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RADVAX: A STRATIFIED PHASE II DOSE ESCALATION TRIAL OF STEREOTACTIC BODY RADIOTHERAPY FOLLOWED BY IPILIMUMAB IN METASTATIC MELANOMA

Principal Investigator: Ramesh Rengan MD PhD
University of Washington
Department of Radiation Oncology
Phone: (206) 598-4110
Fax: (206)598-3498
Email: Rengan@uw.edu

Funding Sponsor: Department of Radiation Oncology
University of Washington

Sub-Investigators Shailender Bhatia, MD
John Thompson, MD
Scott Tykodi, MD
Sylvia Lee, MD

Statistician: Barry Storer, PhD

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List of Abbreviations

SBRT: Stereotactic body radiation therapy
CTLA 4: Cytotoxic t-lymphocyte antigen 4

Study Summary

Title	**RADVAX: A STRATIFIED PHASE II DOSE ESCALATION TRIAL OF STEREOTACTIC BODY RADIOTHERAPY FOLLOWED BY IPILIMUMAB IN METASTATIC MELANOMA**
Short Title	RADVAX
Protocol Number	CC IRB # 9031
Phase	Phase II
Methodology	Open Label
Study Duration	3 years
Objectives	1. The primary objectives are to determine feasibility and immune-related clinical responses associated with SBRT when given in conjunction with ipilimumab 2. The secondary objectives are to determine late toxicity and immune pharmacodynamic changes after SBRT followed by ipilimumab
Number of Subjects	40
Diagnosis and Main Inclusion Criteria	Patients with previously untreated or previously treated metastatic melanoma with bone, lung, liver, or subcutaneous or nodal involvement but without evidence of active brain involvement. Patients who have previously been treated with radiation will be included in the study, so long as a suitable plan for treatment can be developed.
Study Product, Dose, Route, Regimen	Stereotactic Body Radiation Therapy
Duration of administration	Radiation Treatment to be delivered prior to initiation of ipilimumab
Reference therapy	Ipilimumab
Statistical Methodology	This is a stratified phase II study of escalating fractions of stereotactic body radiotherapy (SBRT) combined with immunotherapy for previously untreated or previously treated metastatic melanoma patients. Phase I was stratified by site: bone or lung vs. liver or s.c. Six patients were enrolled per dose cohort. Phase II is stratified by site: bone or lung vs. liver or s.c. In phase II, 20 patients will be treated at the MTD in each stratum. Descriptive statistics will be generated for both phases of the study.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Malignant melanoma is a virulent disease claiming almost 8600 patients annually in the United States.(1) the median survival with metastatic disease is usually less than one year. Systemic therapies are largely ineffective in this disease and there are no approved therapies beyond first line treatment.(2) In 2010 Hodi, et al, published the first phase III randomized trial demonstrating a survival benefit in metastatic melanoma using the immunotherapeutic agent ipilimumab, an anti-CTLA-4 antibody.(3) This was a multi-institutional randomized, double-blind phase III trial in previously treated patients with a diagnosis of unresectable stage III or IV melanoma. Patients were randomized in a 3:1:1 ratio, to treatment with an induction course of ipilimumab, at a dose of 3 mg per kilogram of body weight, plus a gp100 peptide vaccine; ipilimumab plus gp100 placebo; or gp100 plus ipilimumab placebo — all administered once every 3 weeks for four treatments. The median overall survival was 10.0 months among patients receiving ipilimumab plus gp100, as compared with 6.4 months among patients receiving gp100 alone (hazard ratio for death, 0.68; P<0.001). The median overall survival with ipilimumab alone was 10.1 months (hazard ratio for death in the comparison with gp100 alone, 0.66; P = 0.003). No difference in overall survival was detected between the ipilimumab groups (hazard ratio with ipilimumab plus gp100, 1.04; P = 0.76). Grade 3 or 4 immune-related adverse events occurred in 10 to 15% of patients treated with ipilimumab and in 3% treated with gp100 alone. The best overall response rate was 5.7% and 10.9% in the two ipilimumab arms. Although these results are promising, the fact that only approximately 10% of patients responded to ipilimumab suggests that this strategy is not effective for all patients with metastatic disease.

Mechanism of action of ipilimumab and relevance for melanoma

T lymphocytes are prime mediators of tumor immuno-surveillance, particularly for patients with melanoma in whom T cell infiltration into tumors predicts clinical outcome and for whom immunotherapeutic strategies have in some cases shown clinical utility. In the course of interactions between antigen presenting cells (APC) and T cells, surface expression of the co-stimulatory molecules CD80 and CD86 is upregulated. Initially, CD80/86 ligates and activates CD28 which is constitutively expressed on T-cells resulting in their activation. Cytotoxic T-lymphocyte antigen-4 (CTLA-4; CD152) is a cell-surface receptor that is expressed (within approximately 72 hours *in vitro*) on T-lymphocytes in response to their activation by interaction with APCs or pharmacologic stimulation of the T-cell receptor. CTLA4 has a substantially higher affinity for CD80 and CD86 than CD28; its activation down-modulates T-cell proliferation and cytokine secretion, effectively limiting the immune reactivity directed against a given antigen stimulus. Therefore, inhibition of CD80/86 binding to CTLA4 is a potential strategy to prevent down-regulation of the immune response. Ipilimumab, a fully human monoclonal antibody (IgG1) blocks CTLA-4 and has been shown to promote antitumor immunity in patients with metastatic melanoma and was approved for use by the FDA in March 2011 for patients with metastatic melanoma.(4) The effectiveness of this strategy is predicated upon T-lymphocyte activation through interaction with the APC to have occurred. CTLA-4 blockade can then prevent the down-regulation of the anti-tumor immune response. The development of novel strategies that successfully “vaccinate” patients to their melanoma prior to the delivery of CTLA-4 are important area clinical research.

