A Single Arm Phase I/II Study of the Safety, Tolerability, and Efficacy of Stereotactic Body Radiation Therapy (SBRT) combined with concurrent and adjuvant Avelumab for Definitive Management of Early Stage Non-Small Cell Lung Cancer (NSCLC).

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The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

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_____ _____
Signature Date

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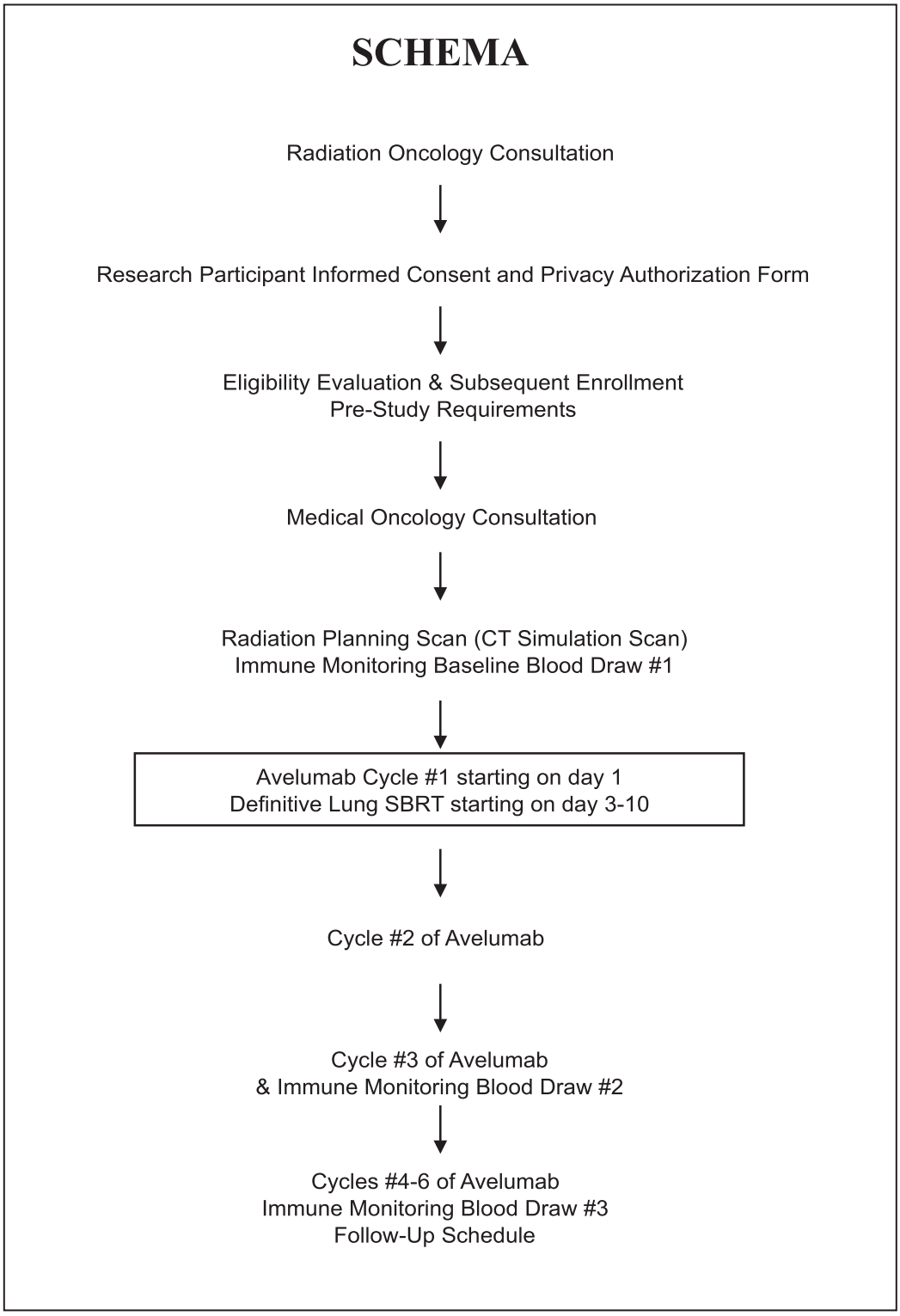
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1. PROTOCOL SYNOPSIS

TITLE	A Phase I/II Study of Stereotactic Body Radiation Therapy (SBRT) combined with concurrent and adjuvant Avelumab for Definitive Management of Early Stage Non-Small Cell Lung Cancer (NSCLC).
STUDY PHASE	Phase I/II
INDICATION	Patients with Stage I node negative NSCLC
PRIMARY OBJECTIVES	ξ Phase I: To assess the safety and tolerability of definitive SBRT combined with concurrent and adjuvant Avelumab in patients with early stage NSCLC. ξ Phase II: To determine whether definitive SBRT combined with concurrent and adjuvant Avelumab improves relapse free survival as compared to SBRT alone historical controls.
SECONDARY OBJECTIVES	ξ To determine whether definitive SBRT combined with concurrent Avelumab improves loco-regional control as compared to SBRT alone historical controls ξ To assess overall survival in patients after completion of SBRT in combination with Avelumab ξ To monitor immune correlates and anti-tumor immune responses in patients undergoing SBRT combined with concurrent Avelumab.
HYPOTHESES	Phase I: Definitive SBRT with concurrent and adjuvant Avelumab for early stage NSCLC can be delivered safely with limited toxicity. Phase II: Definitive SBRT with concurrent and adjuvant Avelumab for early stage NSCLC will result in a 10% absolute improvement in relapse free survival compared to SBRT alone historical controls.

STUDY DESIGN	This is a single arm open label Phase I/II study that will consist of two parts. The Phase I will assess the safety and tolerability of SBRT combined with Avelumab. In Phase II we will determine whether SBRT combined with Avelumab improves relapse free survival. Patients with Stage I NSCLC who are not undergoing surgical resection will be candidates for enrollment. Patients will receive definitive stereotactic body radiation (SBRT) in 4-5 fractions combined with concurrent and adjuvant Avelumab at 10mg/kg for a total of 6 cycles. Patients will be evaluated for safety as measured by the occurrence of adverse events, serious adverse events, and laboratory abnormalities. In addition, at the UCSD site, three blood draws will be obtained to analyze anti-tumor immune responses and immune correlates.
SAMPLE SIZE BY TREATMENT GROUP	Phase I: 12 Patients Phase II: 44 Patients
SUMMARY OF SUBJECT ELIGIBILITY CRITERIA	1. Stage I NSCLC 2. Tumor(s) to be treated is(are) $\leq$ 5.0 cm 3. Age $\geq$ 18 years. 4. Eastern Cooperative Oncology Group (ECOG) performance status $\leq$ 2. 5. Histologic confirmation of NSCLC.
CBI PRODUCT DOSAGE AND ADMINISTRATION	Avelumab (anti-PD-L1) at 10mg/kg will be administered intravenously on study every 2 weeks for 6 cycles. Each cycle is 14 days in length.
CONTROL GROUP	None
PROCEDURES	1. Physical exam 2. Blood draws 3. CT or MRI of Involved Site 4. PET-CT (optional) 5. Stereotactic Body Radiation Therapy (SBRT) 6. IV Avelumab administration

2. ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADL	Activities of daily living
AE	Adverse event
BID	Twice daily
BSA	Body surface area
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
GI	Gastrointestinal
Hgb	Hemoglobin
HPF	High-power field
HTN	Hypertension
IRB	Institutional Review Board
IV	Intravenous
LLN	Lower limit of normal
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 Phase I: To assess the safety and tolerability of definitive SBRT combined with concurrent and adjuvant Avelumab in patients with early stage NSCLC.

3.1.2 Phase II: To determine whether definitive SBRT combined with concurrent and adjuvant Avelumab improves relapse free survival as compared to SBRT alone historical controls.

3.2 Secondary Objectives

3.2.1 To determine whether definitive SBRT combined with concurrent Avelumab improves loco-regional control as compared to SBRT alone historical controls

3.2.2 To assess overall survival in patients after completion of SBRT in combination with Avelumab

3.2.3 To monitor immune correlates and anti-tumor immune responses in patients undergoing SBRT combined with concurrent Avelumab.

4. BACKGROUND

4.1 Early Stage Non-small cell Lung Cancer (NSCLC)

Lung cancer is the number one cause of cancer related mortality in men and women in the US. The majority of patients present after they become symptomatic and are diagnosed with advanced stage disease. However, approximately 10-15% of patients present with early stage I NSCLC. Treatment is critical in these patients as Stage I-II NSCLC left untreated results in a median OS of 1 year and median 5-year OS of 10%. The primary treatment modalities for early stage lung cancer include surgical resection or definitive stereotactic body radiation therapy alone. Nevertheless, even with current standard of care SBRT in patients with early stage NSCLC the 3 year overall survival has been reported at 36-52% due to a high rate of distant metastatic disease. Thus, additional systemic therapies are critically needed in this population to decrease relapse rates and improve overall survival.

