an intermediate review of its safety, efficacy, and role in the neurosurgical treatment armamentarium.* J Neurosurg, 2005. **102**(4): p. 678-91.
23. Lutterbach, J., et al., *Radiosurgery followed by planned observation in patients with one to three brain metastases.* Neurosurgery, 2003. **52**(5): p. 1066-73; discussion 1073-4.
24. Timmerman, R., et al., *Stereotactic body radiation therapy for inoperable early stage lung cancer.* JAMA, 2010. **303**(11): p. 1070-6.
25. Milano, M.T., et al., *A prospective pilot study of curative-intent stereotactic body radiation therapy in patients with 5 or fewer oligometastatic lesions.* Cancer, 2008. **112**(3): p. 650-8.
26. Le, Q.T., et al., *Results of a phase I dose-escalation study using single-fraction stereotactic radiotherapy for lung tumors.* J Thorac Oncol, 2006. **1**(8): p. 802-9.
27. Gibbs, I.C., et al., *Image-guided robotic radiosurgery for spinal metastases.* Radiother Oncol, 2007. **82**(2): p. 185-90.
28. Wulf, J., et al., *Stereotactic radiotherapy for primary lung cancer and pulmonary metastases: a noninvasive treatment approach in medically inoperable patients.* Int J Radiat Oncol Biol Phys, 2004. **60**(1): p. 186-96.
29. Hof, H., et al., *Stereotactic single-dose radiotherapy of lung metastases.* Strahlenther Onkol, 2007. **183**(12): p. 673-8.
30. Kwon, E.D., et al., *Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial.* Lancet Oncol, 2014. **15**(7): p. 700-12.
31. Kiess, A.P., et al., *Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: safety profile and efficacy of combined treatment.* Int J Radiat Oncol Biol Phys, 2015. **92**(2): p. 368-75.
32. Ben-Josef, E. and T.S. Lawrence, *Using a bigger hammer: the role of stereotactic body radiotherapy in the management of oligometastases.* J Clin Oncol, 2009. **27**(10): p. 1537-9.
33. Niibe, Y. and K. Hayakawa, *Oligometastases and oligo-recurrence: the new era of cancer therapy.* Jpn J Clin Oncol, 2010. **40**(2): p. 107-11.
34. Dawson, L.A. and R.K. Ten Haken, *Partial volume tolerance of the liver to radiation.* Semin Radiat Oncol, 2005. **15**(4): p. 279-83.
35. Goodman, K.A., et al., *Dose-escalation study of single-fraction stereotactic body radiotherapy for liver malignancies.* Int J Radiat Oncol Biol Phys, 2010. **78**(2): p. 486-93.
36. Scalapino, K.J. and D.I. Daikh, *CTLA-4: a key regulatory point in the control of autoimmune disease.* Immunol Rev, 2008. **223**: p. 143-55.
37. Hodi, F.S., et al., *Improved survival with ipilimumab in patients with metastatic melanoma.* N Engl J Med, 2010. **363**(8): p. 711-23.
38. Robert, C., et al., *Ipilimumab plus dacarbazine for previously untreated metastatic melanoma.* N Engl J Med, 2011. **364**(26): p. 2517-26.
39. Topalian, S.L., et al., *Safety, activity, and immune correlates of anti-PD-1 antibody in cancer.* N Engl J Med, 2012. **366**(26): p. 2443-54.
40. Drake CG et al., *Survival, safety, and response duration results of nivolumab (Anti-PD-1; BMS-936558; ONO-4538) in a phase I trial in patients with previously treated metastatic renal cell carcinoma (mRCC): Long-term patient follow-up.* J Clin Oncol, 2013. **31**((suppl;

abstr 4514)).
41. Powles, T., et al., *MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer.* Nature, 2014. **515**(7528): p. 558-62.
42. Ansell, S.M., et al., *PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma.* N Engl J Med, 2015. **372**(4): p. 311-9.
43. Hauser, S.H., et al., *Radiation-enhanced expression of major histocompatibility complex class I antigen H-2Db in B16 melanoma cells.* Cancer Res, 1993. **53**(8): p. 1952-5.