Stereotactic Body Radiation Therapy (SBRT)
Stereotactic body radiotherapy (SBRT) is a highly precise treatment technique that delivers large tumoricidal doses of radiation to a small tumor. Although this represents one of the most exciting and active frontiers of research in the radiotherapeutic management of early stage NSCLC, this treatment technique was originally developed in 1951 by a Swedish neurosurgeon, Lars Leksell for the treatment of intracranial metastases.(5) SBRT allows for escalation of dose without extending the overall treatment duration, as would be the case with conventional fractionated radiotherapy. A Phase I dose-escalation trial evaluated patients with T1-2 N0 NSCLC with no restriction on tumor location. Each treatment course was administered over 3 fractions with a starting dose of 8 Gy per fraction. Patients were stratified into 3 dose-escalation groups based on T stage and size (T1, T2 <5 cm, and T2 5–7 cm). This trial demonstrated that the maximally tolerated dose for T2 tumors larger than 5 cm was 22 Gy × 3 for, and was not reached at 20 Gy × 3 for T1 tumors or at 22 Gy × 3 for T2 tumors smaller than 5 cm.(6). There were a total of 10 local failures in the 47 patients treated in this study with nine local failures in patients treated to the lower dose levels (<16Gy x 3). A Phase II trial from the same group of investigators treated 70 patients with Stage I NSCLC with the doses established in the phase I study. With a median follow-up of 17.5 months, the local control was 95%, which appears at least as effective as a definitive surgical resection. Severe toxicity occurred at a median of 10.5 months in 17% of those patients with peripheral lesions versus 46% with central lesions.(7) Several other institutions have subsequently published their experience utilizing SBRT for early lung cancer with a variety of dose fractionation and prescription schemes. The initial data appear promising with 80%–100% local control, 40%–100% 2- to 3-year survival, and 0%–4% grade 3 toxicity), although in general the median follow-up for these studies is relatively short.(8-14). Given these promising results, the RTOG (RTOG 0618) has initiated a phase II study of stereotactic body radiotherapy for operable patients with early stage operable NSCLC. Additionally, Dr. Robert Timmerman initiated a randomized trial of surgical resection vs. stereotactic body radiation for early stage lung cancer in early 2010 (RTOG 1021). While the results of these studies are eagerly anticipated, the ability to treat early stage lung cancer with SBRT is rapidly being incorporated into most Radiation Oncology facilities here in the United States.

SBRT in the setting of metastatic disease
SBRT is being used increasingly in the setting of metastatic disease. Initially, it was integrated as an ablative approach with a goal of tumor sterilization in oligometastatic disease with minimal morbidity and good long-term clinical outcome in these highly selected patients.(15-17) Subsequently, data have emerged that SBRT provides effective palliation in the metastatic setting for palliation of bone, lung, liver, and subcutaneous/nodal metastases with minimal morbidity.(15, 16, 18-20) As such, SBRT is being increasing utilized in the metastatic setting for palliative intent.

SBRT and Immune Activation
There is emerging evidence that hypofractionated radiotherapy is immunostimulatory. In a recently published study in *Blood*, Lee et al demonstrated that the therapeutic effect with ablative hypofractionated radiotherapy was dependent upon activation of CD8+ T-lymphocytes.(21) Additionally, there are pre-clinical data to suggest that CTLA-4 blockade along with ablative radiotherapy to an index lesion can prevent metastatic dissemination of disease.(22, 23) Finally, there are clinical data to suggest that SBRT provides greater local control and a reduction in regional and distant dissemination of disease when compared with surgery alone in NSCLC. One hypothesis to explain these surprising data is that the

immunostimulatory effect of SBRT results in improved control of disease and prevention of spread.(24)

Summary
We propose a stratified phase I/II clinical trial of SBRT to an isolated index lesion followed by ipilimumab in patients with previously untreated or previously treated metastatic melanoma in patients eligible for CTLA-4 blockade. In our protocol, the goal is to “vaccinate” patients against their melanoma via SBRT and then to elaborate the induced immune response with the FDA-approved CTLA-4 blocking antibody ipilimumab.

2 Study Objectives

The overall objective of the study is to determine the feasibility of delivery of SBRT to an index lesion in patients with metastatic melanoma prior to standard of care immunotherapy with ipilimumab.

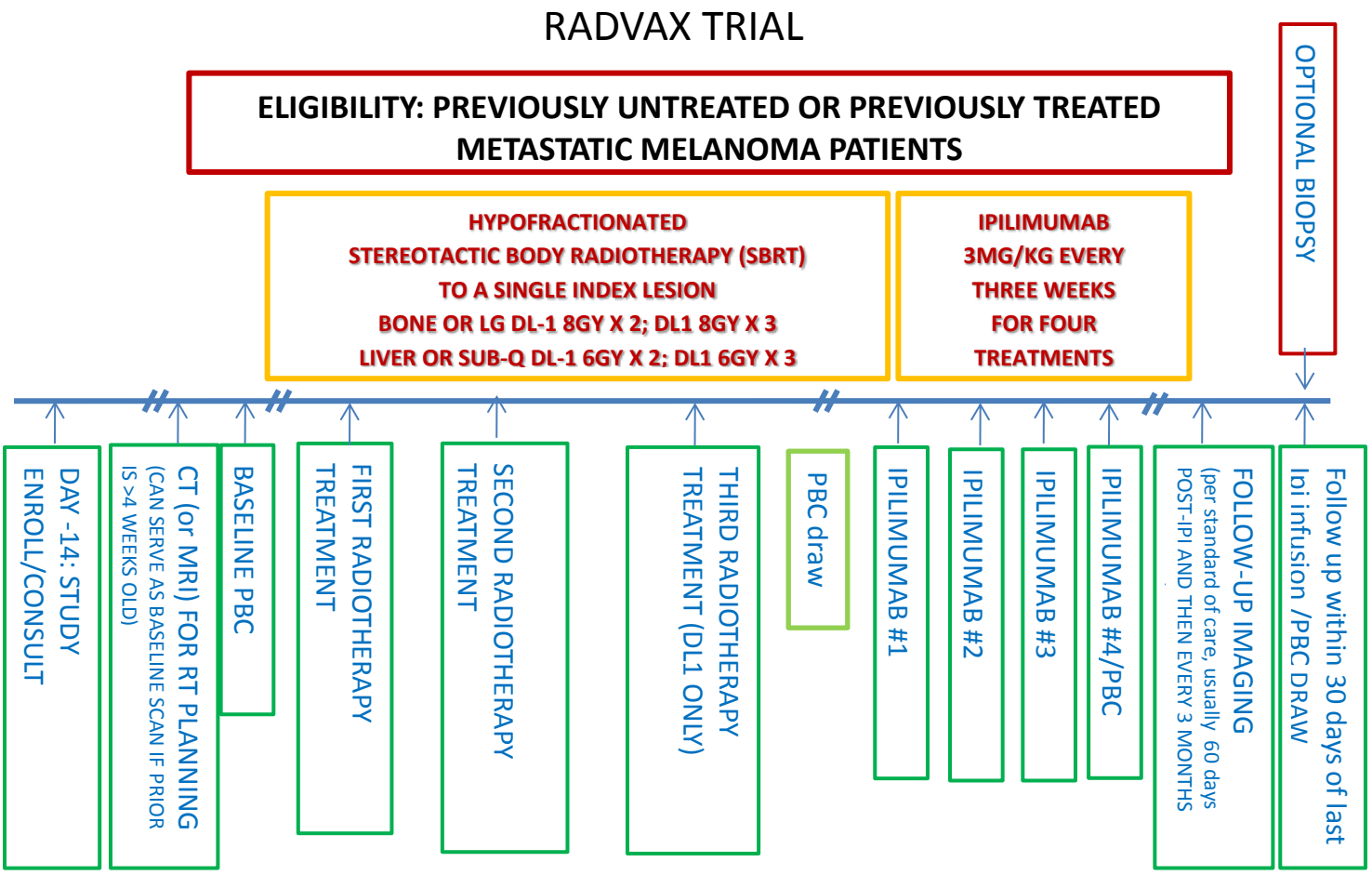
Primary Objective
The primary objectives are to determine feasibility and immune-related clinical responses associated with SBRT when given in conjunction with ipilimumab.

