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A PHASE II TRIAL OF STEREOTACTIC BODY RADIATION THERAPY IN COMBINATION WITH NIVOLUMAB PLUS IPILIMUMAB IN PATIENTS WITH METASTATIC RENAL CELL CANCER

UT Southwestern Medical Center
Johns Hopkins Protocol #: J15233, IRB00086834
BMS Protocol #: CA209-444
IND Number: IND 129041
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7.0 Date Sept. 30, 2019

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INVESTIGATOR'S APPROVAL OF PROTOCOL

Title: A Phase II, Single Arm Trial, Combining Nivolumab Plus Ipilimumab with Stereotactic Body Radiation Therapy in Patients with Metastatic Renal Cell Cancer

Principal investigator Signature: _____

Principal Investigator Print: _____

Date: _____

SYNOPSIS

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Protocol Title: A Phase II, Single Arm Trial, Combining Nivolumab Plus Ipilimumab with Stereotactic Body Radiation Therapy in Patients with Metastatic Renal Cell Cancer

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

For Nivolumab and Ipilimumab:

- There will be an induction period (12 WEEKS) consisting of up to 4 doses of nivolumab plus ipilimumab given every 3 weeks x4 as tolerated, followed by maintenance dosing with nivolumab. A treatment cycle during maintenance is defined as 6 weeks
- Nivolumab will be administered IV over 60 minutes at 3 mg/kg combined with ipilimumab administered IV over 30 minutes at 1 mg/kg every 3 weeks for 4 doses followed by nivolumab administered IV over 60 minutes at 480 mg every 4 weeks up to 2 years

For Stereotactic Body Radiation Therapy (SBRT):

- 5 fractions of 10 Gy per fraction depending on organ site will be delivered within the first 3 weeks after the initiation of nivolumab and ipilimumab (SBRT is preferred to be delivered in the first 2 weeks)

Study Phase: This is single-arm Phase II study in subjects with naïve or pre-treated mRCC

Research Hypothesis: Nivolumab plus ipilimumab and SBRT can be given safely in combination and improves the clinical outcomes (with respect to nivolumab plus ipilimumab alone) in subjects with mRCC

Objective(s):

Primary Endpoints

- To assess the **overall safety and tolerability** of nivolumab plus ipilimumab in combination with SBRT in subjects with mRCC.
- To estimate the **objective response rate** (ORR) of this regimen and compare it to the reported data on the antitumor activity with the combination of nivolumab with ipilimumab in subjects with mRCC.

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Secondary Endpoints:

- **Clinical Endpoints**

- To evaluate **time to progression** (TTP) [defined as time between date of registration and date of documented progression] and **duration of response** (DOR) [defined as the time between the date of first response and the date of disease progression or death, whichever occurs first.].
- To evaluate **progression free survival** (PFS) and **overall survival** (OS)
- To evaluate the **local control** of irradiated lesion

- **Exploratory Correlative studies:**

- To evaluate potential immune related biomarkers of nivolumab plus ipilimumab in combination with SBRT in subjects with mRCC

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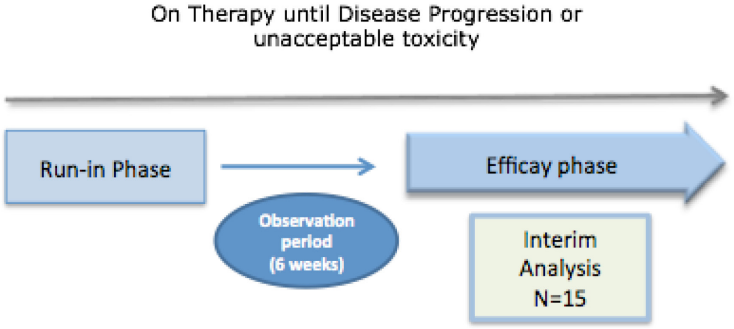
STUDY SCHEMA

Study Design and Timelines

Metastatic Clear Cell Renal Cell Carcinoma
N = 6 Safety run-in phase

N=19 Efficacy phase

Naïve or pre-treated patients with systemic therapy



- 2 site at JHU and UTSW
- Phase II, Single-arm
- Two stage design
  - Stage 1 (safety and tolerability)
  - Stage 2 (efficacy endpoints)

Primary Endpoint:
- Safety and tolerability
- Objective response rate

Exploratory Endpoints:
- Time to progression
- Duration of response
- Progression-free survival
- Overall survival
- Local control of irradiated lesion

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1 INTRODUCTION AND STUDY RATIONALE

1.1 Renal Cell Carcinoma (RCC): Background and Standard Treatments

Renal cell carcinoma accounts for ~3% of all cancers in the U.S. This translates to 58,000 new cases with 13,000 associated deaths.[1] Metastatic disease is found in 30% of subjects at diagnosis. Close to 90 - 95% of metastatic disease is of the clear-cell histology.[2]

Multiple scoring systems are available to characterize prognosis in treatment-naive and pre-treated RCC. Two of the most commonly used are the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic scoring system and the International Metastatic RCC Database Consortium (IMDC) prognostic scoring. Each of these systems categorizes patients as favorable, intermediate, or poor-risk based on how many adverse prognostic factors are present (0: favorable-risk, 1-2: intermediate risk, 3 or more: poor-risk).[3,4] The six parameters of importance for IDMC prognostic score classification are Karnofsky Performance Status (KPS), time from diagnosis to treatment, hemoglobin value, calcium concentration, absolute neutrophil count, and platelet count.[4] The three parameters included in the MSKCC prognostic score for pre-treated patients are KPS, hemoglobin value and corrected calcium concentration.[3] With each system, total number of adverse prognostic factors present has been shown to correlate with OS. Overall, approximately 25% of patients are in the favorable-risk group, 50% are in the intermediate-risk group, and 25% are in the poor-risk group (mOS: ~ 9 months (mo). In an analysis of 1028 patients scored using the IMDC system, median OS for favorable, intermediate, and poor-risk patients is 43.2 mo, 22.5 mo, and 7.8 mo, respectively.[4]

Until 2005, immunotherapy (IL-2 or IFNα) was the only active treatment for mRCC. IL-2 was approved based on a 15% durable response rate.[5,6] However, due to severe acute toxicities, its use is limited to only exceptionally medically fit subjects and to intensive care settings in tertiary care facilities.[7] IFNα was not approved for the treatment of RCC. However, several clinical trials have documented an objective response rate of 6 - 20% and a modest improvement in overall survival (~2.5 mo).[8] Though not as severe as IL-2, IFNα is also associated with significant adverse events.[9] As newer clinically active and less toxic agents have subsequently been approved for the treatment of mRCC, few treatment-naïve patients (< 5%) still receive IL-2 or IFNα monotherapy. However, due to each of these agents' limited role in clinic, newer targeted agents have largely replaced cytokines in the treatment of advanced or metastatic RCC.

The recognition of the importance of hypoxia inducible factor alpha (HIFα) signaling to the pathogenesis of clear-cell RCC led to the development of two new classes of therapeutics to manage this disease. Constitutive HIFα activation leads to the upregulation or activation of several proteins including vascular endothelial growth factor (VEGF). VEGF contributes to the development and progression of RCC in several ways including stimulation of tumor proliferation and neovasculature formation. Constitutive HIFα activation or upregulation occurs by several means including mutation or deletion of the tumor suppressor gene, VHL, as well as activation of the upstream PI3K/Akt/mTOR signaling pathway.

In the treatment-naïve setting, three VEGF pathway agents are currently recommended by the National Comprehensive Cancer Network (NCCN): sunitinib, bevacizumab/IFNα and pazopanib.[10,11] Sunitinib and bevacizumab/IFNα showed improvement in median PFS over the active comparator IFNα (11 mo vs 5.9 mo and 10.2 mo vs 5.4 mo, respectively), whereas pazopanib showed superior mPFS over placebo (11.1 mo vs 2.8 mo).[10,11]

As a class, the most common or clinically important toxicities elicited by VEGF pathway inhibitors are the following: fatigue (33 - 55%), diarrhea (20 - 53%), nausea (26 - 44%), hypertension (17 - 40%), liver function test (LFT) abnormalities (11 - 53%), hand-foot skin reaction (0 - 30%), Grade 3 - 4 neutropenia (1 - 11%), Grade 3 - 4 thrombocytopenia (1 - 8%) and low incidences of medically important events such as thrombosis, proteinuria, reversible posterior leukoencophalopathy syndrome (RPLS), bleeding, hypothyroidism, and drug-related cardiomyopathy.

Two mTOR inhibitors are approved for the treatment of mRCC. Temsirolimus was approved for the treatment of 1st-line MSKCC poor-risk subjects based on the demonstration of improved median OS compared to IFNα (10.9 mo vs 7.3 mo).[12] Everolimus was approved in subjects who failed to at least one prior VEGFR TKI therapy (sunitinib or sorafenib) based on the demonstration of improvement in median PFS as compared to placebo (4.9 mo vs 1.9 mo).[13] As a class, the most common or clinically important toxicities observed with mTOR inhibitors are fatigue (23 - 51%), nausea (15 - 37%), stomatitis (20 - 36%), diarrhea (21 - 27%), dyspnea (9 - 28%), pneumonitis (11%), infections (10 - 27%), Grade 3 - 4 anemia (10 - 20%).[12,13]

These newer agents have provided significant clinical benefit for many patients with mRCC, but infrequently lead to durable response. Therefore, researchers have remained interested in novel immunotherapeutic strategies.