44. Garnett, C.T., et al., *Sublethal irradiation of human tumor cells modulates phenotype resulting in enhanced killing by cytotoxic T lymphocytes.* Cancer Res, 2004. **64**(21): p. 7985-94.
45. Reits, E.A., et al., *Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy.* J Exp Med, 2006. **203**(5): p. 1259-71.
46. Wan, S., et al., *Chemotherapeutics and radiation stimulate MHC class I expression through elevated interferon-beta signaling in breast cancer cells.* PLoS One, 2012. **7**(3): p. e32542.
47. Sharabi, A.B., et al., *Stereotactic Radiation Therapy Augments Antigen-Specific PD-1 Mediated Anti-Tumor Immune Responses via Cross-Presentation of Tumor Antigen.* Cancer Immunol Res, 2014.
48. Verbrugge, I., et al., *The curative outcome of radioimmunotherapy in a mouse breast cancer model relies on mTOR signaling.* Radiat Res, 2014. **182**(2): p. 219-29.
49. Gameiro, S.R., et al., *Radiation-induced immunogenic modulation of tumor enhances antigen processing and calreticulin exposure, resulting in enhanced T-cell killing.* Oncotarget, 2014. **5**(2): p. 403-16.
50. Rovere-Querini, P., et al., *HMGB1 is an endogenous immune adjuvant released by necrotic cells.* EMBO Rep, 2004. **5**(8): p. 825-30.
51. Andersson, U., et al., *HMGB1 as a DNA-binding cytokine.* J Leukoc Biol, 2002. **72**(6): p. 1084-91.
52. Lugade, A.A., et al., *Local radiation therapy of B16 melanoma tumors increases the generation of tumor antigen-specific effector cells that traffic to the tumor.* J Immunol, 2005. **174**(12): p. 7516-23.
53. Harris, T.J., et al., *Radiotherapy augments the immune response to prostate cancer in a time-dependent manner.* Prostate, 2008. **68**(12): p. 1319-29.
54. Takeshima, T., et al., *Local radiation therapy inhibits tumor growth through the generation of tumor-specific CTL: its potentiation by combination with Th1 cell therapy.* Cancer Res, 2010. **70**(7): p. 2697-706.
55. Parker, J.J., et al., *Characterization of direct radiation-induced immune function and molecular signaling changes in an antigen presenting cell line.* Clin Immunol, 2013. **148**(1): p. 44-55.
56. Gupta, A., et al., *Radiotherapy promotes tumor-specific effector CD8+ T cells via dendritic cell activation.* J Immunol, 2012. **189**(2): p. 558-66.
57. Bernstein, M.B., et al., *Radiation-induced modulation of costimulatory and coinhibitory T-cell signaling molecules on human prostate carcinoma cells promotes productive antitumor immune interactions.* Cancer Biother Radiopharm, 2014. **29**(4): p. 153-61.
58. Ishihara, H., et al., *Induction of the expression of the interleukin-1 beta gene in mouse spleen by ionizing radiation.* Radiat Res, 1993. **133**(3): p. 321-6.
59. Hallahan, D.E., et al., *Increased tumor necrosis factor alpha mRNA after cellular exposure*

to ionizing radiation. Proc Natl Acad Sci U S A, 1989. **86**(24): p. 10104-7.
60. Hong, J.H., et al., *Rapid induction of cytokine gene expression in the lung after single and fractionated doses of radiation.* Int J Radiat Biol, 1999. **75**(11): p. 1421-7.
61. Drake, C.G., *Radiation-Induced Immune Modulation*. 2011: Springer New York.
62. Matsumura, S. and S. Demaria, *Up-regulation of the pro-inflammatory chemokine CXCL16 is a common response of tumor cells to ionizing radiation.* Radiat Res, 2010. **173**(4): p. 418-25.
63. Burnette, B.C., et al., *The efficacy of radiotherapy relies upon induction of type i interferon-dependent innate and adaptive immunity.* Cancer Res, 2011. **71**(7): p. 2488-96.