Secondary Objective
The secondary objectives are to determine late toxicity and immune pharmacodynamic changes after SBRT followed by ipilimumab.

3 Study Design

3.1 General Design

This is a stratified phase II study of escalating fractions of stereotactic body radiotherapy (SBRT) combined with immunotherapy for previously untreated or previously treated metastatic melanoma patients. Patients will undergo a short course of high dose SBRT to a single index lesion that measures 1 cm to 5 cm. These fractions will be administered several days apart. Radiotherapy will be immediately followed by ipilimumab, at the FDA-approved dose and schedule.



Study Duration: The expected accrual rate = 15 pts/yr. The protocol is designed for a maximum total of 40 patients. The expected total study duration is 3 to 3 ½ yrs needed to complete both phases, allowing for suspensions for interim analyses.
*Study Enrollment is intended to mean consultation

3.2 Primary Study Endpoints

Late toxicity is defined generally as an adverse event associated with the treatment which occurs beyond 30 days after last injection of ipilimumab (i.e., adverse events which are observed months after treatment are most likely associated with SBRT) and is defined more precisely in Section 5.2.

Clinical response will be scored on a non-index lesion or lesions using immune-related response criteria (irRC). Immune-related progression-free survival (irPFS) is defined as the time from first day of radiotherapy to first documented irPD, death due to any cause or last patient contact alive. Immune pharmacodynamic changes will be examined, as described in Section 7.22.(25) Overall immune response is defined as >2-fold pre-treatment/post-treatment increase in any of the key T cell parameters.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

- Patient ≥18 years old
- Histologically confirmed diagnosis of melanoma
- Previously treated or previously untreated stage IV melanoma by AJCC staging criteria
- Presence of an index lesion between 1 and 5 cm
- ECOG Performance status 0 ,1, or 2
- Signed informed consent document
- Adequate renal, hepatic, and hematologic indices for ipilimumab therapy
- Ability to tolerate stereotactic body radiation therapy (e.g. lie flat and hold position for treatment)

4.2 Exclusion Criteria

- Prior systemic therapy within 14 days of study enrollment. Patients must be adequately recovered from prior systemic therapy side effects as deemed by the treating investigator.
- Clinical contraindication to stereotactic body radiotherapy (e.g. active systemic sclerosis, active inflammatory bowel disease if bowel is within target field, etc)
- Presence of central nervous system metastasis (including active brain metastasis). Active brain metastasis would be defined as untreated brain metastases. If the brain metastases have received prior treatment (usually either with surgery or radiation), they are no longer active.
- Long-term use of systemic corticosteroids. Patients with replacement steroids and not immunosuppressive steroids may enroll in the study.
- Prior RT that precludes the delivery of SBRT

INCLUSION OF WOMEN AND MINORITIES
Female and male patients of all ethnic groups will be eligible for treatment in this protocol. Protocol accrual will be reviewed annually to include a determination of minority representation. An attempt will be made to enroll patients with metastatic melanoma in a distribution that matches the frequency of melanoma in the general population. The following melanoma incidence rates are reported by SEER: White 25.2 cases per 100,000; African-American 1.05 cases per 100,000; Asian/Pacific Islander 1.4 cases per 100,000; Hispanic 3.95 cases per 100,000.(26)

4.3 Subject Recruitment and Screening

Patients will be referred and screened by institutional standard practice. After the eligibility is established, a subject study number will be issued and the patient will be enrolled.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

- Progressive Disease as determined by irRECIST 1.1 criteria.
- Extraordinary Medical Circumstances. If at any time the constraints of this protocol are detrimental to the subject's health, the subject will be removed from protocol therapy. In this event, the reasons for withdrawal will be documented.
- Subject's refusal to continue treatment. In this event, the reasons for withdrawal will be documented.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Every effort will be made to follow subjects off study for toxicity, disease progression and survival.

5 Study Drug

5.1 Description

Ipilimumab is FDA approved for patients with metastatic melanoma and the delivery of this drug will be performed according to the FDA-approved dose and schedule. The Scientific Review Committee (SRC) has advised that an IND exemption is appropriate and will therefore be sought prior to initiation of this trial.

5.2 Dose Limiting Toxicities Definitions

Dose-limiting (Acute) Toxicity is defined as any treatment related Grade 4 or higher immune-related toxicity or Grade 3 or higher non-immune related toxicity which is observed during treatment or within 30 days of the final ipilimumab injection **and** which is probably or definitely related to radiation treatment. This definition will be used for de-escalation to the -1 dose level. All toxicities will be graded by NCI CTC Version 4.0.