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1.2 Nivolumab in Renal Cell Carcinoma

Nivolumab monotherapy has been studied in subjects with RCC in several studies, with the largest amount of data coming from two studies in subjects with mRCC: CA209009 and CA209010. In CA209010, 168 subjects who received at least one prior-anti-angiogenic therapy were randomized to receive nivolumab 0.3mg/kg (n=60), 2mg/kg (n=54) and 10mg/kg (n=54).[14] The mPFS was 2.7 mo, 4.0 mo, and 4.2 mo at 0.3, 2, and 10 mg/kg respectively. The ORR ranged from 20 to 22% across dose levels. Median OS was 18.2 mo at 0.3 mg/kg, but was not yet reached at the two highest dose levels. CA209009 enrolled a similar population to CA209010, but also included 23 subjects with treatment-naive RCC. Among treatment-naive subjects, all of whom received nivolumab 10 mg/kg every 3 weeks, the ORR was 13% (3/23).[14]

CA209010 includes the largest safety database for nivolumab monotherapy in mRCC. All treated subjects (n = 167) were included in the safety analyses. Drug-related AEs of any grade occurred in 74.6%, 66.7%, and 77.8% of subjects treated at 0.3 mg/kg, 2 mg/kg, and 10mg/kg respectively. The most common (≥10% in any group) drug-related AEs included fatigue, dry skin, rash, pruritus, arthralgia, nausea, diarrhea, decreased appetite, dry mouth, and hypersensitivity. Grade 3 drug-related AEs occurred in 5.1%, 16.7%, and 13% of subjects treated at 0.3 mg/kg, 2 mg/kg, and 10 mg/kg, respectively. Related Grade 3 events in at least 2 patients across dose levels included nausea, AST/ALT increased, and anemia. No drug-related Grade 4 or Grade 5 events occurred. No dose-toxicity relationship was identified except for hypersensitivity/infusion reactions which occurred most frequently in the 10 mg/kg treatment group.[14]

1.3 Ipilimumab in Renal Cell Carcinoma

Ipilimumab monotherapy for the treatment of mRCC was studied in the Phase 2 clinical trial MDX010-11.[15] Two sequential cohorts were studied, each with a loading dose of 3 mg/kg followed by 3 doses of either 1 mg/kg (group 3-1; n = 21) or 3 mg/kg (group 3-3; n = 40). Subjects with stable disease (SD) or partial or complete response were allowed additional treatment. In group 3-1 (n = 21), one subject (5%) had a partial response (PR). In group 3-3 (n = 40), 5 subjects (12.5 %) had a PR. Among 14 treatment-naive subjects in group 3-3, 3 (21%) had a PR.[16]

In the Ipilimumab monotherapy Phase 2 clinical trial MDX010-11, the major toxicities were colitis (all Grade 3 & 4; 14% in group 3-1, 33% in group3-3) and hypophisitis (1 grade 3/4, 1 grade 1/2 in group 3-3; none in group 3-1). Most reported adverse events (AEs) were Grade

1/2 (57% in group 3-1, 35% in group 3-3) or Grade 3 (38% in group 3-1, 48 % in group 3-3). There were 6 subjects (15%) with Grade 4 AEs in group 3-3. The most common treatment-related AEs in group 3-1 (total 81%) and group 3-3 (total 93%) were diarrhea (38%and 40%, respectively) and fatigue (33% and 38%, respectively).[15] Most AEs were manageable with appropriate treatment, including high dose corticosteroids and hormone replacement.

1.4 Nivolumab Combined with Ipilimumab in Renal Cell Carcinoma

The combination of nivolumab with ipilimumab is currently being studied in the Phase 1 study CA209016. Subjects with mRCC (favorable/intermediate MSKCC score; Karnofsky performance status ≥ 80%; untreated or any number of prior therapies) were randomized to receive nivolumab 3 mg/kg + ipilimumab 1 mg/kg (arm N3 + I1) or nivolumab 1 mg/kg + ipilimumab 3 mg/kg (arm N1 + I3) IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W until progression/toxicity. The primary objective was to assess safety/tolerability; secondary objective was to assess antitumor activity. Subjects were randomized to N3 + I1 (n = 21) and N1 + I3 (n = 23). Most patients (n = 34; 77%) had prior systemic therapy (N3 + I1: 16; N1 + I3: 18). The confirmed ORR was 43% (N3 + I1) and 48% (N1 + I3). DOR was 4.1+ to 42.1+ wks (7 of 9 responses ongoing) in N3 + I1, and 12.1+ to 35.1+ wks (9 of 11 responses ongoing) in N1 + I3. Best response of SD was seen in 5 (24%) pts (N3 + I1) and 8 (35%) pts (N1 + I3). Median PFS was 36.6 wks (N3 + I1) and 38.3 wks (N1 + I3); with 11 of 21 events reported for N3 + I1 and 10 of 23 events reported for N1 + I3.[17]

The safety of nivolumab combined with ipilimumab was assessed in the Phase 1 study CA209016. Treatment-related AEs were seen in 39/44 pts (89%), including 16/21 (76.2%) in N3 + I1 and 23/23 (100%) in N1 + I3. Across the N3 + I1 and N1 + I3 arms, the most common (≤ 20%) treatment related AEs of any grade were fatigue (61%), diarrhea (32%), nausea (30%), rash (27%), pruritis (25%), ALT increased (23%), AST increased (20%), hypothyroidism (20%), and asymptomatic lipase increased (20%). Grade 3–4 related AEs occurred in 19 pts (29%), including 6/21 (29%) at N3 + I1 and 14/23 (61%) at N1 + I3. The most common (≥5%) drug-related Grade 3-4 events were asymptomatic lipase increased (21%), ALT increased (14%), AST increased (7%), diarrhea (9%), fatigue (5%), amylase increased (5%), colitis (5%), lymphocyte count decreased (5%). No grade 3–4 pneumonitis was seen. No treatment-related deaths were reported. Treatment-related AEs (including Grade 3-4), treatment-related AEs leading to discontinuation, and treatment-related SAEs all occurred more commonly in subjects in the N1 + I3 arm than in the N3 + I1.[17]

Per a study amendment, the N3 + I1 and N1 + I3 arms were expanded to better evaluate safety and efficacy. Mature efficacy data was presented at ASCO 2015. The confirmed ORR was 38.3% (N3 + I1) and 40.4% (N1 + I3). Best response of SD was achieved in 36.2 % of patient in both treatment arms. Median DOR was 67.7 weeks (range 4.1+ to 91.1+) in the N3 + I1 arm and 81.1 weeks (range 6.1+ to 81.1+) in the N1 + I3 arm. Responses were durable, with >60% of patients continuing to experience ongoing response. The PFS rate (95% CI) at 24 weeks was 54% (39–68) in the N3 + I1 arm (N = 47) and 68% (52–79) in the N1 + I3 arm (N = 47). Median OS was not reached in either the N3 + I1 arm or in the N1 + I3.[18]

Table 1. ORR and best Overall Response

	NIVO3 + IPI1	**NIVO1 + IPI3**	**NIVO3 + IPI3**
	N = 47	**N =47**	**N = 6**
Confirmed ORR[a], n (%) 95% CI	18 (38.3) 24.5–53.6	19 (40.4) 26.4–55.7	0
Best overall response[b], n (%) Complete response Partial response Stable disease Progressive disease	 4 (8.5) 14 (29.8) 17 (36.2) 10 (21.3)	 1 (2.1) 18 (38.3) 17 (36.2) 7 (14.9)	 0 0 5 (83.3) 1 (16.7)

[a]Confirmed response only; [b]No unconfirmed complete responses were reported in either arm; unconfirmed partial responses were reported in one patient (2.1%) in the NIVO3 + IPI1 arm and in two patients (4.3%) in the NIVO1 + IPI3 arm. Best overall response was not determinable in one patient (2.1%) in the NIVO3 + IPI1 arm and in two patients (4.3%) in the NIVO1 + IPI3 arm.