Surgical resection is indicated in patients with early stage NSCLC who are medically operable with good performance status. Definitive SBRT alone is the preferred treatment option for medically inoperable patients or those who refuse surgery. SBRT is also an appropriate option for patients with high surgical risk (able to tolerate sublobar resection but not lobectomy [eg, age ≥75 years], poor lung function). Definitive SBRT for early stage lung cancer has an excellent local control rate of greater than 90% which compares favorably with surgery[2]. However, the distant relapse free survival rate with surgery or SBRT for early Stage I NSCLC is approximately 80%, and hence approximately one out of every five patients will develop recurrent disease. Given this high failure rate there is a critical need to improve regional and distant control in the patient population. Checkpoint blockade immunotherapy targeting PD-1/PD-L1 has known activity in NSCLC and thus represents an ideal class of systemic agents to test in this patient population.

Importantly, on Feb 2nd, 2015 the Centers for Medicare & Medicaid Services (CMS) issued a final national coverage determination stating that Medicare will now cover annual Low Dose Computed Tomography (LDCT) for Lung Cancer Screening for patients. This determination was based in part off the results of the National Lung Screening Trial (NLST) which reported a 20% relative reduction in lung cancer mortality with the use of LDCT screening compared to chest x-ray[72]. As with other national screening programs for cancer there is the possibility for a relative increase in the percentage of lung cancer patients diagnosed with early stage disease. Thus, with the use of LDCT it is possible that SBRT will play an even more prominent role in lung cancer treatment in the future.

4.2 Checkpoint Blockade Immunotherapy (CBI) and Avelumab

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[3]. 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[4, 5]. 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[6-8]. CBI is now FDA approved for metastatic melanoma and lung cancer and is helping to establish immunotherapy as a new fourth modality of cancer care. Avelumab (MSB0010718C) is a fully human anti-PD-L1 IgG1 antibody currently being investigated in phase I/II trials.

The anti-PD-1 drug Opdivo (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. Along the same lines, the anti-PD-1 drug Keytruda (Pembrolizumab) recently 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%).

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. Additionally there is increased awareness of these toxicities and established management guidelines for treating irAE. Below is a summary of the major irAE known and their reported frequencies.

Immune-mediated pneumonitis has been reported with Keytruda and Opdivo. Fortunately it is rare with an overall incidence of approximately 3 percent in over 400 patients in the initial clinical experience [9, 10]. For example in a large Phase III clinical trial of 287 patients, pneumonitis including interstitial lung disease occurred in 3.4% (10/287) of patients receiving Opdivo, specifically 1.7% with Grade 3 (5/287), 0.7% with Grade 2 (2/287) and 1% with Grade 1 (3/287). Pneumonitis occurred in 19 (3.5%) of 550 patients, including Grade 2 (1.1%), 3 (1.3%), 4 (0.4%), or 5 (0.2%) pneumonitis in patients receiving Keytruda. Colitis occurred in 4 (0.7%) of 550 patients, including Grade 2 (0.2%) or 3 (0.4%) colitis in patients receiving Keytruda. Hepatitis in large phase I studies of PD-1-blocking antibodies develops in less than 5 percent and grade 3/4 toxicity is extremely rare[6, 9]. Hypophysitis occurred in 1 (0.2%) of 550 patients treated with Keytruda which was Grade 3 in severity. Hyperthyroidism occurred in 10 (1.8%) of 550 patients, including Grade 2 (0.7%) or 3 (0.3%) receiving Keytruda. Hypothyroidism occurred in 38 (6.9%) of 550 patients, including Grade 2 (5.5%) or 3 (0.2%). The most common adverse reactions (reported in at least 20% of patients) were fatigue (44%), decreased appetite (25%), dyspnea (23%), and cough (29%).

Avelumab (MSB0010718C) is a fully human anti-PD-L1 IgG1 antibody currently being

investigated in phase I/II trials. The safety and tolerability of avelumab in a phase I dose escalation trials has been reported (NCT01943461). Additionally the safety and clinical activity in patients with advanced NSCLC progressing after platinum-based chemotherapy has been reported (NCT01772004). In this study (NCT01772004) a prespecified analysis of 184 patients with ≥ 3 months follow-up (range 3-13) was performed. Patients were treated with avelumab at 10 mg/kg Q2W until progression, confirmed complete response (CR), or toxicity. Tumors were assessed every 6 weeks (w) (RECIST 1.1) and unconfirmed best overall response (BOR) was evaluated. Median age was 65y (range 31-83) and ECOG PS was 0 (30%) or 1 (70%). Histology was adenocarcinoma (62%), squamous cell carcinoma (29%), or other (9%). Any grade drug-related treatment-emergent adverse events (TEAEs) occurred in 139 (75.5%) pts; the most common (> 5%) were fatigue, nausea, infusion-related reactions (IRRs), chills, decreased appetite, and diarrhea. Drug-related grade ≥ 3 TEAEs occurred in 22 (12%) pts, including 4 IRRs. Drug-related deaths were reported (n = 3; radiation pneumonitis, acute respiratory failure, and disease progression). Objective responses (OR) were observed in 22 (12%) pts (95% CI: 7.6, 17.5; 1 CR, 21 partial responses; 18 were ongoing at data cutoff). BOR of stable disease was observed in 70 pts (38%). Median progression-free survival (PFS) was 11.6 w (95% CI: 8.4, 12.1) and the PFS rate at 24 w was 25.4% (95% CI: 18.3, 33.2). The conclusion from this report was that in patients with previously treated NSCLC, Avelumab was administered safely with a toxicity profile similar to other anti-PD-1/anti-PD-L1 agents.

Importantly, 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 definitive treatment regimens[1, 11]. Here we will study the combination of SBRT with concurrent and adjuvant Avelumab in NSCLC as a definitive treatment modality.

4.3 Stereotactic Body Radiation Therapy (SBRT)

Radiation therapy has a long and established history in the field of oncology[12]. Recently, technological advances have allowed radiation oncologists to effectively treat tumors anywhere in the body using SBRT[13]. 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 in early stage NSCLC.

Specifically, RTOG 0236 (Timmerman R, JAMA. 2010) was a Phase II Study evaluating 55 patients with peripheral T1-T2N0 NSCLC[2]. The patients received SBRT 18Gy x3 fractions over 1.5-2 weeks. With a median followup of 2.9 years the authors reported a 3 year local control of 98%, 3 year loco-regional control of 87% and 3 year Distant Metastasis rate of 22% with a median OS of 48 months. The authors reported 13% Grade 3 toxicity, 4% Grade 4 toxicity, and no Grade 5 toxicity and concluded that definitive SBRT for patients with inoperable NSCLC results in high rates of local tumor control.

In a Phase II study from out of Indiana by Fakiris AJ et al., (J Radiat Oncol Biol Phys. 2009 Nov 1;75(3):677-82.) 70 medically inoperable patients, cT1 (n=34) or cT2 (n=36), with biopsy proven NSCLC received SBRT to 60-66 Gy in 3 fractions. With a median followup of 4.2 years the authors reported a 3-year LC of 88%, nodal failure 9%, DM 13%, and a 3-year OS and CSS of 43% and 82% respectively. Grade 3 to 5 toxicity occurred in 5 of 48 patients with peripheral lung tumors (10.4%). The authors concluded that SBRT results in high local control in medically inoperable Stage I patients

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 SBRT combined with concurrent and adjuvant Avelumab can be delivered safely with limited toxicity.

4.4 Rationale and Preclinical Data 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 [14-19]. 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[20-22]. 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[18, 23-28]. 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[29-36]. 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[15, 16, 37]. 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[25, 34, 38-40]. 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)[15, 18, 24, 36, 37, 40-49]. A number of excellent reviews have also highlighted the potential benefits and ongoing

clinical trials of radiation combined with immunotherapy[32, 50-54]. Thus taken together radiation may be an ideal therapy to combine with CBI.