Late toxicity Late toxicities will be graded according to the RTOG/EORTC late morbidity scoring system. The time frame for late toxicity is open-ended and late toxicities have been known to occur a year or more after therapy. Follow-up for late toxicity will cease when a patient experiences disease progression, since 2nd line therapies may then be initiated.

Non immune-related toxicity (SBRT-related toxicity) is defined as any toxicity observed within the tissues contained within the radiation portal and is consistent with tissue reaction to radiation exposure at any time during follow-up.

Immune-related toxicity is defined as an adverse event that is associated with exposure to ipilimumab and that is consistent with an immune phenomenon.

6 Study Procedures

6.1 General Study Design

This is a stratified phase II (with allowance for a (-1) dose level) study of stereotactic body radiotherapy (SBRT) combined with immunotherapy for previously untreated or previously treated metastatic melanoma patients. Patients will undergo a short course of high dose SBRT to a single index lesion that measures 1 cm to 5 cm. These fractions will be administered several days apart. Radiotherapy will be immediately followed by ipilimumab, at the FDA-approved dose and schedule.

6.2 Stereotactic Body Radiation Therapy

All subjects will be immobilized in a custom designed device in the appropriate position to isolate the index lesion. Radiotherapy treatment planning CT scans (with contrast, unless contraindicated) will be required to define the gross target volume (GTV) and planning target volume (CTV). The treatment planning CT scan should be acquired with the subject in the same position and using the same immobilization device as for treatment. Treatment planning will be done using a 3D based CT treatment planning system. All tissues to be irradiated must be included in the CT scan. Planning CT scan will be done at 3 mm intervals from encompassing the region of interest with sufficient margin for treatment planning.

6.2.1 Stereotactic Targeting and Treatment

SBRT has now been formally defined and described in a published guideline from the American College of Radiology and American Society for Therapeutic Radiology and Oncology (Potters 2004). This protocol will respect that guideline. The term stereotactic, for the purposes of this protocol, implies the targeting, planning, and directing of therapy using beams of radiation along any trajectory in 3-D space toward a target of known 3-D coordinates. The coordinate system is defined by reliable “fiducial” markers. This differs from conventional radiation therapy, in which therapy is directed toward less-than-reliable skin marks or bony landmarks that are indirectly referenced to the tumor (surrogates). This protocol will require treatments to be conducted with the use of a fixed 3-D coordinate system defined by fiducials. The coordinate system defined by the fiducials should be directly related to the radiation-producing device in a reproducible and secure fashion. Capability should exist to define the position of targets within the patient according to this same 3-D coordinate system. As such, the patient is set up for each treatment with the intention of directing the radiation toward a target according to the known 3-D coordinates as determined in the process of treatment planning. The nature of the fiducials themselves may include radiopaque markers or rods placed at known locations in a frame or fixed structure adjacent to the patient as well as use of the tumor itself as a fiducial (e.g., acquiring tomographic views of the tumor simultaneously with the treatment). Metallic “seeds” placed within the tumor will be allowed to constitute a fiducial so long as the methods are validated and a plan is in place to identify seed migration (e.g., redundant seeds placed).

6.2.2 Target Contouring

Gross Tumor Volume (GTV) is defined as all known gross disease encompassing the selected index lesion. The GTV will consist of the index lesion as visualized on CT.

Internal Gross Tumor Volume (IGTV) is defined for mobile index lesions at the discretion of the treating physician. A 4-D CT scan will be acquired in order to account for the motion of the lesion during. The IGTV will be defined as the union of the visualized index lesion on all gated CT data sets.

Planning Target Volume (PTV) will be defined as per the convention for photon beam radiotherapy. A 3-dimensional margin will be created on the GTV or IGTV (if available) to allow for daily set-up variance.

6.2.2 Normal Structures

Organ at risk volume (OAR) is contoured as visualized on the planning CT or MR scan. Planning PAR is the OAR expanded for setup uncertainty or organ motion. The physician will contour the OAR. The dosimetrist will create the PAR by expanding the OAR by 2-3 mm, depending on the situation.

6.2.3 Dose fractionation and specification

The prescription dose per fraction to the PTV will be 8 Gy per fraction for a bone or lung index lesion and 6Gy per fraction for any liver or subcutaneous index lesion.

The total dose for dose level 1 (our starting dose level) will be one will be 24Gy over 3 fractions for a bone or lung index lesion and 18Gy over three fractions for any liver or subcutaneous index lesion.

If we encounter a dose limiting toxicity, we will then reduce our total dose to dose level -1. The total dose for dose level -1 will be 16Gy over 2 fractions for a bone or lung index lesion and 12Gy over two fractions for any liver or subcutaneous index lesion.

Dose rate: For the purpose of this study, dose rate utilized will be that which is commissioned by the manufacturer and the medical physics group for external beam radiotherapy delivery by the University of Washington Department of Radiation Oncology. There will be no special dose rate modifications required for this study.

6.2.4 Treatment Planning

Three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, noncoplanar beams are preferable. Typically, ≥ 10 beams of radiation will be used with roughly equal weighting. Generally, more beams are used for larger lesion sizes. When static beams are used, a minimum of 7 non-opposing beams should be used. For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized. For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized. In order to obtain acceptable coverage, field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e., no additional "margin" for dose buildup at the edges of the blocks or MLC jaws beyond the PTV). The only exception should be when observing the minimum field dimension of 3.5 cm when treating small lesions (see above). As such, prescription lines covering the PTV will typically be the 60-90% line (where the maximum dose is 100%); however, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. The treatment isocenter or setup point in stereotactic coordinates will be determined from system fiducials (and can be adjusted pre-treatment depending on the results from localization imaging studies) and translated to the treatment record.