Grade 3–4 related AEs occurred in 36 pts, including 16/47 (34%) at N3 + I1 and 30/47 (63.8%) at N1 + I3. The most common (≥20%) drug-related Grade 3-4 events were lipase increased including 6/47 (12.8%) at N3 + I1 and 12/47 (25.5%) at N1 + I3; ALT increased including 2/47 (4.3%) at N3 + I1 and 9/47 (19.1%) at N1 + I3; AST increased including 2/47 (4.3%) at N3 + I1 and 4/47 (8.5%) at N1 + I3 and diarrhea including 1/47 (2.1%) at N3 + I1 and 7/47 (14.9%) at N1 + I3. Grade 3-4 colitis was observed in 6/47 (12.8) at N1 + I3 only. No grade 3–4 pneumonitis was seen. No treatment-related deaths were reported. Treatment-related AEs (including Grade 3-4), treatment-related AEs leading to discontinuation, and treatment-related SAEs all occurred more commonly in subjects in the N1 + I3 arm than in the N3 + I1 arm.[18]

Table 2. Treatment-related Select AEs[a,b]

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Category, n (%)	NIVO3 + IPI1		NIVO1 + IPI3		NIVO3 + IPI3	
	N = 47		N = 47		N = 6	
	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4
Skin disorder	18 (38.3)	0	24 (51.1)	1 (2.1)	3 (50.0)	0
GI disorder	11 (23.4)	1 (2.1)	21 (44.7)	11 (23.4)	3 (50.0)	2 (33.3)
Endocrinopathy	11 (23.4)	1 (2.1)	20 (42.6)	0	5 (83.3)	0
Hepatic	7 (14.9)	2 (4.3)	15 (31.9)	10 (21.3)	3 (50.0)	0
Renal disorder	5 (10.6)	1 (2.1)	7 (14.9)	1 (2.1)	2 (33.3)	0
Infusion reaction	4 (8.5)	0	3 (6.4)	0	1 (16.7)	0
Pulmonary	2 (4.3)	0	3 (6.4)	0	0	0

[a]Select AEs were defined as AEs with potential immune-mediated etiology that may require special monitoring and specific unique interventions.[b]Treatment-related select AEs are ordered by decreasing frequency in the NIVO3 + IPI1 arm.

More recently the Checkmate 214 study data were released confirming the activity of nivolumab/ipilimumab with a 42% response rate in intermediate and poor-risk patients and improvement in overall survival. The combination of Nivolumab plus Ipilimumab is now approved for kidney cancer in the first line.

1.5 Stereotactic Body Radiation Therapy in Renal Cell Carcinoma

SBRT is an external beam radiation therapy (RT) method used to very precisely deliver a high dose of radiation to an extracranial target within the body, using either single-fraction treatment or a hypofractionated regimen. Although RCC has traditionally been considered radioresistant, it is expected that the use of higher dose-per-fraction regimens associated with SBRT may improve response rates and local control compared to conventional RT. Tinkle *et al;*[19] compared patients who received SBRT with those who received EBRT for either locally recurrent or metastatic RCC. This study reported that 1-year local control estimate was 88% for patients receiving SBRT, compared to 50% for those receiving external beam radiation therapy (EBRT) (*p=0.001*). In addition, the use of SBRT was the most important independent factor predictive of local control on multivariable analysis. A systematic review of SBRT for primary RCC found that amongst 10 reports in the literature, local control was 94%, with grade 1-2 adverse events of 21%. The most widely employed fractionation regimen was 40 Gy in five fractions.[20] However, the optimal fractionation regimen for SBRT in combination with immunotherapy remains unclear, with data from preclinical models suggesting superiority for single-fraction SBRT [21,22] and conflicting data showing superiority for fractionated SBRT. [23,24] In the clinical cases that have been reported in patients receiving combined SBRT and

immunotherapy, the doses utilized have been fractionated and have not consistently been doses that would be considered completely tumor ablative. This suggests that SBRT serves as a priming mechanism for the immune response both locally and systemically also called **abscopal effect**.[25,26] The abscopal effect refers to a phenomenon in which local radiotherapy is associated with the regression of metastatic cancer at a distance from the irradiated site. This phenomenon has been associated with increase in tumor-specific T-lymphocytes and a decrease in myeloid-derived suppressor cells in melanoma patients treated with ipilimumab and radiation.

In summary, an approach utilizing established doses of fractionated SBRT (5 fractions of 8-10 Gy per fraction depending on site) which are considered acceptable from a toxicity perspective for the given target site and regional normal seems warranted.[27-29]

1.6 Rationale to Support Trial Design

The immune-checkpoint modulators PD-1 and CTLA-4 have very different roles in regulating the immune response with different temporo-spatial effect that indicate a more tumor-directed effect by PD-1, while CTLA-4 has significant T-cell activation in the peripheral circulation. The differing mechanisms of effector T-cell activation provide scientific rationale to evaluate the combination of nivolumab with ipilimumab for the treatment of mRCC.

Data from CA209016 demonstrate a level of clinical activity for the combination of nivolumab combined with ipilimumab, as measured by ORR, that is substantially greater than that of either nivolumab or ipilimumab monotherapy in mRCC.[17,18] However, as data accumulate, it is becoming abundantly clear that, even with combined immune checkpoint blockade, a substantial proportion of patients fail to derive clinical benefit. RT has been shown to result in a number of potential beneficial immunologic effects, especially when given at high doses such as with SBRT.[30] For example, SBRT in combination with HD IL-2 has showed clinical activity and manageable toxicity for treatment of metastatic RCC in two different early-stage clinical trials.[31,32]

Preclinical models suggest that focal high-dose radiation can make tumors more immunogenic.[21,22,24] Among the effects of radiation therapy, SBRT may induce necrotic tumor-cell death, a prerequisite for eliciting an antitumor immune response. [30]

Although a detailed understanding of the effect of SBRT on the immune system is still needed, *in vivo* studies have shown that radiation induces release of damage-associated molecular patterns (DAMPs) such as HMGB1, HSP and calreticulin into the extracellular matrix and thereby promotes the recruitment and activation of antigen-presenting cells (APCs) such as

dendritic cells (DCs) for antigen presentation. Subsequently, the APCs migrate to the draining lymph nodes for the presentation of the antigens and efficiently present tumor antigens in the cell surface MHC molecules to T cells. Then, T cells initiate an adaptive immune response resulting in antibody production and the expansion of cytotoxic T cells. These are delivered to both the primary and metastatic tumor sites. Increased trafficking of CD8+ T cells to both irradiated tumor and their draining lymph node has been observed after RT.[30]

Other changes in the tumor microenviroment induced by radiation have been reported. For example, increase in MHC-I expression which mediates antitumor immunity by enhancing presentation of neo-antigen by the tumor cells and DCs. Induction of death pathways is another mechanism by which RT can triggers intratumoral immunostimulatory signals. Upregulation of the FAS death receptors on the tumor cell surface in response to radiation renders tumor cells particularly susceptible to massive CD8+ T cell-mediated cytotoxic attack.[30]

Preclinical studies also suggest the possibility that radiation can enhance the efficacy of CTLA-4 and PD-1 blockade. Because checkpoint blockade is thought to require a pre-established antitumor immune response, the immune-modulating effects of RT as a means to induce endogenous antigen-specific immune responses and generate an in situ, patient specific tumor vaccine may improve on the number of patients who benefit from combined immune-checkpoint blockade.[33]

Although some clinical cases and retrospective series suggest that RT may have enhanced efficacy of immune checkpoint blockade in patients and is generally believed to be safe, prospective trials are underway to test this hypothesis and little is known about this strategy.

Very recently, preliminary results of a dose escalation Phase I/II trial of SBRT followed by ipilimumab in patients with metastatic melanoma has been reported (NTC01497808).[34] The authors identified tumor regressions in radiated and unirradiated lesions (an abscopal effect) in some of the patients treated with ipilimumab and radiation. However, the majority of patient did not respond (64%). Detection of PD-L1 in melanoma cells from the participants was associated with resistance to this regimen. This finding suggests that PD-1 expression in tumor cells is a major impediment to antitumor immune response induced by SBRT and ipilimumab. [34]

The same group aimed to reproduce these clinical observations in a melanoma mouse model data. They investigated immune-mechanism both of response and resistance between radiation and immune checkpoint inhibitors. Results from mice studies demonstrated that while anti-CTLA4 predominantly inhibits T-regulatory cells (Treg cells) and promotes

expansion of T cells (thereby increasing the CD8 T-cell to Treg (CD8/Treg) ratio), radiation enhances the diversity of the T-cell receptor (TCR) repertoire of intratumoral T cells. Additionally, resistance was due to upregulation of PD-L1 in tumor cells and was associated with T-cell exhaustion that impairs the CD8+/Treg ratio. Based on these preclinical findings, it is expected that dual checkpoint blockade of PD-1 and CTLA-4 synergizes with SBRT and the combination induces non-redundant immune mechanism in cancer patients.[34]

1.7 Dosing for the Nivolumab Combination with Ipilimumab

Data from CA209016 demonstrated a level of clinical activity, as measured by ORR, for the combination of nivolumab combined with ipilimumab that is substantially greater than that of either nivolumab or ipilimumab monotherapy in mRCC. The dosing regimen including nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg was chosen because it exhibits similar clinical activity than nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg along with a more favorable safety profile.[17,18]

1.8 Dosing for the Stereotactic Body Radiation Therapy

As mention in the section 1.5; an approach utilizing established doses of fractionated SBRT (5 fractions of 8-10 Gy per fraction depending on site) (which are considered acceptable from a toxicity perspective) in combination with immune-checkpoint inhibitors seems reasonable.