Our group has pioneered combining stereotactic radiation with anti-PD-1 CBI **[See Figure 1**]. We have demonstrated the ability of stereotactic radiotherapy to induce endogenous antigen-specific immune responses when combined with anti-PD-1 checkpoint blockade immunotherapy. Using the small animal radiation research platform (SARRP), image guided

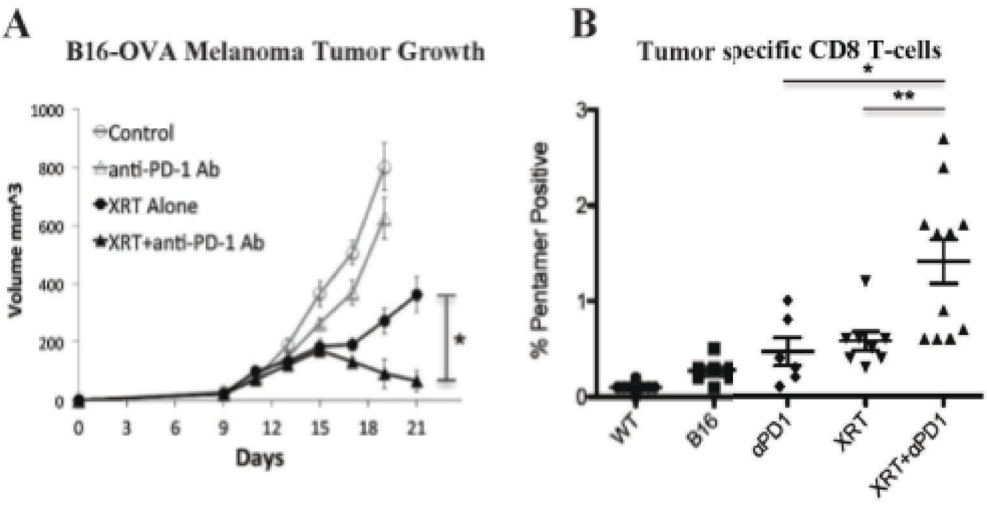


Figure 1) Radiation combined with anti-PD-1 immunotherapy improves local tumor control (A) and development of systemic anti-tumor immune reponses (B). Sharabi et al., *Cancer Immunol Res. 2015 Apr;3(4):345-55*

stereotactic radiotherapy delivered to B16-OVA Melanoma or 4T1-HA Breast Carcinoma tumors resulted in development of antigen-specific T-cell and B-cell mediated immune responses. These immune-stimulating effects of radiotherapy were significantly increased when combined with either anti-PD-1 or regulatory T cell (Treg) depletion, resulting in improved local tumor control. Phenotypic analyses of antigen-specific CD8 T cells revealed that radiotherapy increased the percentage of antigen-experienced T-cells and effector memory T-cells. Mechanistically we found that radiotherapy up-regulates tumor associated antigen-MHC complexes, enhances antigen cross-presentation in the draining lymph node, and increased T-cell infiltration into tumors. Importantly, our group has shown that a combination of PD-L1 blockade and irradiation in an autochthonous model of NSCLC significantly improved local tumor response in the irradiated lung(A. Walker, A. Sharabi, C. Drake, P.T. Tran, *In Preparation*). We also demonstrated evidence of partial tumor response in the unirradiated lung. An increase in T cells was observed in both irradiated and unirradiated lungs after radiation and checkpoint blockade consistent with an abscopal effect (A. Walker, A. Sharabi, C. Drake, P.T. Tran, *In preparation*). These preclinical findings support clinical trials combining SBRT with CBI in patients with NSCLC. These findings demonstrate the ability of radiotherapy to prime an endogenous antigen-specific immune response and provide additional mechanistic rationale for combining radiation with PD-1 blockade in the clinic **[See Figure 2**].

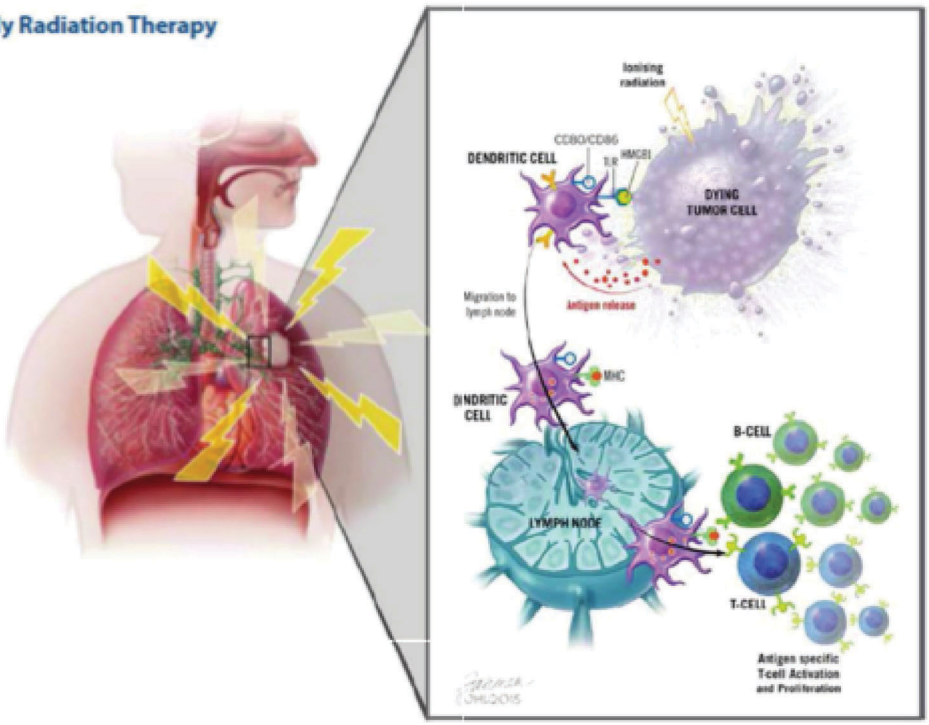


Figure 2: Stereotactic Body Radiation Therapy (SBRT) combined with immunotherapy enhances anti-tumor immune responses[1].

Given these pre-clinical and emerging clinical data the combination of definitive SBRT with concurrent and adjuvant Avelumab has the potential to significantly increase both loco-regional control as well as distant disease control in early stage NSCLC. This proposed study represents a logical extension of the current understanding of immunotherapy and radiation therapy and potential for synergy between these two modalities. Additionally, the combination of SBRT with Avelumab has the potential for synergy in inducing anti-tumor immune responses and deserves further investigation. Here we will test the safety and tolerability of SBRT combined with concurrent and adjuvant Avelumab.

5. PARTICIPANT SELECTION AND ENROLLEMENT CRITERION

5.1 Inclusion Criteria

5.1.1 Patient's tumor(s) to be treated is(are) ≤ 5.0 cm or ≤250 cm^3

5.1.2 Patient must have stage I NSCLC and is not undergoing surgical resection; *only patients who are deemed medically inoperable or refuse surgery after thoracic surgery consultation will be eligible*

5.1.3 Histological confirmation of malignancy (primary tumor).

5.1.4 Patient must be ≥ 18 years of age.

5.1.5 Patient must have a life expectancy ≥ 9 months.

5.1.6 Patient must have an ECOG performance status ≤ 2.

5.1.7 Patient must have acceptable organ and marrow function as defined as:

Absolute Neutrophil Count	$\geq 1.5 \times 10^9$/L
Platelets	$\geq 100 \times 10^9$/L
Total bilirubin	<1.5 x institutional upper limit of normal
AST(SGOT)/ALT(SGPT)	<2.5 X institutional upper limit of normal
Renal Function	estimated creatinine clearance ≥ 60 mL/min according to the Cockcroft-Gault formula (or local institutional standard method)
Pulse Oximetry	≥92% on Room Air at Rest
Hemoglobin	≥ 10.0 g/dL

5.1.8 Negative serum pregnancy test at screening for women of childbearing potential.

5.1.9 Highly effective contraception for both male and female subjects if the risk of conception exists. (Note: The effects of the trial drug on the developing human fetus are unknown; thus, women of childbearing potential and men able to father a child must agree to use 2 highly effective contraception, defined as methods with a failure rate of less than 1 % per year. Highly effective contraception is required at least 28 days prior, throughout and for at least 60 days after avelumab treatment.

5.1.10 Patient must have the ability to understand and the willingness to sign a written informed consent document.

5.2 Exclusion Criteria

Subjects are not eligible for the trial if they fulfill any of the following exclusion criteria:

5.2.1 Prior organ transplantation, including allogeneic stem cell transplantation

5.2.2 Significant acute or chronic infections including, among others:
- Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
- Known history of testing positive for HBV surface antigen and / or confirmatory HCV RNA (if anti-HCV antibody tested positive)

5.2.3 Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent:
a. Subjects with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible
b. Subjects requiring hormone replacement with corticosteroids are eligible if the

steroids are administered only for the purpose of hormonal replacement and at doses ≤ 10 mg or 10 mg equivalent prednisone per day

c. Administration of steroids through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) are acceptable

5.2.4 Current use of immunosuppressive medication, EXCEPT for the following: a. intranasal, inhaled, topical steroids, or local steroid injection (eg, intra-articular injection); b. Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent; c. Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).