Dose specifications: Successful treatment planning will require accomplishment of **all** of the following criteria:

1. **Maximum dose:** The treatment plan should be created such that 100% corresponds to the maximum dose delivered to the patient. This point must exist within the PTV.
2. **Prescription isodose:** The prescription isodose surface must be ≥ 60% and < 90% of the maximum dose.
3. **Prescription Isodose Surface Coverage:** The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface (PTV V95%RX = 100%) and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose (PTV V90%RX > 99%).
4. **High Dose Spillage**: The cumulative volume of all tissue outside the PTV receiving a dose > 105% of prescription dose should be no more than 15% of the PTV volume. Conformality of PTV coverage will be judged such that the ratio of the volume of the prescription isodose meeting criteria 1 through 4 to the volume of the PTV is ideally < 1.2 (see table below). These criteria will not be required to be met in treating very small tumors (< 2.5 cm axial GTV dimension or < 1.5 cm craniocaudal GTV dimension) in which the required minimum field size of 3.5 cm (see Section 6.2) results in the inability to meet a conformality ratio of 1.2. The “None” and “Minor” entries in this table define the Per Protocol, Variation Acceptable and Deviation Unacceptable Compliance Criteria (see Section 6.7).
5. **Intermediate Dose Spillage**: The falloff gradient beyond the PTV extending into normal tissue structures must be rapid in all directions and meet the following criteria:
    a. *Location*: The maximum total dose over all fractions in Gray (Gy) to any point 2 cm or greater away from the PTV in any direction must be no greater than D2CM where D2CM is given by the table below.
    b. *Volume*: The ratio of the volume of the 34 or 12 Gy isodose volume to the volume of the PTV must be no greater than R50% where R50% is given by the table below (adapted from RTOG 0915). This table is used for all prescription requirements in Section 6.2.4 irrespective of calculation algorithm and total treatment dose.

Table 1: 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 Volume, $R_{50\%}$		Maximum Dose (in % of dose prescribed) @ 2 cm from PTV in Any Direction, D_{2cm} (Gy)	
	Deviation		Deviation		Deviation	
	None	Minor	None	Minor	None	Minor
1.8	<1.2	<1.5	<5.9	<7.5	<50.0	<57.0
3.8	<1.2	.<1.5	<5.5	<6.5	<50.0	<57.0
7.4	<1.2	<1.5	<5.1	<6.0	<50.0	<58.0
13.2	<1.2	<1.5	<4.7	<5.8	<50.0	<58.0
22.0	<1.2	<1.5	<4.5	<5.5	<54.0	<63.0
34.0	<1.2	<1.5	<4.3	<5.3	<58.0	<68.0
50.0	<1.2	<1.5	<4.0	<5.0	<62.0	<77.0
70.0	<1.2	<1.5	<3.5	<4.8	<66.0	<86.0
95.0	<1.2	<1.5	<3.3	<4.4	<70.0	<89.0
126.0	<1.2	<1.5	<3.1	<4.0	<73.0	>91.0
163.0	<1.2	<1.5	<2.9	<3.7	<77.0	>94.0

6.3 Ipilimumab Administration

Ipilimumab will be given in the outpatient setting. Patients will receive ipilimumab at 3 mg/kg i.v. delivered as per the package insert every 3 weeks (+/- 2 days) for treatments. Patients will be monitored in the clinic after the infusion and discharged when deemed stable by the clinical staff. Medications to treat hypersensitivity reactions should be immediately available, and may include epinephrine, diphenhydramine, methylprednisolone and nebulized albuterol.

6.4 Study Visit Schedule

After the subject consents and is deemed eligible for the study baseline imaging appropriate for RECIST criteria will be obtained (if not previously done or it has been greater than 60 days since the last scan) and a blood draw for purpose of immunological studies will be drawn. Baseline and post-treatment imaging will be evaluated by immune-related Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. This will be referred to as irRECIST 1.1 criteria described in section 7.1.1. Subjects will then be seen in the outpatient clinics to assess treatment-related toxicities once during radiation treatment. At this visit, a history and targeted physical examination will be performed.

During ipilimumab administration following radiotherapy, subjects will be evaluated by one of the investigators or their designated nurse practitioner at the time of each infusion. A history and directed physical examination will be performed.

6.5 Study Calendar

	Eligibility/Pre-Treatment	Post-SBRT; Pre- Ipi	Ipilimumab Clinic Visits	EOS visit
Tests and Observations				
History and PE	X		X	X(as per

				standard of care, usually within 60 days of final ipilimumab infusion)
ECOG score	X		X	X
Radiographic imaging appropriate for ir-RECIST 1.1 criteria (should be the same modality at baseline and EOS) [b]	X			X(as per standard of care, usually within 60 days of final ipilimumab infusion)
Biopsy	X			X[C]
Laboratory				
CBC w/diff, Hgb, Platelets…[b]	X	X[d]	X[d]	
CMP[b]	X	X[d]	X[d]	
Pregnancy Test	X[a]			
Toxicity Assessment	X	X	X	X
Immune studies (Eight 8.5 ml yellow top tubes and one 10 ml SST tube)	X	X[d]	X[d]	x

X[a]- Required for women of childbearing potential. If pre-treatment is 30 days from eligibility, you should repeat a pregnancy test within 24 hours of treatment initiation.

X[b]- Measurements cannot be more than 60 days from the beginning of treatment.

X[C]- As clinically indicated, tumor blocks and/or slides from EOS biopsy or surgery will be collected on all patients.

X[d]- The post-SBRT; pre-Ipi Ipilimumab #1 Immune studies and routine clinic blood draw may be combined if last SBRT and the first injection of Ipilimumab will occur within 5 days of each other.

6.6 Post-treatment Evaluation and follow-up

Patients will be evaluated per standard of care, usually within 60 days after last ipilimumab treatment (End of Study visit, EOS) to determine feasibility and safety (acute toxicity) for the initial phase of the study. Follow-up imaging appropriate for ir-RECIST 1.1 criteria will be obtained within 60 days of the final dose of ipilimumab for restaging. The same imaging modality should be used at follow-up as at baseline. Specimens for immune correlates will also be drawn at this visit. Patients will then be referred to the referring physician for subsequent follow up, according to standard of care. Every effort will be made to obtain records of patients during this follow up, and permission will be sought for the investigators and/or study team to re-contact the patient directly with regard to health status and toxicity.

7 Assessment of Tumor Response

7.1.1 Tumor Response (Immune-related response criteria)

Overall clinical response which will be assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, using primarily CT scans, immune response criteria and/or clinical benefit as assessed by the investigator). This will be referred to as irRECIST

7.1.2 1.1. Immunological Outcome Assessment

Blood samples from patients for immune studies will be obtained as in the Schedule of Activities table for assays such as those noted below. The extent of immune assessment will depend on availability of cells or serum.