1.9Overall Risk/Benefit Assessment

The combination of nivolumab and ipilimumab has encouraging anti-tumor activity (durable responses and stable disease) in a Phase 1 study for subjects with mRCC. Given the potential for the induction of non-redundant immune mechanism with dual checkpoint blockade of PD-1 and CTLA-4 in combination with SBRT, there exists an opportunity to further improve outcomes in mRCC. The immunostimulatory potential of SBRT may lead to enhance clinical activity in subjects also receiving nivolumab plus ipilimumab. As nivolumab, ipilimumab and SBRT have non-overlapping mechanisms of action; their combination may be associated with increased efficacy that outweighs the potential incremental increase in toxicity in first- or second-line mRCC setting.

We are hoping that the use of nivolumab plus ipilimumab in combination with SBRT to up to two metastatic lesions lead to greater clinical benefit than use the combination of nivolumab and ipilimumab alone without excessive toxicity.

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INVESTIGATIONAL PLAN and PATIENT SELECTION

2.1 Study Design

This is a multi-institution, single-arm phase II study to determine the safety and efficacy of SBRT (up to 2 metastatic sites preferentially lung, mediastinum or bone in combination of nivolumab and ipilimumab in patients with metastatic RCC (with a clear-cell component and at least 1 measurable metastatic lesion that is not being irradiated). The primary endpoints are safety and tolerability as well as ORR of the combination of nivolumab plus ipilimumab with SBRT.

The study is planned based on a two-stage design that allows early termination for lack of efficacy. A safety run-in phase will be included comprising the first 6 patients at minimum to ensure that the combination of nivolumab plus ipilimumab and SBRT is safe. Then, we will determine whether the combination of nivolumab plus ipilimumab and SBRT yields a clinically compelling antitumor activity measured as ORR, and evaluate other endpoints including TTP, DOR, PFS, OS and local control of irradiated sites.

Safety Run-in phase

There is no previous experience with SBRT used concurrently with nivolumab and ipilimumab in this study population. **Therefore, to ensure that the combination is safe, the first six patients will be treated and observed for toxicity for 6 weeks after radiation before continuing with further accrual.** Therefore, six patients will be enrolled at the proposed dose of nivolumab and ipilimumab in combination with SBRT. If 4 out of the first 6 patients experience Grade 3/4 toxicity or a lower grade toxicity requiring immune suppressive therapy during the safety run-in observation period (6 weeks after completion of SBRT), enrollment will cease and the study will be halted until further safety analysis of the combination regimen can be performed. If less than 4 out of the first 6 patients experience Grade 3/4 toxicities or require steroids, we will proceed with additional accrual with this regimen.

Toxicity Event: ≥grade 3 adverse event (CTCAE v 4.0) with an attribution of possible, probable, or definite, as well as need for steroids/ immunosuppressive therapy and lower grade toxicity

Efficacy phase:

A minimax Simon two-stage design is planned with the maximum sample size of 25 (including the 6 in the safety run-in phase). A total of 15 patients will be entered in the first

stage. If 6 or less achieve an objective response, then the response data will be reviewed carefully and study termination will be discussed. If a number of patients have near partial responses or evolving tumor shrinkage the team may decide to continue with accrual to get a larger sample size. If 7 or more patients have an objective response, then the second stage will proceed automatically with additional 10 patients. If a total of 17 or more patients respond, we will conclude this regimen is promising and warrants further study.

2.2 Duration of Study

Enrollment in the **run-in phase** of the study is expected to take approximately 3-6 months. Enrollment in the **efficacy phase** of the study is expected to take approximately 18 additional mo. Subjects may discontinue from treatment because of disease progression, unacceptable toxicity, withdrawal of consent, or at the discretion of the investigator. The end of the trial will occur on the day of the last visit of the last subject.

2.3 Study Population

For entry into the study, the following criteria MUST be met.

2.3...1 Inclusion Criteria

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered

1) Signed Written Informed Consent

- Willing and able to provide informed consent

2) Target Population

- Histological confirmation of RCC with a clear-cell component
- Metastatic (AJCC Stage IV) RCC
- Prior adjuvant or neoadjuvant therapy for localized or locally advanced RCC is allowed provided recurrence occurred = or > 6 months after the last dose of the adjuvant or neoadjuvant therapy
- Any number of prior systemic treatment regimen in the advanced/metastatic setting is allowed (cytokine, anti-angiogenic, mTOR inhibitor or clinical trial) including previously untreated patients
- Karnofsky Performance Status (KPS) of at least 70%
- Life expectancy of at least 3 months
- At least 2 metastatic sites of which at least 1 must be measurable as per RECIST 1.1

- Archival Formalin-fixed paraffin-embedded (FFPE) tumor tissue must be available for correlative studies (Note: Fine Needle Aspiration [FNA] and bone metastases samples are not acceptable for submission)
- Patients with favorable, intermediate and poor risk categories will be eligible for the study. *Patients must be categorized according to favorable versus intermediate/poor risk status at registration.* **International Metastatic RCC Database Consortium (IMDC) must be used to determine prognostic factors (Appendix 1)**

2.3.2 Exclusion Criteria:

1) Target Disease Exceptions

- Subjects with previously treated brain or CNS metastases are eligible provided that the subject has recovered from any acute effects of radiotherapy and is not requiring steroids, and any whole brain radiation therapy was completed at least 4 weeks prior to study drug administration, or any stereotactic radiosurgery was completed at least 2 weeks prior to study drug administration. Liver metastases will not be included as part of the radiated lesions to be treated.

2) Medical History and Concurrent Diseases

- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways. Prior treatment with HD IL-2 is allowed.
- Any active or recent history of a known or suspected autoimmune disease or recent history of a syndrome that required systemic corticosteroids (> 10 mg daily prednisone equivalent) or immunosuppressive medications except for syndromes which would not be expected to recur in the absence of an external trigger. Subjects with vitiligo or type I diabetes mellitus or residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement are permitted to enroll. Patients with psoriasis not requiring active, systemic treatment are allowed.
- Any condition requiring systemic treatment with corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days prior to first dose of study drug. Inhaled steroids and adrenal replacement steroid doses up to 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease

- Uncontrolled adrenal insufficiency
- *Requirement for anti-coagulation with Coumadin, low molecular weight heparin and anti-thrombin inhibitors will be accepted if anticoagulation has been stable for at least 4 weeks and no recent history of prior bleeding complications.*
- Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix, breast or low risk Gleason 6 prostate cancer
- Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
- Any positive test for hepatitis B or hepatitis C virus indicating acute or chronic infection
- Known medical condition (eg, a condition associated with diarrhea or acute diverticulitis) that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results
- Major surgery (eg, nephrectomy) less than 28 days prior to the first dose of study drug
- Anti-cancer therapy less than 14 days prior to the first dose of study drug or palliative, focal radiation therapy less than 14 days prior to the first dose of study drug
- Presence of any toxicities attributed to prior anti-cancer therapy, other than alopecia, that have not resolved to Grade 1 (NCI CTCAE v4) or baseline before administration of study drug

3) Physical and Laboratory Test Findings

- Any of the following laboratory test findings:
  - WBC < 2,000/mm^3
  - Neutrophils < 1,500/mm^3
  - Platelets < 100,000/mm^3
  - AST or ALT > 3 x ULN (> 5 x ULN if liver metastases are present)
  - Total Bilirubin > 1.5 x ULN (except subjects with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL)
  - Serum creatinine > 1.5 x upper limit of normal (ULN) or creatinine clearance < 40 mL/min (measured or calculated by Cockroft-Gault formula)

4) Allergies and Adverse Drug Reaction

- History of severe hypersensitivity reaction to any monoclonal antibody or study drug components

5) Other Exclusion Criteria

- Prisoners or subjects who are involuntarily incarcerated
- Not suitable for SBRT treatment
- Subjects who are compulsorily detained for treatment of either a psychiatric or physical illness

2.3.3. Age and Reproductive Status

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 62 must have a documented serum follicle stimulating hormone (FSH) level less than 40 mIU/mL.

Women of childbearing potential (WOCBP) receiving nivolumab will be instructed to adhere to contraception for a period of 23 weeks after the last dose of investigational product. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product. These durations have been calculated using the upper limit of the half-life for nivolumab (25 days) and are based on the protocol requirement that WOCBP use contraception for 5 half-lives plus 30 days and men who are sexually active with WOCBP use contraception for 5 half-lives plus 90 days.

Highly effective methods of contraception include:

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- Nonhormonal IUDs, such as ParaGard®

- Tubal ligation
- Vasectomy
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

Less effective methods of contraception include:

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male Condom without spermicide
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female Condom*.

  *A male and female condom must not be used together

2.4 Follow-up Visits

At least three follow-up visits (X1, X2 and X3) are required for all subjects. Visit X1 will take place 30 days (+/- 1 week) after the last dose of study medication in the cycle where nivolumab was discontinued, visit X2 will take place 8 weeks (+/- 1 week) after last dose of nivolumab was administered and visit X3 will take place 15 weeks (+/- 1 week) after last dose of nivolumab was administered. The duration of the follow-up period up to the X3 visit is equal to approximately 5 half-lives of nivolumab. If additional X follow-up visits are required due to ongoing study drug- related toxicity, they should take place every 8 weeks (+/- 1 week) until study drug-related toxicity has resolved, stabilized or been deemed irreversible.