5.2.5 Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.

5.2.6 Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI CTCAE v 4.03), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma)

5.2.7 Persisting toxicity related to prior therapy of Grade >1 NCI-CTCAE v 4.03; however, alopecia and sensory neuropathy Grade ≤ 2 is acceptable

5.2.8 Pregnancy or lactation

5.2.9 Known active alcohol or drug abuse

5.2.10 All other significant diseases (for example, colitis, pneumonitis, pulmonary fibrosis, inflammatory bowel disease, uncontrolled asthma), which, in the opinion of the Investigator, might impair the subject's tolerance of trial treatment

5.2.11 Any psychiatric condition that would prohibit the understanding or rendering of informed consent

5.2.12 Vaccination within 4 weeks of the first dose of avelumab and while on trial is prohibited except for administration of inactivated vaccines

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

5.2.14 Patient refuses to sign informed consent.

6. TREATMENT PLAN

6.1 Diagnostic Procedures

A PET-CT may be performed (optional) for diagnostic purposes and can be used for treatment planning with fusion.

6.2 Study Procedures

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) Blood work per Standard of Care for immunotherapy used.
5) Plasma and Peripheral blood mononuclear cells will be collected and subsequently frozen for immune monitoring assays.

Blood chemistry and hematology assessments: must be performed at baseline, prior to each avelumab dose, at end of treatment visit and at 30 days post-treatment safety follow-up. Urine pregnancy test for women of childbearing potential must be performed at baseline and least every month during treatment. Free T4 and TSH must be performed at baseline and at least every 8 weeks during treatment and at end of treatment or 30 days post-treatment safety follow-up (if not performed in the previous 8 weeks).In addition, a CT Chest with contrast or MRI will be performed on Cycle 4 (+/- 4 days) of Avelumab treatment.

6.3 Therapeutic Procedures

6.3.1 Avelumab Administration

Each cycle of Avelumab is 14 days. Avelumab is administered on an outpatient basis. Avelumab 10mg/kg body weight, diluted with 0.45% or 0.9% saline solution, will be administered as a 60 minute intravenous (IV) infusion every 2 weeks, on day 1 of each cycle. No Avelumab dose reductions are permitted on this study. Specific instructions for the preparation infusion fluid and administration of infusion solution are provided in the Pharmacy Manual.

After the initial cycle, the patient will receive 5 additional cycles of adjuvant Avelumab per protocol for a total of 6 cycles. Patients will be evaluated for adverse events/toxicities after receiving the first dose of Avelumab.

6.3.2 SBRT Procedures

Upon enrollment on the protocol patients will be seen by at least one of the Co-Investigator Medical Oncologists. As per standard of care a 4D 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 radiation dose will be prescribed using the current clinical practice standard of care of either 12Gy x 4 fractions or 10Gy x 5 fractions at the discretion of the treating radiation oncologist.

Adjacent normal structures including but not limited to the chest wall, spinal cord, lung, airways at risk, vessels at risk, heart, esophagus, aorta, liver, and stomach within 5 cm of the GTV will be identified for the purpose of limiting incidental radiation to these structures.

The patient will receive the first fraction of SBRT within 3-10 days after starting the 1st cycle of Avelumab. SBRT will be administered using image-guidance as per standard of care. 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 images of the patient's body site of interest will be obtained. Cone beam scan will be obtained immediately prior to treatment and will be repeated until the treatment shift, required to align the Radiation planning scan and the cone beam scan performed on the day of treatment. Cone beam scanning is standard of care for definitive stereotactic body radiation therapy.

6.3.3 The SBRT dose constraints for surrounding critical structures are as follows

- **chest wall at risk: V30<60; max point dose 48 Gy;**
- **spinal cord: V13.6 Gy<1.2cc; V 20.8 Gy<0.35cc; point max: 26 Gy**
- **great vessel at risk: V43 Gy<10cc; point max: 49 Gy**
- **esophagus at risk: V18.8 Gy<5cc; point max: 30 Gy**
- **airway at risk: V15.6 Gy<4cc; point max 34.8 Gy**
- **heart at risk: V28<15cc; point max< 34 Gy**
- **Combined lung constraints:**
  - MLD <4 Gy
  - V20 <4%
  - V10 <12%
  - combined lung: V11.6 Gy<1500cc
  - combined lung: V12.4 Gy<1000cc
  - Ratio of Prescription Isodose Volume to the PTV volume <1.2
  - Ratio of 50% Prescription Isodose Volume to the PTV Volume varies. Please refer to Table A below for guidance.

Table A: Conformality of Prescribed Dose for Calculations Based on Deposition of Photon Beam Energy in Heterogeneous Tissue

PTV Volume (cc)	Ratio of Prescription Isodose Volume to the PTV Volume		Ratio of 50% Prescription Isodose Volume to the PTV Voume, $R_{50\%}$		Maximum Dose (in % of dose prescribed) @ 2 cm from PTV in Any Direction, D_{2cm} (%)		Percent of Lung Receiving 20Gy Total or More, V_{20} (%)	
	Deviation		Deviation		Deviation		Deviation	
	None	Minor	None	Minor	None	Minor	None	Minor
1.8	<1.2	<1.5	<5.9	<7.5	<50.0	<57.0	<10	<15
3.8	<1.2	<1.5	<5.5	<6.5	<50.0	<57.0	<10	<15
7.4	<1.2	<1.5	<5.1	<6.0	<50.0	<58.0	<10	<15
13.2	<1.2	<1.5	<4.7	<5.8	<50.0	<58.0	<10	<15

22.0	<1.2	<1.5	<4.5	<5.5	<54.0	<63.0	<10	<15
34.0	<1.2	<1.5	<4.3	<5.3	<58.0	<68.0	<10	<15
50.0	<1.2	<1.5	<4.0	<5.0	<62.0	<77.0	<10	<15
70.0	<1.2	<1.5	<3.5	<4.8	<66.0	<86.0	<10	<15
95.0	<1.2	<1.5	<3.3	<4.4	<70.0	<89.0	<10	<15
126.0	<1.2	<1.5	<3.1	<4.0	<73.0	<91.0	<10	<15
163.0	<1.2	<1.5	<2.9	<3.7	<77.0	<94.0	<10	<15

Note: For values of PTV dimension or volume not specified, linear interpolation between table entries is required.

6.4 Follow-Up Procedures

Subsequent to SBRT, patients will be followed clinically, radiographically, and with bloodwork. A detailed medical and physical examination will be performed at 4 weeks, 8 weeks, and 16 weeks, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months. A complete blood count (CBC) and comprehensive chemistry panel and CT Chest with contrast will be performed at 6 weeks and 3 months and will continue at intervals of every 6 months until 2 years post SBRT treatment.

Recist 1.1 measurements at 6 months and 1 year and 2 years will be used to determine radiographic response for loco-regional control and relapse free survival.

6.5 Duration of Therapy

The patient will receive 4-5 fractions of SBRT radiation total administered every other day. The patient will receive Avelumab administered every 2 weeks for a total of 6 cycles. Thus the total duration of therapy is expected to last approximately 3 months.

6.6 Duration of Follow-Up

It is anticipated that this study will last 3 years.

6.7 Criteria for Removal of Subjects from Study Treatment and Study

- Unacceptable adverse events grade IV or greater with an attribution of possibly related while on CBI or after SBRT.
- Subject withdraws consent for follow-up;
- Subject is lost to follow-up;
- Subject dies;
- Study is terminated for any reason.

ξ The patient has a confirmed positive serum pregnancy test;

ξ General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator;

ξ Administrative Decision

Subject can elect to discontinue treatment at any time. If participants withdraw from the study, they will be followed for survival data.

6.8 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 Avelumab have been reported and are detailed 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 early stage NSCLC include definitive surgical resection with or without systemic chemotherapy versus definitive radiation therapy alone. Only patients who are medically inoperable or those who refuse surgery after thoracic surgery consultation will be enrolled in this study.

6.9 Permitted and Prohibited Concomitant Therapies

Permitted concomitant therapy

Concomitant medication also includes all prescription, over-the-counter (OTC), herbal supplements, blood transfusions, and IV medications. The patient needs to notify the investigational site about any new medications he/she takes after the start of the study drug.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded in the patient's medical record.

Prohibited concomitant therapy

Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than avelumab.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an adverse event of suspected immunologic etiology.

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

6.10 Costs

Patients and/or their insurance companies will be responsible for the cost of all radiation treatment visits, consultation, procedures, and SBRT treatments.