64. Gerber, S.A., et al., *IFN-gamma mediates the antitumor effects of radiation therapy in a murine colon tumor.* Am J Pathol, 2013. **182**(6): p. 2345-54.
65. Dovedi, S.J., et al., *Acquired Resistance to Fractionated Radiotherapy Can Be Overcome by Concurrent PD-L1 Blockade.* Cancer Res, 2014. **74**(19): p. 5458-68.
66. Chakraborty, M., et al., *Irradiation of tumor cells up-regulates Fas and enhances CTL lytic activity and CTL adoptive immunotherapy.* J Immunol, 2003. **170**(12): p. 6338-47.
67. Stone, H.B., L.J. Peters, and L. Milas, *Effect of host immune capability on radiocurability and subsequent transplantability of a murine fibrosarcoma.* J Natl Cancer Inst, 1979. **63**(5): p. 1229-35.
68. Lee, Y., et al., *Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment.* Blood, 2009. **114**(3): p. 589-95.
69. Yoshimoto, Y., et al., *Radiotherapy-induced anti-tumor immunity contributes to the therapeutic efficacy of irradiation and can be augmented by CTLA-4 blockade in a mouse model.* PLoS One, 2014. **9**(3): p. e92572.
70. Chakravarty, P.K., et al., *Flt3-ligand administration after radiation therapy prolongs survival in a murine model of metastatic lung cancer.* Cancer Res, 1999. **59**(24): p. 6028-32.
71. Cao, Z.A., D. Daniel, and D. Hanahan, *Sub-lethal radiation enhances anti-tumor immunotherapy in a transgenic mouse model of pancreatic cancer.* BMC Cancer, 2002. **2**: p. 11.
72. Demaria, S., et al., *Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated.* Int J Radiat Oncol Biol Phys, 2004. **58**(3): p. 862-70.
73. Demaria, S., et al., *Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer.* Clin Cancer Res, 2005. **11**(2 Pt 1): p. 728-34.
74. Dewan, M.Z., et al., *Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody.* Clin Cancer Res, 2009. **15**(17): p. 5379-88.
75. Zeng, 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, 2013. **86**(2): p. 343-9.
76. Wada, S., et al., *Combined treatment effects of radiation and immunotherapy: studies in an autochthonous prostate cancer model.* Int J Radiat Oncol Biol Phys, 2013. **87**(4): p. 769-76.
77. Deng, L., et al., *Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice.* J Clin Invest, 2014. **124**(2): p. 687-95.
78. Belcaid, Z., et al., *Focal radiation therapy combined with 4-1BB activation and CTLA-4 blockade yields long-term survival and a protective antigen-specific memory response in a murine glioma model.* PLoS One, 2014. **9**(7): p. e101764.

79. Friedman, E.J., *Immune modulation by ionizing radiation and its implications for cancer immunotherapy.* Curr Pharm Des, 2002. **8**(19): p. 1765-80.
80. Formenti, S.C. and S. Demaria, *Combining radiotherapy and cancer immunotherapy: a paradigm shift.* J Natl Cancer Inst, 2013. **105**(4): p. 256-65.
81. Zeng, J., et al., *Immune modulation and stereotactic radiation: improving local and abscopal responses.* Biomed Res Int, 2013. **2013**: p. 658126.
82. Demaria, S., et al., *The optimal partnership of radiation and immunotherapy: from preclinical studies to clinical translation.* Radiat Res, 2014. **182**(2): p. 170-81.
83. Zamarin, D. and M.A. Postow, *Immune checkpoint modulation: Rational design of combination strategies.* Pharmacol Ther, 2015.
84. http://packageinserts.bms.com/pi/pi_yervoy.pdf.
85. http://packageinserts.bms.com/pi/pi_opdivo.pdf.
86. http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf.
87. https://www.gene.com/download/pdf/tecentriq_prescribing.pdf
88. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761049s000lbl.pdf
89. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761069s000lbl.pdf