2.5 Survival Follow-up

After follow-up visits, study subjects will be contacted every 3 months for survival data. Other potential data such as the subjects' follow-up treatment or care may be requested during these contacts. The contacts can be via telephone or correspond with disease assessment visits, if

subject went off treatment for other than progressive disease, or other scheduled visits.

2.6 Subsequent therapy

Subjects for whom treatment is discontinued should be treated according to clinical circumstances and should be managed at the local clinician's discretion.

2.7 Concomitant Treatments

2.7.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study:

- Immunosuppressive agents (except to treat a drug-related adverse event). Systemic corticosteroids > 10 mg daily prednisone equivalent (except as stated in Section 2.7.3 below or to treat a drug-related adverse event).
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy surgical resection except for palliative surgical resection).
- Supportive care for disease-related symptoms may be offered to all subjects on the trial.
- Any concurrent meds should be evaluated for being absolutely necessary. Particularly drugs with potential liver toxicity should be avoided if possible

2.7.2 Other Restrictions and Precautions

Palliative (limited-field) radiation therapy and palliative surgical resection are permitted, if the following criteria are met:

- The subject will be considered to have progressed at the time of palliative therapy and must meet criteria to continue with treatment beyond progression. (Section 3.5)

2.7.3 Permitted Therapy

Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, up to 10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted. Concomitant medications are recorded at baseline and throughout the treatment phase of the study in the appropriate section of the case report form (CRF). All medications (prescriptions

or over the counter medications) continued at the start of the study or started during the study and different from the study drug must be documented in the concomitant therapy section of the CRF.

2.8 Discontinuation of Subjects following any Treatment with Study Drug

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment
- Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Protocol defined disease progression (subjects may be permitted to continue treatment beyond initial disease progression see Section 3.5)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Additional protocol specified reasons for discontinuation (see Section *3.4.5*)

In the case of pregnancy, the study subject will be permanently discontinued in an appropriate manner. All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 3 (Study Assessment and Procedures). The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate CRF page.

2.9 Post Study Drug Study Follow up

In this study, **overall response rate** is a key endpoint of the study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome

and/or survival follow-up data as required and in line with Section 3 (Study Assessment and Procedures) until death or the conclusion of the study.

2.9.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

2.9.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

UTSouthwestern Harold C. Simmons Comprehensive Cancer Center | NCI Designated Comprehensive Cancer Center

TREATMENT PLAN/THERAPEUTIC INTERVENTION

3.1 Treatment Plan

3.1.1 Study Drug

Study drug includes both Investigational (Investigational Medicinal Product) and Non-Investigational Therapy and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial
- Study required premedication, and other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection

Nivolumab 100 mg (10 mg/mL) will be packaged in an open-label fashion. Five or ten nivolumab 10 mL vials will be packaged within a carton. The vials are not subject or treatment group specific. Each site will complete a drug request form and submit the form to BMS to receive the medication and obtain re-supply.

Ipilimumab will be supplied as a sterile, preservative-free solution in 40 mL vials at a concentration of 5 mg/mL. Each vial contains a concentrated solution with the equivalent of 200 mg of ipilimumab.

Table 3. Product Description: Treatment Period

Product Description / Class and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Packaging/ Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection[a]	100 mg (10 mg/mL)	10 mL per vial/	5 vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2° to 8°C. Protect from light and freezing
Ipilimumab	200 mg (5 mg/mL)	40 mL per vial/Openlabel	4 vials per carton/Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2° to 8°C. Protect from light and freezing

[a] Nivolumab is labeled as BMS-936558-01 Solution for Injection.

3.1.2 Investigational Products

An investigational product, also known as investigational medicinal product (IMP) in some regions, is defined as pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational products are:

- Nivolumab (BMS-936558)
- Ipilimumab

3.1.3 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

In this protocol, non-investigational product(s) is/are: medications used to treat nivolumab or ipilimumab infusion-related reactions (eg, steroids, anti-emetics); these non-investigational products should be sourced by the investigator sites if available and permitted by local regulations.

3.1.4 Storage and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS and the principal investigator immediately.

If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab and ipilimumab include laboratory coats and gloves.

Investigational product documentation must be maintained that includes all processes

required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Infusion-related supplies (eg, IV bags, in-line filters, 0.9% NaCl solution) should be purchased locally if permitted by local regulations.

For nivolumab and ipilimumab, please refer to the current version of the Investigator Brochures and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information.

Nivolumab is to be administered as an approximately 60-minute IV infusion. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Ipilimumab is to be administered as an approximately 30-minute IV infusion. At the end of the infusion, flush the line with a sufficient quantity of normal saline or 5% dextrose solution.

When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first.

3.2 Timing of Dose for Each Subject and Duration of Therapy

Table 4. Schedule for SBRT						
SBRT is to be delivered anytime between Day 1 of Week 1 and Day 1 of Week 4 of the NIVO/IPI combination dosing						
	Week 1 D1	Week 2	Week 3	Week 4 D1	Week 5	Week 6
SBRT	5 fractions of 10 Gy					

Table 5. Dosing Schedule for Cycle 1 and Cycle 2						
1 cycle = 6 weeks						
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/Kg IV	**Day 1** Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/Kg IV			**Day 1** Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/Kg IV		

Table 6. Dosing Schedule for Cycle 3 and Beyond (up to 2 years) every 4 weeks
1 cycle = 8 weeks

	Week 1		Week 5			
	Day 1 Nivolumab 480 mg IV		**Day 1** Nivolumab 480mg IV		480mg IV	

When nivolumab and ipilimumab are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The second infusion will always be ipilimumab, and will be administered at least 30 minutes after completion of the nivolumab infusion.

Ipilimumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution. Nivolumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution.

The dosing calculations should be based on the actual body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. (The weight used to calculate the dose should always be the most recently recorded weight). All doses should be rounded to the nearest milligram. There will be no dose modifications allowed.

During cycles 1 and 2, subjects may be dosed no less than 19 days from the previous dose of drug. Starting from cycle 3, subjects may be dosed no less than 26 days from the previous dose of drug. Patients may be dosed up to 3 days after the scheduled date if necessary or 2 days prior to expected date. Treatment compliance will be monitored by drug accountability as well as the subject's medical record and CRF.

Maintenance nivolumab will be allowed up to 2 years from the start of treatment.

3.3 Stereotactic Body Radiation Therapy

Prior to entry into the protocol, all patients need to be discussed with Dr. Danny Song (JHU), Dr. Raquib Hannan (UTSW) or co-investigator Radiation Oncologist from the Radiation Therapy Department to determine eligibility/feasibility for SBRT. The cancer lesion(s) to be radiated should be determined by the Radiation Oncologist in collaboration with the Principal Investigator/Medical Oncologist using the criteria stated below.

3.3.1 Lesion selection criteria and dosing

The most common sites of involvement with metastatic RCC are lung (45%), bone (29%), lymph node (22%), liver (20%), and adrenal (9%)[1]. Dosing, patient setup/immobilization, and dose constraints for lung sites will be in accordance with established experience specific to

those sites. Bone and lymph node sites will be treated and dosed in accordance with their anatomic location (extremity, thorax, or abdomen/pelvis) and surrounding dose-sensitive structures. The gross target volume (GTV) for SBRT will be a minimum of 1cm in short-axis diameter (in order to help assure an adequate volume of tumor cells for immune stimulation), and a maximum of 5cm in long-axis diameter. Liver lesions will not be considered for SBRT for patients on the protocol, as this could potentially lead to higher rates of liver failure and/or autoimmune hepatitis in the setting of concomitant immunotherapy.

Five fractions of SBRT at 10 Gy per fraction will be delivered within the first 3 weeks after the initiation of nivolumab and ipilimumab. Given the parallel goals of radiation of enhancing antitumor immune response and stimulating auto-vaccination (rather than to treat all known tumor tissue), as well as maintaining consistency in target dose prescription for purposes of analysis, the planning target volume and treatment margins may be defined in a manner which may involve potentially less than complete prescription dose coverage of the involved tumor. A working hypothesis of the trial is that optimal immune stimulation will occur with an ablative dose of radiation; the most robust dose-response relationships for SBRT come from the lung SBRT experience, where a biologically equivalent dose (BED) of approximately 100 Gy (equivalent to 10 Gy x 5 fractions) has been shown to be a threshold dose for optimal local control[2,3]

If all relevant normal tissue constraints cannot be met while treating the entire metastatic focus, then planned target volume (PTV) margins will be modified downward in an iterative process to a minimum of 0mm (from GTV) in order to achieve normal tissue constraints. If normal tissue constraints still cannot be met, then consideration will be given to treating another lesion if a suitable alternative exists. If no suitable alternative target exists, then an **nPTV** will be generated which impinges upon the GTV in areas of proximity to critical normal tissues, until all protocol-specific SBRT tissue constraints have been met. For example, if the entire GTV can not be treated with 5 x 10 Gy because of surrounding normal tissue constraints, then only part of the gross target volume can be exposed to 5 x 10 Gy while the surrounding margin receives 5 x 8 Gy. Liver lesions will not be considered as a radiated target.