Analysis of antigen presenting cell (APC) activation. For this assay, peripheral blood lymphocytes are analyzed for evidence of APC activation. Using unmanipulated peripheral blood, B cells and dendritic cells before and after treatment can be analyzed using flow cytometry to measure cell surface immune markers using a panel of immune parameters such as CD19, CD123, CD11c (to define the subsets) and CD86, MHC class I and II, CD70, and CD54 to measure activation. Dead cells are excluded using 7-AAD and non-B cells or non-DC are excluded using a panel of mAb, all analyzed on a "dump" channel. For each parameter and each APC, the percentage of cells positive for the marker and/or MFI at time points after CP-870,893 infusion are compared to baseline and the change are calculated as $\%_{after}/\%_{baseline}$ or $MFI_{after}/MFI_{baseline}$.

Analysis of T cell activation. Three main assays are available to assess T cells before and after treatment:

1. Multi-parameter flow cytometry. Together with complete blood count differentials, flow cytometry are used to measure both the percentages and absolute count (cells/mm^3) of important T cell subsets defined by immunophenotyping, such as total CD3+ cells, CD3+ CD8+ T cells, CD3+ CD4+ T cells, and CD3+ CD4+ Foxp3+ regulatory T cells. For each subset, differentiation status (e.g. naïve, central memory, effector memory) or activation status are assessed using additional markers such as CD45RA, CD45RO, CCR7, CD28, CD27, CD57, CD25, CD69, HLA-DR, CTLA4, and PD-1. When possible, trends can be tracked in T cell subsets based on analysis of multiple post-treatment samples. NK cells subsets can also be assessed using CD16 and CD56, with CD69 as an activation marker.
2. Antigen-specific T cell assays. To determine if treatment is associated with the induction of tumor antigen-specific CD8+ T cell responses, a series of assays to measure specific T cell responses, comparing pre and post treatment samples, are available. The immune assessment approach employed depends in large part on the patient's HLA type. Priority will be placed on assessment of specific T cells after one round of in vitro stimulation. For patients expressing common HLA alleles such as HLA-A2, in vitro stimulation of peripheral T cells can be performed using peptides derived from melanoma antigens known to bind to HLA alleles that match the patient. For HLA-A2 patients, specific T cell induction can be enumerated with peptide/HLA-A2 tetramers and function can be measured by intracellular IFN-gamma production in response to peptide loaded T2 cells. For non-HLA-A2 patients, T cell response can be measured using peptide-loaded autologous PHA blasts.
3. Tumor-specific T cell assays. For patients of any HLA type, tumor-specific responses can be measured using RNA loaded APC for in vitro stimulation of patient T cells. In this approach, CD40-activated B cells are generated from patient baseline samples, electroporated

with either total tumor RNA pooled from allogeneic melanoma cell lines or autologous total tumor RNA (when available) vs. GFP mRNA as a control. After 7 days in culture, stimulated autologous T cells can be scrutinized for responses specific for intracellular IFN-gamma response to autologous PHA blasts electroporated with tumor RNA vs. GFP mRNA.

Serum cytokine analysis. For this assay, serum can be used to determine concentrations of cytokines including IL-1, TNF-alpha, IL-6 and others using Luminex or Cytokine Bead Array platforms.

Specimens collected at the University of Washington and Seattle Cancer Center will be de-identified, frozen, and analyzed at the end of the study.

As research collaborations are developed with other immunology laboratories, de-identified specimens may be sent to labs for additional immunological testing. In addition, some specimens may be retained at the University of Washington for future, immunological research.

8 Statistical Plan

8.1 Design

This is a stratified Phase II study of escalating fractions of stereotactic body r*adiotherapy* (SBRT) combined with immunotherapy for previously untreated or previously treated metastatic melanoma patients. Patients will undergo a short course of high dose SBRT to a single index lesion that is suitable for SBRT. These fractions will be administered several days apart. Radiotherapy will be immediately followed by ipilimumab, at the FDA-approved dose and schedule.

Stratified Phase II study: With safety data from an identical University of Pennsylvania study, SBRT fractions of two and three fractions has been shown to be safe. At UW/SCCA the Phase II study begins with Dose Level 1. If three fractions of SBRT are found to not be safe, the dose level will be reduced to Dose level -1 for the phase II portion of that stratum.

Stratification by Site of Index Lesion						
	Stratum 1: bone or lung			**Stratum 2: liver or subcutaneous**		
Dose Level	Dose per fraction	Fractions	# Patients	Dose per fraction	Fractions	# Patients
-1	8 Gy	2	6	6 Gy	2	6
1	8 Gy	3	6	6 Gy	3	6

The MTD has been defined by the Phase I trial at the University of Pennsylvania as 3 fractions of SBRT. The Phase II study can commence at UW/SCCA at dose level 1 (above). Patients will be treated at the MTD defined for their index lesion site. In Phase II, patients will be stratified by disease site: Stratum 1: phase 1 bone or lung and Stratum 2: phase 1 liver or subcutaneous. Stratum-specific response rates will be calculated. Enrollment will proceed independently for the

two strata. Forty total patients will be enrolled in this phase. Thus a maximum of 40 patients will be entered at the MTD. Twenty patients will be enrolled in each stratum

8.2 Objectives:

Phase II study: The primary objectives are to determine for each stratum, immune-related clinical response rate, immune-related progression-free survival rate at 6 months (irPFS6), and overall survival rate at 12 months (OS12). The secondary objectives are to gather additional data on acute and late toxicity and immune pharmacodynamic changes.

8.3 Endpoints

Toxicity: CTCAE version 4.0 grades will be employed. Any patient who receives any amount of radiotherapy or study medication will be included in the toxicity analysis.

Dose-limiting toxicity (DLT) is defined generally as associated with the treatment, and for ipilimumab, that the event must be consistent with an immune-related effect. DLT is experienced during study treatment or within 30 days after last injection of ipilimumab, as long as the patient has not started another systemic treatment for cancer and is defined more precisely in Section 5.2.

Maximum tolerated SBRT fraction (MTD) is defined as the SBRT fraction dose level at which 0-1/6 patients experience DLT and at least 2 patients treated at the next higher dose level experience DLT (or the apparent MTD is Dose level 1).