The sponsor will cover the cost of the study drug Avelumab and support for its administration. The sponsor will cover the cost of the research blood draws.

6.11 Compensation

None

7. DRUG INFORMATION

7.1 Avelumab

Please refer to the Product Label and Investigator's Brochure for more comprehensive information.

Other names for the drug: MSB0010718C

Mechanism of action (or Product description):
Avelumab binds PD-L1 and blocks the interaction between PD-L1 and PD-1. This removes the suppressive effects of PD-L1 on anti-tumor CD8+ T cells, resulting in the restoration of cytotoxic T cell response.

Availability: Clinical supplies are provided by Pfizer, and will be affixed with a clinical label in accordance with regulatory requirements.

Dosage Forms and Strengths:
Avelumab drug product is a sterile, clear, and colorless concentrate for solution presented at concentrations of 10 mg/mL and 20 mg/mL in European Pharmacopeia (Ph. Eur.) and United States Pharmacopeia (USP) type I glass vials closed with a rubber stopper and sealed with an aluminum Flip Off® crimp seal closure.

Each single-use 10 mg/mL vial contains 80 mg of avelumab as a preservative-free acetate-buffered solution (pH 5.5) containing Mannitol, Methionine, and Polysorbate 20 (Tween 20).

Each single-use 20 mg/mL vial contains 200 mg of avelumab as a preservative-free acetate-buffered solution (pH 5.2) containing Mannitol, and Polysorbate 20 (Tween 20).

Preparation and Delivery:
Avelumab will be prepared according to the product label unless otherwise directed in the Pharmacy Manual.

Avelumab drug product must be diluted with 0.45% or 0.9% saline solution (sodium

chloride injection) supplied in an infusion bag. Detailed information on infusion bags and medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the manual of preparation.

To prepare the dilutions, subsequent preparation steps must be accomplished by adequate trained personnel under a laminar flow box using aseptic techniques:
Prior to the preparation of the dilution for final infusion, allow each vial to equilibrate to room temperature. Use a disposable syringe equipped with a needle of suitable size to remove a volume of sodium chloride solution to be replaced by avelumab from the infusion bag and discard the removed solution. Use a new disposable syringe equipped with a needle of suitable size to inject a volume of avelumab drug product identical to the discarded volume of sodium chloride solution into the infusion bag. Gently invert the mixture 10 times. Infusion bags must not be shaken, in order to avoid foaming or excessive shearing of the protein solution. The preparation must be carefully inspected as it should result in a homogeneous looking clear solution, free of visible particles.

Avelumab is administered on an outpatient basis. Avelumab 10mg/kg body weight, diluted with 0.45% or 0.9% saline solution, will be administered as a 60 minute intravenous (IV) infusion every 2 weeks. No Avelumab dose reductions are permitted on this study. Specific instructions for the preparation infusion fluid and administration of infusion solution are provided in the Pharmacy Manual.

PreMedication:
Subjects will receive avelumab by IV infusion following pretreatment with H1 blockers and acetaminophen once every 2 weeks. Premedication with an antihistamine and with paracetamol (acetaminophen) (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent) approximately 30 to 60 minutes prior to each dose of avelumab is mandatory. This regimen may be modified based on local treatment standards and guidelines as appropriate provided it does not include systemic corticosteroids.

Storage and stability:
Avelumab drug product must be stored at 2°C to 8°C until use. The storage condition is based on data from ongoing long term stability studies with avelumab.

Avelumab drug product stored at room (23°C to 27°C) or higher temperatures for extended periods of time might be subject to degradation. Avelumab drug product must not be frozen. Rough shaking of the solution must be avoided.

For application in clinical trials, avelumab drug product must be diluted with 0.45% or 0.9% saline solution (sodium chloride injection) supplied in an infusion bag. The chemical and physical in-use stability for the infusion solution of avelumab in 0.45% or 0.9% saline solution has been demonstrated for a total of 24 hours at room temperature. However, from a microbiological point of view, the diluted solution should be used immediately and is not intended to be stored unless dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions prior to

administration are the responsibility of the user.

No other drugs should be added to the solution for infusion containing avelumab.

Route of administration for this study: Intravenous infusion over 1 hour.

Side effects:
For the purpose of regulatory reporting requirements during clinical development, the following AEs will be considered as expected and met the threshold of casual association (based on comprehensive evaluation) defined by the Sponsor:

- Infusion-related reactions including hypersensitivity reactions
- Immune-mediated adverse reactions like immune-mediated colitis, immune-mediated hepatitis including autoimmune hepatitis, immune-mediated thyroid disorders including hyperthyroidism, hypothyroidism, thyroiditis and autoimmune thyroiditis, immune-mediated pneumonitis, immune-mediated skin reactions including rash, pruritis, rash generalized, rash macula-papular, erythema, pemphigoid, other immune mediated reactions including myocarditis, adrenal insufficiency, uveitis, iritis, myositis.

Special Precautions for Administration:
- Setting: Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.
- Observation period: Following avelumab infusions, patients must be observed for 2 hours post-infusion for potential infusion-related reactions.

Safety assessments:
- Blood chemistry and hematology assessments: must be performed at baseline, prior to each avelumab dose, at end of treatment visit and at 30 days post-treatment safety follow-up.
- Urine pregnancy test for women of childbearing potential must be performed at baseline and least every month during treatment.
- Free T4 and TSH must be performed at baseline and at least every 8 weeks during treatment and at end of treatment or 30 days post-treatment safety follow-up (if not performed in the previous 8 weeks).

7.2 Study Drug Accountability

The Principal Investigator and Co-investigators are responsible for ensuring accountability for the investigational agent, including reconciliation of materials and maintenance of drug records.

Dispensing and administration of avelumab will be recorded following institutional practices. An accurate accounting will be available for verification. Accountability records will include

- Confirmation of delivery to the site
- Inventory at the site
- Dispensing for each patient
- Return or alternative disposition of unused study drug

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

8. MANAGEMENT ALGORITHMS FOR TOXICITIES

8.1 DOSING DELAYS/DOSE DISCONTINUATION

The following ADRs require permanent treatment discontinuation of avelumab:

• Any Grade 4 ADRs require treatment discontinuation with avelumab except for single laboratory values out of normal range that are unlikely related to study treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management. Patients who experience grade IV toxicity will continue to be followed until toxicity resolution to Grade ≤ 1 or return to baseline.

Any Grade 3 ADRs require treatment discontinuation with avelumab except for any of the following:

• Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management

• Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade ≤ 1

• Single laboratory values out of normal range (excluding Grade ≥ 3 liver function test increase) that are unlikely related to study treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management

• Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor

• Change in ECOG PS to ≥ 3 that does not resolve to ≤ 2 within 14 days (infusions should not be given on the following cycle, if the ECOG PS is ≥ 3 on the day of study drug administration)

Any Grade 2 ADR should be managed as follows:

• If a Grade 2 ADR resolves to Grade ≤ 1 by the last day of the current cycle, treatment may continue.

• If a Grade 2 ADR does not resolve to Grade ≤ 1 by the last day of the current cycle, infusions should not be given on the following cycle. If at the end of the following cycle the event has not resolved to Grade 1, the subject should permanently discontinue treatment with a avelumab ADR (except for hormone insufficiencies, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted).

• Upon the second occurrence of the same Grade 2 ADR (except for hormone insufficiencies that can be managed by replacement therapy) in the same subject, treatment with avelumab has to be permanently discontinued.

• Infusion-related reactions, hypersensitivity reactions (Grades 1 to 4), and tumor lysis syndrome should be handled according to guidelines provided.

8.2 Treatment of Avelumab Related Infusion Reactions

A. Symptoms
- ξ Fever
- ξ Chills
- ξ Rigors
- ξ Diaphoresis
- ξ Headache

B. Management

Table 1 Treatment Modification for Symptoms of Infusion-Related Reactions

NCI-CTCAE Grade	Treatment Modification for Study Drug
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the study drug infusion rate by 50% and monitor closely for any worsening. The total infusion time for study drug should not exceed 120 minutes.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for δ 24 h.	Stop study drug infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop the study drug infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn immediately from study drug treatment and must not receive any further study drug treatment.

IV = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs.

Once the avelumab infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions. If the subject has a second infusion-related reaction Grade ≥ 2 on the slower infusion rate, the infusion should be stopped and the subject should be removed from study treatment. If a subject experiences a Grade 3 or 4 infusion-related reaction at any time, the subject must discontinue study drug. No Avelumab dose reductions are permitted on this study. Patients who experience grade IV toxicity will continue to be followed until toxicity resolution to Grade ≤ 1 or return to baseline.