3.3.2 Simulation procedure

Patients will undergo simulation and immobilization in accordance with site-specific protocols established in the Dept. of Radiation Oncology.

Patients being treated to lung/thoracic or abdominal lesions will have respiratory movement of the target volume accounted for either with 4D-CT scanning or with Active Breathing Control (ABC) and inspiratory breath hold. Patients with greater than or equal to 5 mm of breathing

motion identified on 4D-CT should have ABC performed to minimize breathing motion. All other patients will have an Internal Target Volume (ITV) delineated using end-inspiratory and end-expiratory phases of the 4D-CT scan. A wingboard and/or alpha cradle may be utilized for patient positioning. Patients who have target volumes in close proximity to the upper GI tract (stomach, duodenum, small bowel) shall be instructed to be NPO for 3 hours prior to simulation and each daily treatment.

IV contrast should be utilized during CT simulation for patients with targets in the mediastinum. Patients being treated to pelvic lesions will be positioned with the Combifix device. Bladder filling (patient instructed to drink 30 oz. of water prior to simulation) is to be utilized if doing so will help eliminate or minimize small bowel from the treatment field.

For extremity lesions, immobilization with alpha cradle and/or Vac-Loc bags will be utilized.

CT simulation will be performed with minimum 3mm slice thickness. MRI simulation may be utilized if target volume or normal anatomy delineation will be enhanced with its use. Diagnostic MRI scans may also be utilized to provide complementary anatomic information to CT simulations. MRI and CT simulation images will be fused using either Pinnacle or Velocity.

The target volume (PTV or nPTV) for centrally located or mediastinal sites should not directly involve critical structures such as central bronchial tree (within 2cm of carina or hilum, as defined in RTOG 0813), esophagus, great vessels, or brachial plexus.

3.3.3 Target delineation

Spinal metastases may involve vertebral body alone, vertebral body and pedicle, or posterior elements only (as defined in NRG-BR-001). For each of these metastases, GTV delineation will include at a minimum the involved vertebral body and both pedicles, or the involved posterior elements and both pedicles.

Other targets will be delineated primarily based on CT simulation images, using the windowing settings specific for the anatomic location within which the target is contained. Additional imaging modalities such as MRI may be utilized at the radiation oncologist's discretion; rigid image registration is recommended if utilizing complementary imaging modalities in addition to CT simulation scans.

3.3.4 Normal tissue delineation and constraints

The following normal tissue delineation definitions are for purposes of consistency in those cases where ambiguity could potentially lead to inter-individual variations in contouring, and to adhere to well-defined generally accepted SBRT practice when available.

Spinal cord will be contoured based on the bony limits of the spinal canal, starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV.

Cauda equina is defined as beginning at the conus (usually L1 or L2) and including the entire spinal canal to the filum terminale in the sacrum.

Sacral plexus will includes the nerve roots beginning at L5 and extending to S3 bilaterally from neuroforamina to the coalescing of nerves at the obturator internus.

Esophagus is to be defined to include all layers from mucosal to adventitia, starting at least 10cm cranial and caudal to the extent of PTV.

Brachial plexus is to be contoured if target volume (PTV) is within 10 cm, using the technique as described by Hall et al[4]. It originates from nerves existing neuroforamina from C5 to T2, and commonly defined on CT using subclavian and axillary vessels as surrogate structures.

Heart will be contoured including the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the inferior aspect of the aortic arch (i.e. aortopulmonary window) and extend inferiorly to the apex of the heart.

Trachea and proximal bronchial tree will be defined as two structures; distal 2cm of trachea will be included in what is defined as proximal bronchial tree. Proximal bronchial tree will include the caudal 2cm of distal trachea plus proximal airways bilaterally as defined by Timmerman et al[5] / RTOG 0813.

Lungs will be contoured separately as well as combined into a single structure for DVH purposes. GTV and trachea / proximal bronchial tree are to be excluded.

Skin is to be defined as the outer 5mm of body surface.

Great vessels (aorta, vena cava) will be contoured including entire thickness to the adventitia. Contours should extend from 10cm caudal to 10cm cranial from extent of PTV.

Duodenum will be defined from stomach, to where the superior mesenteric artery crosses over the 3rd part of duodenum.

Small bowel will be defined from duodenum (see above) to ileocecum. If small bowel and large bowel cannot be delineated with confidence, then the more generous contour should be utilized.

Large bowel will be defined from ileocecum to rectum (including sigmoid).

Rectum is to be defined from the peritoneal reflection cranially, typically extending 12-15 cm from anal verge to the valve of Houston, located approximately at level of S3. Caudal extent is at the junction with the anal canal, defined on axial CT at approximately level of bottom of ischial tuberosities.

Renal hilum will be contoured where renal vessels and renal pelvis are adjacent as they enter/exit the kidney.

Ureter is to be contoured from 10cm cranial to 10cm caudal to extent of PTV, and terminates at renal hilum and vesicoureteral junction, respectively.

Bile ducts are identified by portal vein from its juncture with the splenic vein to its right and left birfurcation in the liver as a surrogate.

Liver is entire liver minus GTV.

Kidneys will be defined in their entirety, but excluding the pelvis / collecting system.

Penile bulb is best delineated on MRI images, but can be visualized on CT if MRI unavailable. As defined by Wallner et al[6], it is to be contoured as the cranial portion of the corpus spongiosum, between the corpora cavernosal and beneath the genitourinary diaphgram.

Normal tissue constraints

The dose will be prescribed to the minimal isodose line that completely covers the GTV (or ITV if applicable) plus a 0-5 mm margin to create a planning target volume (PTV). In order to achieve normal tissue dose constraints, PTV margins may be utilized which may not encompass the entire target volume with setup uncertainty and anatomic motion; PTV margins may be utilized which are negative (i.e. PTV smaller than GTV volume) in order to achieve protocol-specified doses while respecting normal tissue tolerances; such PTV volumes will be termed 'nPTV'. All relevant adjacent normal structures including but not limited to the heart, esophagus, aorta, spinal cord, kidneys, rectum, bowel, liver, and stomach within 5 cm of the GTV will be identified for the purpose of limiting incidental radiation to these structures.

Dose heterogeneity within the PTV may be high, and within the paradigm of SBRT is considered acceptable without constraints. The dose to any tissue outside of the PTV should not exceed 5% of the prescription dose.

3.3.5 Treatment delivery technical factors

Treatment will be initiated within three weeks of the initial treatment planning simulation study. Treatment will be delivered with a minimal inter-fraction interval of 36 hours, and no greater than 84 hours between fractions.

Only photon (x-ray) beams with energies greater than or equal to 6MV are allowed. Tumors located within the lungs should be treated with energies of no greater than 10MV, except for specific beams where large soft tissue distances must be traversed to reach target. Dynamic conformal arcs and flattening-filter-free beams are acceptable. All dose calculations should

be performed with tissue heterogeneity corrections.

Image-guided therapy (IGRT) utilizing on-board cone-beam imaging is required for each fraction prior to delivery of treatment. Patients should be aligned to the visible target volume. In cases where soft tissue contrast is poor on CBCT imaging, fiducial markers should be utilized for more accurate setup.

3.4 Intervention Plan

3.4.1 Antiemetic Premedications and Supportive Care Medications

Antiemetic premedications should not be routinely administered prior to dosing of drugs. Symptomatic antiemetics may be administered at the Investigator's discretion. Palliative and supportive care for disease-related symptoms will be offered to all patients on this trial.

3.4.2 Bisphosphonates

The use of bisphosphonates (e.g., zoledronic acid) or denosumab is permitted if patient has been using them prior to the study for at least 1 month.

3.4.3 Dose Delay Criteria for Nivolumab and Ipilimumab

Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab and ipilimumab). All study drugs must be delayed until treatment can be resumed. Imaging studies and the collection of blood and tissue for correlative studies should continue as planned even if dosing is interrupted. Radiation treatment should continue if the treatment is unlikely to worsen adverse event.

Nivolumab and ipilimumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for AST, ALT, or total bilirubin:
  - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity
- Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay.

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication

During cycles 1 and 2, both nivolumab and ipilimumab must be delayed at the same time. Following the up to 4 administrations of the induction combination therapy with NIVO/IPI, Dose 1 of maintenance nivolumab will begin 3 weeks after the 4th dose of induction therapy. If the 4th dose of induction therapy has not been administered due to treatment delays or the discontinuation of combination therapy because of primarily ipilimumab related side effects such as colitis, high grade diarrhea or hepatitis before Day113, that dose/doses will be omitted and maintenance dosing will begin.

The schema is noted in Figure 3.4.2 below.