Late toxicity is defined generally as an adverse event associated with the treatment which occurs beyond 30 days after last injection (i.e., adverse events which are observed months after treatment are most likely associated with SBRT) and is defined more precisely in Section 5.2.

Response: Immune-related clinical response will be scored on a non-index lesion using immune-related response criteria (irRC) according to irRECIST 1.1 (48). Patients who do not complete a clinical response evaluation, with the exception of those patients with rapidly progressing disease, will be scored as unevaluable. The immune-related clinical response rate is defined as the proportion of patients treated at the MTD who achieve either a complete or partial immune-related response. Unevaluable patients are included in denominator for the calculation of the objective response rate.

Immunologic outcomes include: 1) analysis of lymphocyte subsets and lymphocyte activation, 2) analysis of antigen-specific T cells and 3) tumor-specific T cells, as described in Section 7.2.2. For T cell response analyses, overall immune response is defined as >2 fold pre-treatment/post-treatment increase in any of the key T cell parameters.

8.4 Plans for De-escalation

A DLT rate ≥33% is considered unacceptable. Enrollment will proceed independently in the two strata. If a DLT is observed, then all subsequent patients will be treated at Dose Level -1.

8.4.1 Escalation Design

Because of the successful outcome with 2 and 3 fractions of SBRT in the University of Pennsylvania Phase 1 trial, the initial dose level in this study will be Dose level 1 (3 fractions of SBRT).

Dose level 1. This trial will begin enrolling at dose level 1, 3 fractions of SBRT, which has been shown to be safe in the Phase 1 trial at University of Pennsylvania. However, if one DLT has been observed in any patient, then all remaining patients must be followed for 30 days after the 4th or final injection. Two or more DLTs will cause de-escalation to Dose level -1, which will be the MTD.

Dose level -1. If two or more DLTs are observed in Dose Level 1, then all subsequent patients will be treated at Dose Level -1. If DLTs are observed at dose level -1, this will cause termination of the study.

Replacement of patients: Subjects/patients who discontinue from the study for reasons unrelated to the study (e.g. personal reasons or adverse events after registration but prior to receiving study therapy) may be replaced as required for the study to meet its objectives. Patients that have received study therapy, but who withdraw for reasons unrelated to toxicity prior to the required observation period to determine absence of DLT, will not count toward dose escalation rules and may be replaced as required. The decision to remove a subject/patient and to replace dropouts will be made by the principal investigator. The replacement will receive the same treatment or treatment sequence (as appropriate) as the allocation number replaced.

8.4.2 Operating Characteristics

To assure safety in this Phase II trial, the operating characteristics of the above-defined escalation rule have been determined. The operating characteristics denote the probability of escalation to the next SBRT fraction dose level, for a *true* DLT rate at the current dose level. For a true DLT rate that is high, we desire the probability of escalation to be low. As noted in the table below, the probability of escalating beyond a certain dose level, if that dose level truly has e.g. a 40% DLT rate, is 0.23.

Operating characteristics of the escalation rule									
	True DLT rate at a particular dose level								
Probability	10%	20%	30%	40%	50%	60%	70%	80%	90%
of escalating	0.89	0.66	0.42	0.23	0.11	0.04	0.01	0.002	<0.001

8.4.3 Assessment of Late Toxicity

Late toxicity is defined as an adverse event which occurs beyond 30 days from last injection of ipilimumab, as detailed in Section 5.2. Adverse events which are observed months after treatment will be recorded. We will monitor for both immune-related and SBRT-related events as described in Section 5.2.

8.5 Plans for Data Analysis

Toxicity: Any patient who receives any amount of radiation or study medication will be analyzed for toxicity. All dose-limiting toxicities and late toxicities will be graded and tabled by lesion site

stratum and SBRT fraction dose level. Toxicity attribution to either SBRT or ipilimumab will be described if possible.

Response: Clinical response at a non-index lesion will be scored using the immune-related response criteria (irRC) referred to as irRECIST 1.1 and discussed by others.(25,26) The index lesion will not be included in measuring response. The number of immune-related responses will be tabled by stratum and SBRT fraction dose level. **At the MTD**, the immune-related response rate and 95% exact CI will be estimated separately for previously untreated and previously treated metastatic patients and will inform our decision-making. The table below displays 95% exact CIs for selected numbers of responses.

95% Exact Confidence Interval for Event Rate based on 14 patients in each stratum at the Maximum Tolerated SBRT Fraction					
No. of Events	**%**	**95% exact CI**	**No. of Events**	**%**	**95% exact CI**
2	14.3	1.8 – 42.8	10	71.4	41.9 – 91.6
4	28.6	8.4 – 58.1	12	85.7	57.2 – 98.2
6	42.9	17.7 – 71.1	14	100.0	80.7*
8	57.1	28.9 – 82.3	* lower bound of 95% 1-sided CI		

Immune-related progression-free and overall survival will be estimated by the Kaplan-Meier method separately for previously untreated and previously treated metastatic patients who were treated at the MTD. The estimated 6 month irPFS and 12 month OS rates and 95% CIs will inform our decision-making, as they are considered by many to be better measures of clinical benefit. Interestingly, PFS6 and OS12 rates were approximately 25% and 45%, respectively, in 137 previously treated metastatic melanoma patients treated with ipilimumab alone.(3) Evaluation using historical benchmarks has been proposed by Korn et. al. for Phase II decision-making in metastatic melanoma (27).

Immunologic Endpoints: For measures of lymphocyte activation, outcomes will first be described using plots and descriptive statistics. Natural log transformation may be applied, as necessary, prior to statistical comparison. Within-patient differences (e.g., baseline vs. post-treatment) will be examined by Student's t test for paired data or nonparametric Wilcoxon signed ranks test. For lymphocyte analyses, outcomes will first be described using plots and descriptive statistics. For T cell response, the number of immune responses (>2 fold pre/post increase) will be tabled by fraction dose level. The overall immune response rate and 95% exact CI will be estimated separately for previously untreated and previously treated metastatic patients treated at the MTD.