Severe Hypersensitivity Reactions and Flu-Like Symptoms

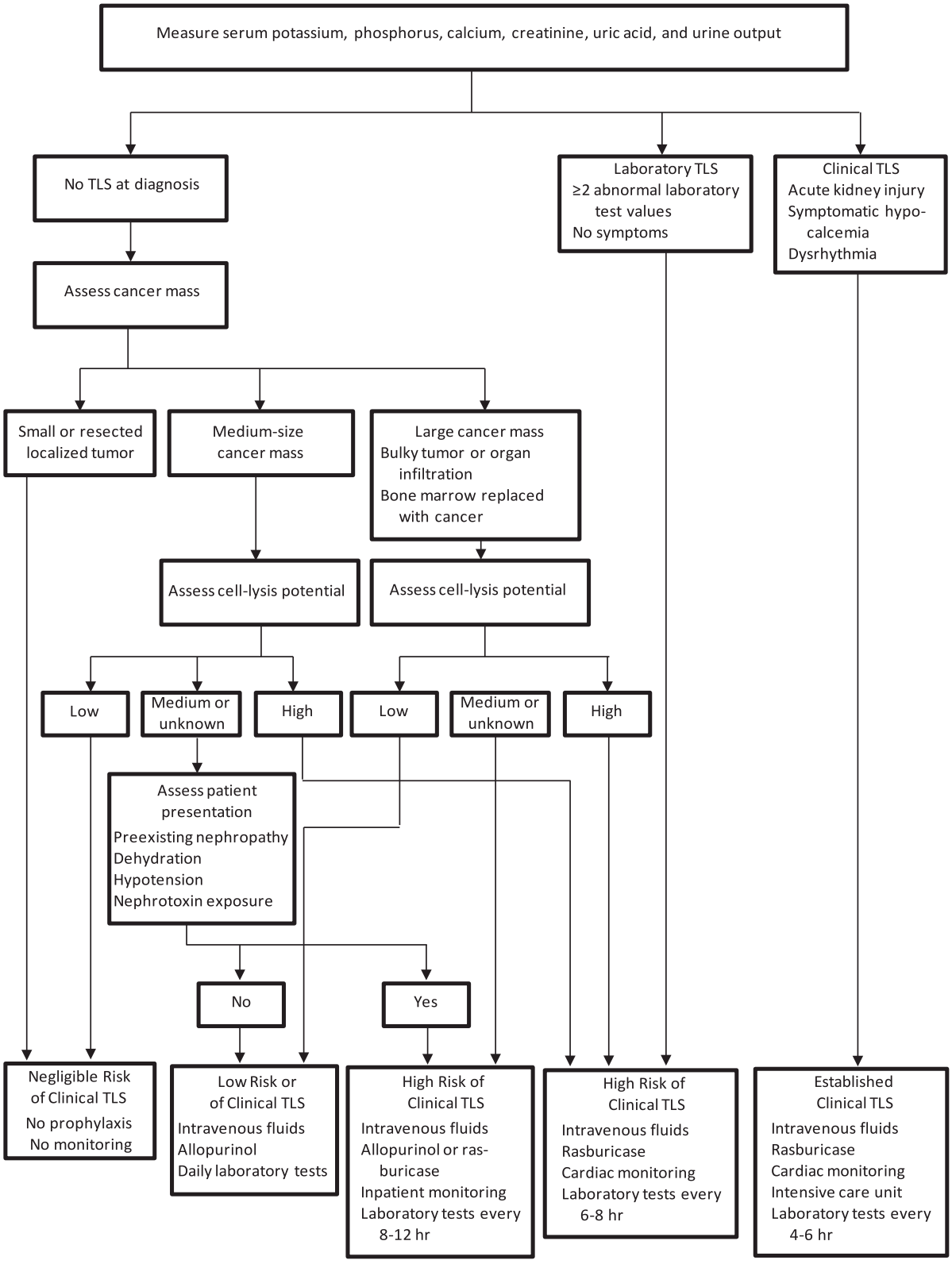
If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. Subjects should be instructed to report any delayed reactions to the Investigator immediately.

For prophylaxis of flu-like symptoms, 25 mg of indomethacin or comparable nonsteroidal anti-inflammatory drug (NSAID) dose (for example, ibuprofen 600 mg, naproxen sodium 500 mg) may be administered 2 hours before and 8 hours after the start of each dose of avelumab IV infusion. Alternative treatments for fever (for example, paracetamol) may be given to subjects at the discretion of the Investigator.

Tumor Lysis Syndrome

In addition, since avelumab can induce antibody-dependent cell-mediated cytotoxicity, there is a potential risk of tumor lysis syndrome. Should this occur, subjects should be treated per the local guidelines and the management algorithm below (Howard 2011).

Assessment and Initial Management of Tumor Lysis Syndrome



TLS = tumor lysis syndrome

Immune-Related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, immune-related AEs (irAEs) may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):

Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring

Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)

Grade 3 to 4: treat with high dose corticosteroids
Treatment of irAEs should follow guidelines set forth in the table below Table.

Table 2 Management of Immune-Related Adverse Events

Gastrointestinal irAEs		
Severity of Diarrhea / Colitis (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (for example, loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Delay avelumab therapy Symptomatic treatment	If improves to Grade 1: Resume avelumab therapy If persists > 5 to 7 days or recur: 0.5 to 1.0 mg/kg/day methylprednisolone or equivalent When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy per protocol. If worsens or persists > 3 to 5 days with oral steroids: Treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 hrs; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Discontinue avelumab therapy per protocol 1.0 to 2.0 mg/kg/day methylprednisolone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade 1, then taper over at least 1 month If persists > 3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis

Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 to 2 Covering ≤ 30% body surface area	Symptomatic therapy (for example, antihistamines, topical steroids) Continue avelumab therapy	If persists > 1 to 2 weeks or recurs: Consider skin biopsy Delay avelumab therapy Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy If worsens: Treat as Grade 3 to 4
Grade 3 to 4 Covering > 30% body surface area; life threatening consequences	Delay or discontinue avelumab therapy Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent	If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections Resume avelumab therapy
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 Radiographic changes only	Consider delay of avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-image at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	Delay avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent Consider bronchoscopy, lung biopsy	Re-image every 1 to 3 days If improves: When symptoms return to near Baseline, taper steroids over at least 1 month and then resume avelumab therapy and consider prophylactic antibiotics If not improving after 2 weeks or worsening: Treat as Grade 3 to 4
Grade 3 to 4 Severe new symptoms; New / worsening hypoxia; life-threatening	Discontinue avelumab therapy Hospitalize Pulmonary and Infectious Disease consults	If improves to Baseline: Taper steroids over at least 6 weeks If not improving after 48 hours or worsening:

	2 to 4 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Management**	**Follow-up**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and / or total bilirubin > ULN to 1.5 x ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and / or total bilirubin > 1.5 to ≤ 3 x ULN	Delay avelumab therapy Increase frequency of monitoring to every 3 days	If returns to Baseline: Resume routine monitoring, resume avelumab therapy If elevations persist > 5 to 7 days or worsen: 0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or Baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy
Grade 3 to 4 AST or ALT > 5 x ULN and / or total bilirubin > 3 x ULN	Discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade 2: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines
Endocrine irAEs		
Endocrine Disorder	**Management**	**Follow-up**
Asymptomatic TSH abnormality	Continue avelumab therapy If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include T4 at subsequent cycles as clinically indicated; consider endocrinology consult	
Symptomatic endocrinopathy	Evaluate endocrine function Consider pituitary scan Symptomatic with abnormal lab / pituitary scan:	If improves (with or without hormone replacement):

	Delay avelumab therapy 1 to 2 mg/kg/day methylprednisolone IV or by mouth equivalent Initiate appropriate hormone therapy No abnormal lab / pituitary MRI scan but symptoms persist: Repeat labs in 1 to 3 weeks / MRI in 1 month	Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections Resume avelumab therapy Subjects with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (for example, severe dehydration, hypotension, shock out of proportion to current illness)	Delay or discontinue avelumab therapy Rule out sepsis Stress dose of IV steroids with mineralocorticoid activity IV fluids Consult endocrinologist If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy	

ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; irAE = immune-related adverse event; IV=intravenous; LFT = liver function test; LLN = lower limit of normal; MRI = magnetic resonance imaging; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; T4 = free thyroxine; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

9. CORRELATIVE/SPECIAL STUDIES (Section applicable to UCSD site only)

9.1 Specimen handling and storage

9.1.1 Patient samples collected for this study will be retained in the laboratory of Dr. Andrew Sharabi for analysis and future cancer research. Specimens will be stored indefinitely or until there is no remaining sample available. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens. Samples will be labeled with the protocol number, subject's de-identified study number and collection date.