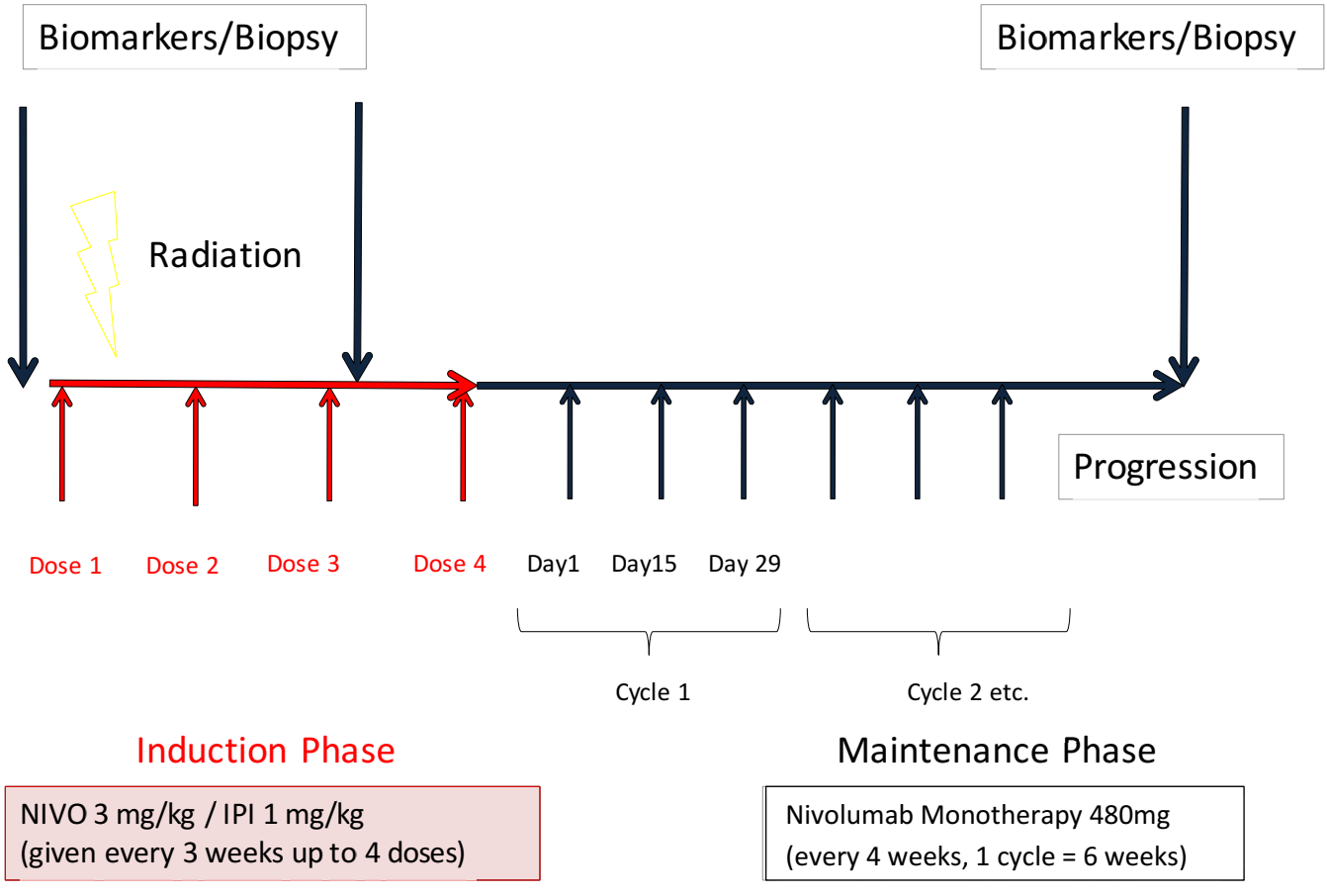

Figure 3.4.2 Dosing/Treatment Schema for nivolumab/ ipilimumab plus SBRT
* Cycle 1 of maintenance will begin 3 weeks after the 4th dose of induction therapy or after Day 113 if the 4th dose of induction therapy has not been administered due to treatment delays.

3.4.4 Dose Modifications for Nivolumab and Ipilimumab

Dose reductions or dose escalations of nivolumab or ipilimumab are not permitted.

3.4.5 Criteria to Resume Treatment on Nivolumab and Ipilimumab

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled timepoint per protocol. However, if the treatment is delayed past the next scheduled timepoint per protocol, the next scheduled timepoint will be delayed until dosing resumes. If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in discontinuation section.

Subjects may resume treatment with study drug when the AEs resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or AST/ALT or total bilirubin
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

3.4.6 Discontinuation Criteria for Nivolumab and Ipilimumab

Treatment with nivolumab and ipilimumab should be permanently discontinued for any of the following:

If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as to allow for prolonged steroid tapers to manage drug-related adverse events. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the overall PI (Dr. Hammers) must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.

Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments and

the collection of blood and tissue samples for correlative studies should continue as per protocol even if dosing is interrupted. Radiation treatment should continue if the treatment is unlikely to worsen the adverse event.

• Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the pre-treatment period or requires systemic treatment

• Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, and infusion reactions:

− Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation

• Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:

- Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
    - AST or ALT>8xULN
    - Total bilirubin > 5 x ULN
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

• Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events, which do not require discontinuation:

− Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis.

− Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab or ipilimumab dosing

3.4.7 Treatment of Nivolumab or Ipilimumab-Related Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, each is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.0) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For Grade 1 symptoms: (Mild reaction; Infusion interruption not indicated; intervention not indicated)**.** Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours).

Stop the nivolumab and ipilimumab infuse, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the CRF. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab or ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly

responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: (life-threatening; pressor or ventilatory support indicated). Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. **Nivolumab or Ipilimumab will be permanently discontinued.**

Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

3.5 Treatment Beyond Disease Progression

Accumulating evidence indicates that a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.

Subjects, regardless of study arm, will be permitted to continue treatment beyond initial investigator assessed progression as long as they meet the following criteria:

- Investigator-assessed clinical benefit
  and
- Subject is tolerating study drug.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

Subjects should discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions).

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological

lymph nodes, which must have an increase in short axis to at least 15 mm).

3.6 Treatment Compliance

Trained medical personnel will administer nivolumab and ipilimumab and dispense other study medication. Treatment compliance will be monitored by drug accountability, as well as by recording nivolumab and ipilimumab administration in the CRF.

In case the treatment has to be interrupted during an infusion, the medical personnel should evaluate the percentage of dose received by the patient and document it in the patient record. Any reason for non-compliance should also be documented.

3.7 Destruction and Return of Study Drug

3.7.1 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Investigator unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period. It is the investigator's 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

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disposal are kept.

3.7.2 Return of Study Drug

Study drug will not be returned to BMS. Study drug will be destroyed per local institutional policy.

3.8 Immunotherapy Adverse Event Management

Early recognition and intervention are recommended according to the management algorithms; and in addition include ophthalmologic evaluations for any visual symptoms in order to evaluate for nivolumab or ipilimumab related uveitis.

Because of the potential for clinically meaningful nivolumab or ipilimumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected **pulmonary toxicity, GI toxicity, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity, and renal toxicity**.

These adverse event management algorithms are included in the Appendix Toxicities.

3.9 Adverse events associated with Stereotactic Body Radiation Therapy (SBRT):

Common side effects (may occur in more than 20 % people receiving treatment; some may be serious): Fatigue, nausea, vomiting, skin reddening or sensitivity, mild pain, diarrhea, decreased appetite, lung scarring, temporary changes in blood work (blood counts or liver enzymes) without symptoms

Occasional side effects (may occur in from 4%- 20% people receiving treatment; some may be serious): Skin thickening or numbness, sores or ulcers near the cancer location, cough, shortness of breath, rib pain and/or rib fracture, abdominal pain, fever, irritation of the esophagus (swallowing tube); fracture or damage to the spine.

Rare side effects (may occur in 3 % or fewer of patients receiving treatment; may be serious): Irritation of the lining around the heart or the heart muscle; severe shortness of breath; irritation or damage to spinal cord or nerves; paralysis; damage to nerves in the chest or abdomen; damage to the esophagus, stomach, or intestines requiring hospitalization or surgery; irritation of the large blood vessels around the heart; coughing blood; irritation of the

voice box causing hoarseness or pain; jaundice; abdominal swelling; low blood counts; kidney damage; death.

There is also anticipated possible additive toxicities of irradiation during immunotherapy. Anticipated examples could include increased incidence of pneumonitis in irradiated lung fields and increased incidence of colitis if normal bowel is included in irradiated abdominal fields.