With several post-treatment samples intended, trends over time may be investigated by repeated measures ANOVA (if data are complete). Alternatively, mixed effects models will describe trends in individual APC and T cell outcomes measured during immunotherapy, including drug doses as fixed effects. Although the number of subjects is modest, serial blood measures for immune monitoring are intended. (Thus, longitudinal modeling may be successful. We will attempt to extend this investigation to longitudinal methods for multivariate data with the goal of modeling jointly the inter-dependency among several longitudinal outcomes. For example, a joint analysis may determine how the association between the induction of CD86 on APCs and antigen-specific T cells evolves over time. Because the number of immunologic outcomes to be modeled jointly will be small (several at most), we will attempt to use the pairwise model fitting approach for maximum likelihood estimation as previously described.(27)

8.6 Sample Size/Power

If the Phase II study investigates both SBRT fraction dose levels for both strata, then a total of 40 patients will be enrolled on the study. There will be 40 patients enrolled at the Phase II dose. An objective response rate of 10.9% (by modified WHO criteria) was observed by Hodi et. al. in 137 previously treated metastatic melanoma patients treated with ipilimumab alone.(3) We anticipate that the combination of SBRT and ipilimumab will result greater efficacy for each stratum. If the true immune-related response rate is 20%, then the probability of observing no responses in 14 patients in either stratum, is <0.05.

With regard to statistical power, our preliminary clinical data on 16 patients treated on the single-infusion CD40 mAb trial indicate the mean difference $\pm$ SD_{diff} between post- and pre-treatment percentages of CD19+ B cells expressing CD86 were: 17.1% $\pm$ 11.1%, with effect size of 1.5 SD_{diff} units. By pooling over strata at the MTD, with a total of 28 patients enrolled, there is >80% power to detect a more modest effect size of ¾ SD_{diff} units, based on a paired t-test at 2-sided alpha level of 0.005 after adjusting for testing of multiple APC measures. Moreover, at the end of our current Phase I study of anti-CTLA-4 antibody (tremelimumab) and anti-CD40 antibody (CP-870,893) (UPCC 05609), we will evaluate pre/post differences in percentages of CD19+ B cells expressing CD86 and other relevant immune outcomes and we will update the power calculation for those effect sizes.

8.7 Study Duration

With an estimated accrual of 15 patients per year, it is anticipated that accrual will continue for 3.0 to 3.5 years, allowing for observation time within and between dose levels.

9 Safety Assessment and Adverse Event Reporting

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

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

Adverse Event

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

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

Serious Adverse Event

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

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

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

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

9.2 Adverse Events

Assessment of adverse events will include type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 4.03), timing, seriousness, and relatedness; and laboratory abnormalities. Patients who receive 1 or more study treatments will be evaluable for toxicity.

9.2 .1 Adverse Event Reporting

In the event of an adverse event the first concern will be for the safety of the subject. The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment. Thereafter, only non-hematological related AEs of Grade 3 and can reasonably be attributed to the study treatment will be reported.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

9.2.2 Adverse Event Causality
The Investigator will use the following definitions to assess the relationship of the adverse event to the use of study treatment:

Related - An adverse event has a strong temporal relationship to study drug, recurs on rechallenge or is known to be an effect of the study drug. Another reasonable etiology either doesn't exist or is unlikely.

Possibly Related - An adverse event has a strong temporal relationship to the study drug and an alternative etiology is either equally or less likely when compared to the potential relationship to study drug.
Not Related - An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has little or no temporal relationship to study drug or has a much more likely alternative etiology).

9.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators are required to report to the Sponsor-Investigator ANY serious adverse event (SAE) as soon as possible. An SAE is any sign, symptom or medical condition that emerges during treatment or during a post-treatment follow-up period that (1) was not present at the start of treatment and it is not a chronic condition that is part of the patient's medical history, OR (2) was present at the start of treatment or as part of the patient's medical history but worsened in severity and/or frequency during therapy, AND that meets any of the following regulatory serious criteria:

- Results in death
- Is life-threatening
- Requires or prolongs inpatient hospitalization (planned hospitalizations are not considered an SAE)
- Is disabling or incapacitating
- Is a congenital anomaly/birth defect
- Is medically significant or requires medical or surgical intervention to prevent one of the outcomes listed above.

Serious adverse events require immediate notification to the following party below, beginning from the time of the first study treatment through and including 30 calendar days after the last treatment administration of ipilumimab. All emergent SAEs should be communicated to:

Ramesh Rengan MD PhD
Phone: (206)598-4110
Mobile: (206)890-7195
Fax: (206)598-3786
or via the UW Paging operator (206)598-6190

SAEs will be reported to the Cancer Consortium IRB in accordance with the AE reporting policy.

10.0 Regulatory, Quality and Administrative Requirements

10.1 Confidentiality

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

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

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

10.2 Data and Safety Monitoring Plan

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

The monitors are independent contractors and are external to the Cancer Consortium (University of Washington and Fred Hutchinson Cancer Research Center). Study monitors will perform ongoing source data verification to confirm that critical protocol data transcribed on the CRFs by authorized site personnel are accurate, complete, and verifiable from source documents. To facilitate source documentation verification, the investigator(s) and institution(s) must provide the Monitor direct access to applicable source documents and reports for trial-related monitoring, audits, and IRB/EC review. The investigational site must also allow inspection by applicable regulatory authorities.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating patients. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

10.3 Compliance with Laws and Regulations

The proposed study will be conducted according to the International Conference on Harmonization E6 Guideline for Good Clinical Practice (GCP) and the Declaration of Helsinki and the requirements of the Federal Regulations. Please refer to:

- International Conference on Harmonization and GCP: http://www.fda.gov/oc/gcp/guidance.html
- Declaration of Helsinki: http://www.fda.gov/oc/health/helsinki89.html
- Code of Federal Regulations, Title 21: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm]

10.4 Informed Consent

The informed consent documents must be signed and dated by the patient, or the patient's legally authorized representative, before his or her participation in the study. The case history for each patient shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent documents must be provided to the patient or the patient's legally authorized representative.

10.5 Institutional Review Board

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. In addition, any advertising materials must be a proved by the IRB. The study will be conducted in accordance with applicable national and local health authority and IRB requirements.
The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case the IRB must be updated at least once a year. In addition, the Principal Investigator is required to promptly notify the IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to serious adverse events that are not already identified in the Investigator Brochure and that are considered possibly or probably related to the study drug by the Investigator.

10.6 Retention of Records

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

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