9.1.2 The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

9.1.3 The study coordinator or research staff will transport the specimen to the laboratory of Andrew B. Sharabi, M.D., PhD for storage and processing.

9.1.4 Specimen will be labeled with the protocol number, subject's de-identified study number and collection date.

9.1.5 The samples will be centrifuged within 45 minutes of collection and plasma and peripheral blood mononuclear cells will be processed and stored at -80°C for future analysis.

9.2 Methodology

9.2.1 80cc Blood samples will be collected from patients into sodium heparin coated vacutainers (BD Vacutainer® Green BD Hemogard™) at time points specified under the study protocol. PBMC and Serum will be isolated via standard Ficoll gradient centrifugation.

9.2.2 We will perform Multiparametric Flow cytometry and additional immunologic assays on peripheral mononuclear cells (PBMC) from patient derived blood samples to quantify changes in T-cell and B-cell activation and proliferation before, during and after SBRT combined with Avelumab: T-cell subsets (CD3, CD4, CD8, CD25, FOXP3, CD69, CD44, CD62L, PD-1, IFN-gamma, TNF-alpha), B cells (CD19, CD20), Macrophage I/II and myeloid-derived suppressor cells (MDSC) (CD16, CD68, CD206) and Natural killer cell activity (CD56, CD16).

9.2.3 We will perform Next generation sequencing including T-cell receptor sequencing (ImmunoSeq), using TCR-Beta CDR3 Kit (Adaptive Biotechnologies). TCR-β CDR3, regions will be amplified and sequenced using the survey ImmunoSeq assay in a multiplexed PCR method.

9.2.4 Assessment of humoral immune responses will be performed using high-content protein microarray. Candidate antigens will be verified using multiplexed antigen-conjugated, spectrally distinguishable, fluorescent proprietary microspheres

9.3 Correlative Study Endpoints:

9.3.1 Statistical and Graphical analyses will be performed in the "R" computing environment, Prism (GraphPad), and FlowJo (FlowJo, LLC).

9.3.2 For ImmunoSeq Analysis: Shannon entropy will be calculated on the clonal abundance of all productive TCR and BCR sequences in the data set. This normalized entropy value will then inverted (1 − normalized entropy) to produce the clonality metric.

9.3.3 For analytical assessment of serum anti-tumor immune responses: changes in serum antibody levels will be reported relative to pretreatment. To assess the statistical significance of pre- to post-treatment changes in levels of IgGs, normalized signal intensities (log2) will be tested using a moderated paired t test.

10. STUDY CALENDAR

Parameter	Pre TX	CBI Cycle#1, Day 1	SBRT 4-5 Fx~	CBI Cycle#2, Day 1	CBI Cycle#3, Day 1	CBI Cycle #4, Day 1	CBI Cycle #5, Day 1	CBI Cycle #6, Day 1	FU% 1 mo∑	FU% 6wks∑	FU% 2mo∑	FU% 3mo∑	FU% 6mo@	FU% 12mo@	FU% 18mo@	FU% 24mo@	FU% 30mo@	FU% 36mo@
Informed Consent	X																	
Demographics	X																	
Med HX & Medication Rev	X								X		X	X	X	X	X	X	X	X
Physical Exam	X				X			X	X		X	X	X	X	X	X	X	X
Standard of Care Labs#	X	X+		X+	X+	X+	X+	X+	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test	X																	
Urine Pregnancy Test				X		X		X										
Free T4 and TSH	X	X				X			X									
CT or MRI Chest Imaging	X					XΣ				X		X	X	X	X	X		
CT Abd/Pelvis or PET Scan	X																	
Avelumab Administration^		X		X	X	X	X	X										
Research Blood Draw	X*				X*			X*										
Recist 1.1 Measurement	X												X	X		X		
AE Evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

#: Standard of Care Labs include: CBC and CMP
+ Prior to each Avelumab dose @ +/- 10 day ∑ +/- 4 days

^ Each cycle of Avelumab is 14 days. Drug is administered on day 1 of each cycle.
~ SBRT: to be administered in 4-5 fractions at the discretion of the treating Radiation Oncologist
% Follow-up appointments will be scheduled based on date of SBRT completion. These will begin during Avelumab treatment.
* indicates optional

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect-Solid Tumors

For the purposes of this study, patients should be re-evaluated for response 6 months after the initial treatment, 12 months 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.

11.2 Definitions

Evaluable Population: will consist of all patients who have received 1 cycle of CBI treatment preceding SBRT.

Safety Population: Will consist of all subjects who were enrolled and have received CBI combined with SBRT. This will be used to assess the clinical safety and tolerability of the study.

Evaluable for Objective Response: Only those patients who have measurable disease present at baseline, have completed all fractions of SBRT, 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.

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 targeted lesion.
Objective Response (OR):	At least a 30% decrease in the sum of the longest diameter (LD) of targeted lesion.
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of Targeted lesion.
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 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.

11.5.3 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.

Relapse-Free Survival (RFS) 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

11.5.4 Response Review

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

12. ADVERSE EVENT REPORTING REQUIREMENTS

12.1 General

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 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.

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.

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 <u>expected</u> 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

 Causality assessment is the determination of whether there is a reasonable possibility that the Pfizer product or blinded therapy caused or contributed to an AE. The Principal Investigator should provide a rationale and medical justification for this determination.

 This assessment is to be recorded on the IIR SAE Form (or other agreed reporting method) along with a description of the SAE that is sufficiently detailed to allow for complete medical assessment of the case and determination of possible causality.

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 SBRT. The procedures related to the study are phlebotomy, PET imaging (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 reasonable to extrapolate expected toxicity rates 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 10-20% in patients treated with conventional 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.

Importantly SBRT has a significantly better tolerated with a limited side effect profile compared to conventional large field radiation. For example the rates of Radiation

Pneumonitis with SBRT have been reported as less than 5%. At this point, the incidence of RT pneumonitis from SBRT combined with immunotherapy for small pulmonary tumors is unknown. However, if the proposed radiation dose constraints are used the risk should be <10% 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 could 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 will be graded according to the Common Toxicity Criteria, National Cancer Institute, version 4.0.

12.5 Reporting Procedures

12.5.1 General

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject following use of a Pfizer medication (or blinded therapy) or medical device (collectively, Pfizer product). There does NOT need to be a causal relationship between the event and the Pfizer product.

An SAE is any AE that:

- Results in death
- Is life-threatening (i.e., causes an immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity (i.e., substantial disruption of the ability to conduct normal life functions)
- Results in a congenital anomaly or birth defect or that is considered to be: An important medical event

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.

All AE or SAE will be captured on the appropriate study-specific case report forms or **IIR Serious Adverse Event Report Form**. Refer to the IIR SAE Manual INTERVENTIONAL IIRs Nov 2013 for additional details regarding AE reporting.

12.5.2 Required Reporting Times Frames to Pfizer, Principle Investigator, and Regulatory Authorities

The time frame for reporting an SAE to Pfizer is:

- ξ Immediately upon awareness, if the SAE is fatal or life-threatening (i.e., causes an immediate risk of death) —regardless of the extent of available information

OR

- ξ Within 24 hours of first awareness of the SAE, if the SAE is not fatal or life threatening

These timeframes are applicable to all reportable SAEs

A report of an SAE, as provided on the IIR SAE Form (or other agreed reporting method) must contain at least the following four elements:

1. An identifiable subject(s)
   There must be sufficient information that an SAE has been experienced by a specific individual.
   Note: Patient names are NOT required and should not be reported.

2. Suspect product
   The report must identify the suspect Pfizer product (i.e. the Pfizer product that the study subject received and that is the focus of the study).

3. SAE
   The report must contain at least a description of an SAE (diagnosis or signs and symptoms) or an otherwise reportable event (i.e. exposure during pregnancy, exposure during breastfeeding and occupational exposure).
   Notes:
   - Do not report a procedure as an SAE, but instead report the SAE for which the procedure was indicated.
   - Avoid recording “Death” as an SAE whenever possible. Report the cause of death as the SAE with “Resulted in death” checked as a seriousness criterion.
   - In the case of a subject’s death, include a summary of autopsy findings, if available.

4. Identifiable reporting source
   The report must contain information that clearly identifies the reporter, which establishes that there was firsthand knowledge of the identifiable subject.

It is important that information regarding an SAE be reported within the established timelines as described in the ‘Required Reporting Times Frames’ section above. If a report is delayed, then the reason for the delay should be clearly explained.

- Examples of reasons for delay:
  - ξ Information missed due to clerical issues at the site
  - ξ Correction of previously transmitted information

Serious adverse events, or a follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time study treatment initiation through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, requires expedited reporting as described below:

A) The Study Chair and Site Principal Investigator must be notified within 24 hours of learning of any serious adverse events (SAEs).

B) The Institutional Review Board (IRB) of each site must be notified by the site principal investigator according to their local policies.

C) The UCSD Human Research Protections Program (HRPP) and Moores Cancer Center Data and Safety Monitoring Board (DSMB) must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR). The following events meet the definition of UPR:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

D) The FDA must be notified by the Study Chair according to the following timelines:

- Within 7 calendar days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and
- Within 15 calendar days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

12.5.3 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.

12.5.4 Exposure During Pregnancy, Breastfeeding and Occupational Exposure

- Exposure During Pregnancy occurs when a fetus (from pre-embryo to birth) may have been exposed at any time during pregnancy to a Pfizer product (or blinded therapy).

- Exposure During Pregnancy is reportable to Pfizer regardless of whether there is an associated SAE. The specific details that need to be included in the report of an Exposure During Pregnancy depend on whether the exposure was maternal or paternal. The anticipated date of delivery should be included in the Narrative section of the report, for both maternal and paternal exposures. The Principal Investigator must then follow the subject throughout the pregnancy and is to notify Pfizer of the outcome as a follow-up to the initial Exposure During Pregnancy report.

- If the outcome of the pregnancy meets any of the criteria for seriousness, report it to Pfizer as an SAE. To the extent known, provide information about the mother or the father and the pregnancy within the Narrative or other appropriate field of the agreed reporting method **[Use Exposure_During_Pregnancy_(EDP)_Supplemental_Form]**

- An exposure during breastfeeding occurs if an infant or child may have been exposed through breast milk to the Pfizer product during breastfeeding by a female taking the Pfizer product. Exposure during breastfeeding is reportable to Pfizer regardless of whether there is an associated SAE in the infant or child.

- An occupational exposure is an exposure to a Pfizer product for human use as a result of one's occupation. An occupational exposure is reportable regardless of whether there is an associated SAE.

12.5.5 Follow-up Information

When new, updated, or corrected information about a previously reported SAE is obtained, a follow-up report should be submitted to Pfizer on a new IIR SAE Report Form (or other agreed reporting method) that includes the data that are new or revised from the previous report. Follow-up information should never be added to a previously submitted report form. Ensure that any new events included on a follow-up report are marked as serious and a causality assessment is provided for each of them. Patients who experience grade IV toxicity will continue to be followed until toxicity resolution to Grade ≤ 1 or return to baseline.

12.5.6 Otherwise Reportable Events

Certain types of events, as identified below, are reportable to Pfizer under the reporting processes and requirements for SAEs, even if there is no associated adverse event. These are considered “otherwise reportable events” and generally reflect circumstances that could lead to an increased risk of an adverse event. Like an SAE, an otherwise reportable event is to be reported to Pfizer within 24 hours of awareness on an IIR SAE Form (or other agreed reporting method) and followed up to determine outcome, including the

later occurrence of an associated SAE.

13. DATA AND SAFETY MONITORING PLAN

A Data Monitoring Committee (DMC) will be established to provide oversight of safety and efficacy evaluation of the entire study and to provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of subjects. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for Avelumab + SBRT. The DMC will act in an advisory capacity to the sponsor and will monitor subject safety and evaluate the available efficacy data for the study. The DMC will meet at least every 6 months or more frequently as needed on an ad-hoc basis. Information regarding DMC membership, responsibilities, and procedures are detailed in the DMC charter. The DMC will be informed should a safety signal emerge and may convene an ad-hoc meeting on its own initiative. Ultimately, decisions regarding the study protocol will be made by the sponsor in conjunction with feedback from investigators and the DMC.

Patient safety will be monitored on an ongoing basis. Safety conference calls with investigators and representatives of the sponsor will be held as necessary. The DMC will review all available data (safety and efficacy) data at each meeting. At the conclusion of each DMC meeting the committee, will provide the sponsor with a recommendation to continue, modify or terminate the study protocol based upon their review.

All reportable anticipated and unanticipated protocol events/problems and amendments that are submitted to the IRB will also be reviewed by the DMC 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

Phase I: The Phase I primary endpoint is safety and tolerability as described in Section 3.1.1. Tolerability and safety of will be determined after all patients have completed six doses or have discontinued dosing prior to completing six doses. Safety analyses will be performed in all treated subjects. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Phase II: The Phase II primary endpoint is to determine the relapse free survival rate at a median followup of 2 years in early stage NSCLC treated with definitive SBRT combined with 6 cycles of concurrent and adjuvant Avelumab.

15.2 Sample Size/Accrual Rate

Phase I: The purpose of the Phase I part of this study is to evaluate the tolerability and safety profile SBRT combined with concurrent and adjuvant Avelumab at 10mg/kg. For this purpose, 12 subjects will be enrolled. Although the sample sizes are not based on statistical power considerations, data from these subjects will provide toxicity and dosing information on administration Avelumab in combination with SBRT in patients with early Stage NSCLC. The accrual rate is estimated at 3 patients per month.

Phase II: The primary endpoint will be relapse free survival (RFS) rate at median followup of 2 years. The accrual rate is estimated at 3 patients per month, and the patients will be

followed for up to 3 years. A total of 56 patients will be entered in the study accounting for a 10% dropout rate. This study would have 80% power to detect a 10% absolute improvement in RFS at 2 years from 80% to 90% using a one-sided t-test at significance level 0.10. RFS estimate at 2 years was based upon analysis of relevant literature[55-57].

15.3 Safety Run-In Phase

There is no significant published experience with SBRT used concurrently with Avelumab 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 treatment. 6 patients will be enrolled at the proposed dose of Avelumab and SBRT. If ≤ 3 patients among the safety cohort have a defined toxicity event within 30 days of therapy, we proceed with additional accrual with this regimen to complete a total of 12 patients. If ≥ 4 patients among the safety cohort have defined toxicity events we will suspend the study and have the study reviewed by IRB and DSMB committees for further recommendations.

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

15.4 Analysis of Primary Objectives

Phase I: If no more than one-third of the subjects permanently discontinue study medication prior to completing six doses due to treatment related adverse events then this combination will be deemed as tolerable and return to the IRB, DMC, and Sponsor for further evaluation and approval prior to proceeding to the Phase II cohort.

If ≥ 4 patients in the Phase I cohort permanently discontinue study medication prior to completing six doses due to treatment related adverse events then we will suspend the study and return the study to the IRB and DSMB committees for further evaluation and recommendations.

Phase II: The primary efficacy analysis will be the relapse free survival (RFS) rate in patients with early Stage NSCLC receiving SBRT combined with concurrent and adjuvant Avelumab compared to SBRT alone historical controls. The analysis population includes all registered subjects who have received SBRT and at least 2 cycles of Avelumab.

15.5 Analysis of Secondary Objectives

- To determine whether SBRT combined with concurrent and adjvaunt Avelumab results in improved loco-regional control, relapse free survival, and overall survival we will evaluate the recist criterion scans and survival rates at 6 months, 12 months and 24 months.
- To analyze whether SBRT combined with concurrent and adjuvant Avelumab impacts anti-tumor immune responses we will perform immunologic assays quantifying lymphocyte specificity and activation, including Immune cell Sequencing, ProtoArrays, Immunoassays, cell free DNA analyses, 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 (RFS), 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.

15.6 Evaluation of Toxicity

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

15.7 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.

16.0STUDY MANAGEMENT

16.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed according to UCSD conflict of interest policy.

16.2 Institutional Review Board (IRB) Approval and Consent

The IRB should approve the consent form and protocol prior to any study-related activities. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each

consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

16.3 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the UCSD Moores Cancer Center Clinical Trials Office

- A copy of the official IRB approval letter for the protocol and informed consent.
- A copy of the IRB-approved consent form.
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation. (NOTE: this is required if UCSD holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- CAP and CLIA Laboratory certification numbers and institution lab normal values.
- Executed clinical research contract.

16.4 Registration Procedures

All patients must be registered with the UCSD Moores Cancer Center Clinical Trials Office before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the UCSD Study Coordinator . To register a patient, call 858-246-2892 Monday through Friday, 8:00AM-4:30PM. Study sites other than UCSD must fax informed consent documentation, completed eligibility checklist, and all source documentation for eligibility confirmation to the UCSD Clinical Trials Office (Fax: 858-822-5360). Once eligibility is confirmed, patient will be given a unique sequential study number.

16.5 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory authority, or Institutional Review Board access to subject's medical information relevant to the study.

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