4 STUDY ASSESSMENTS AND PROCEDURES

4.1 Flow Chart/Time and Events Schedule

Procedure	Screening Visit	Notes
Eligibility Assessment		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed prior to treatment
Medical History	X	
Candidate for SBRT as assessed by Radiation Oncology	X	
Tumor Tissue	X	Patient must have lesion which is not radiated and accessible for core biopsies
Safety Assessment		
Physical Examination	X	
Vital Signs and Oxygen Saturation	X	Including BP, HR, & temperature. Obtain at the screening visit and within 72 hours prior to first dose
Physical Measurements (including Performance Status)	X	Height and weight and Karnofsky Performance Status
ECG	X	Within 28 days prior to treatment
Assessment of Signs and Symptoms	X	Within 28 days prior to treatment
Concomitant Medication Collection	X	Within 28 days prior to treatment
Laboratory Test	X	CBC w/differential, Chemistry panel including:

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		LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, albumin, Mg, Na, K, Cl, glucose, amylase, lipase, TSH, Free T4, Free T3, Hep B/C(HBV sAG, HCV antibody or HCV RNA), within 28 days prior to treatment. **Within 72 hrs prior to re-dosing** to include CBC w/ differential, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3),FSH(women under 62)
Pregnancy Test (WOCBP only)	X	Within 28 days prior to treatment. A serum or urine pregnancy testing is required **within 24 hrs** of study treatment then every 4 weeks. [more frequently if required by local standard]. After discontinuation from nivolumab these should be repeated at approximately 30 days and approximately 70 days [or more frequently if required by local standard].
Efficacy Assessment		
Screening/Baseline Tumor Assessments	X	CT with contrast of the chest, abdomen, pelvis and all known sites of disease (or CT Chest w/o contrast and MRI of abdomen with or without contrast if reduced GFR or allergy). MRI (preferred) or CT scan of the Brain if known history of brain involvement.
Exploratory Biomarker Testing		
Research Biopsy*	X	Within 28 days prior to treatment (optional) and during week 7 on therapy (optional)
Blood Sample	X	Within 28 days prior to treatment and during week 7 on therapy

*Comment on Biopsies: Participating sites should follow best clinical/institutional practices to minimize the harm from tumor biopsies. We recommend (but not mandate) the periprocedural use of tranexamic acid to potentially decrease the risk of bleeding. We recommend tranexamic acid 650 mg po bid for 6 doses, first dose 2 hours prior to biopsy.

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4.2 Initial Registration

Eligible patients will be registered on study centrally at UT Southwestern Medical by the Lead Site Study Coordinator.

To register a patient, the following documents must be completed and emailed at Allison.Beaver@utsouthwestern.edu M—F 8am to 5pm CST.

- Signed/dated patient consent form
- Eligibility checklist
- Copies of pre hormone therapy/chemotherapy or radiation therapy
- Screening labs(including pregnancy test)/vital signs and EKG
- CT reports
- Other materials may also be sent if considered pertinent for confirming patient eligibility, e.g. CT/MRI of C/A/P

The Lead Center will review the documents to confirm eligibility. To complete the registration process the Lead Center will:

- Assign a patient study number
- Patients found to be ineligible for participation after being consented will be considered screen failures, and documented as such in the Screening and Enrollment Log
- New subjects will receive a number beginning with 001 upon study consent such that the first subject consented is numbered 001, the second subject consented receives the number 002, etc.
- Upon confirmation of eligibility and enrollment as per the afore-mentioned instructions, the subject will be assigned a secondary number in the order of enrollment. For example, subject 001 will become 001-01 upon enrollment. If subject 002 screen fails, and subject 003 is the next subject enrolled, subject 003 will become 003-02 and so-on.

- For UTSW, each newly consented subject should be numbered using the schema provided above. Upon registration, the registrar will assign the additional registration/randomization code according to the numbering schema outlined above, which should then be entered as the patient study id in Velos upon updating the status to enrolled.

- The numbering schema should clearly identify the site number; the sequential number of the subject enrolled as well as the status of the subjects enrolled so that the number of subjects consented versus the number of subjects actually enrolled may be easily identified.

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4.3 Study Calendar

The Investigator may perform more frequent examinations than shown in Table below if clinically indicated. Data from such additional examinations are also to be reported in the eCRF.

* baseline visit and W1D1 can be combined	Screening	Baseline Visit*	Induction Phase Cycle [a] 1 and 2				Maintenance Phase Cycle [a] 3 and every subsequent cycle (8 weeks) (up to 2 years)			30 day Follow-up[r] (X1)	Follow-up Visits [s] (X2 and X3)	Survival Follow-Up[t]
	D -28 to 0	D-3 to D 1	W1D1* (C1W1)	W4D1 (C1W4)	W7D1 (C2W1)	W10D1 (C2W4)	W1D1	W5D1				
Informed consent	X											
Inclusion/Exclusion Criteria	X [p]											
Archival Tumor Tissue[b]	X											
Nivolumab [c]			X	X	X	X	X	X				
Ipilimumab [d]			X	X	X	X						
SBRT [e]			X [e]									
Medical history	X	X										
Physical assessment	X	X	X	X	X	X	X	X		X	X	
Vital signs [f]	X	X	X	X	X	X	X	X		X	X	
Height	X											
Performance status [g]	X	X	X	X	X	X	X	X		X	X	
Pulse Oximetry [h]			X	X	X	X	X	X				
EKG	X											
Adverse Events Assessment			X	X	X	X	X	X		X	X	
Concomitant Medications	X	X	X	X	X	X	X	X		X	X	
Disease Assessment [i]	X	every 6 weeks (± 1 wk) for the first 13 months from treatment and every 12 weeks (± 1 wk) thereafter, until disease progression is documented or treatment is discontinued (whichever occurs later)										
CBC with diff [J]	X	X [q]	X	X	X	X	X	X		X	X	
Comp Panel [K]	X	X [q]	X	X	X	X	X	X		X	X	

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TSH, free T4, free T3 [u]	X	X [q]	X	X	X	X	X	X		X		
Pregnancy test [l]	X	X	X	X	X	X	X	X		X	X	
	Screening	**Baseline Visit**	**Induction Phase Cycle [a] 1 and 2**				**Maintenance Phase Cycle[a] 3 and every subsequent cycle (8 weeks) (up to 2 years)**			**30 day Follow-up [r] (X1)**	**Follow-up Visits [s] (X2 and X3)**	**Survival Follow-Up [t]**
	D-28 to 0	D-3 to D1	W1D1 (C1W1)	W4D1 (C1W4)	W7D1 (C2W1)	W10D1 (C2W4)	W1D1	W5D1				
Hep B or Hep C [m]	X											
Research biopsy [n]	X				X					X		
Blood sample [o]	X				X					X		
Survival Follow-Up [t]												X

a. 1 cycle = 6 weeks
b. Archival Formalin-fixed paraffin-embedded (FFPE) tumor tissue must be available for correlative studies (Note: Fine Needle Aspiration [FNA] and bone metastases samples are not acceptable for submission)
c. Nivolumab is to be administered as an approximately 60-minute IV infusion. Cycle 1 of maintenance will begin 3 weeks after the 4th dose of induction therapy or after Day 113 if the 4th dose of induction therapy has not been administered due to treatment delays or the discontinuation of combination therapy because of primarily ipilimumab related side effects
d. Ipilimumab is to be administered as an approximately 30-minute IV infusion. When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first.
e. SBRT (5 fractions of 10 Gy) is to be delivered anytime between Day 1 of Week 1 (Cycle 1) and Day 1 of Week 4 (Cycle 1) of the nivolumab and ipilimumab combination dosing (within the first 3 weeks after the initiation of nivolumab and ipilimumab). SBRT is preferred to be delivered in the first 2 weeks.
f. Temp, Pulse, B.P., Weight
g. Karnofsky Performance Status
h. Oxygen saturation by pulse oximetry should be obtained prior to dosing (at rest and with exertion) Also perform if any new or worsening pulmonary symptoms present
i. CT with contrast of the chest, abdomen, pelvis and all known sites of disease (or CT Chest w/o contrast and MRI of abdomen with or without contrast if reduced GFR or allergy). MRI (preferred) or CT scan of the Brain if known history of brain involvement (all known sites of disease should be assessed at baseline)
j. CBC w/differential and platelets
k. Full Chemistry Panel including: LDH, AST, ALT, ALP, T.Bili, BUN, creatinine, Ca+, Mg+, Na-, K+, HCO3-, Cl-, glucose, albumin, T.Protein, amylase, lipase
l. WOCBP only (serum or urine) at screening and within 24 hours of dosing
m. HepB sAg & HCV Ab or HCV RNA
n. Multiple tumor biopsies – pre-treatment (optional), at week 7 of treatment (optional) and at the time of progression (optional)
o. Blood samples will be collected for research at pre-treatment, at week 7 of treatment and at the time of progression
p. Prior to entry into the protocol, all patients need to be discussed with Dr. Danny Song (JHU), Dr. Raquib Hannan (UTSW) or co-investigator Radiation Oncologist from the Radiation Therapy Department to determine eligibility/feasibility for SBRT. The cancer lesion(s) to be radiated should be determined by the Radiation Oncologist in collaboration with the Principal Investigator/Medical Oncologist
q. Cycle 1 Day 1 labs do not need to be performed if done ≤ 72 hours of dosing as part of the Day -3 to +1 labs
r. Perform 30 days ± 1week from last dose of study drug

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s. X2 will take place 8 weeks (+/- 1 week) after last dose of nivolumab was administered and visit X3 will take place 15 weeks (+/- 1 week) after last dose of nivolumab was administered. If additional X follow-up visits are required due to ongoing study drug- related toxicity, they should take place every 8 weeks (+/- 1 week) until study drug-related toxicity has resolved, stabilized or been deemed irreversible.
t. Study subjects will be contacted every 3 months for survival data. Other potential data such as the subjects' follow-up treatment or care may be requested during these contacts. The contacts can be via telephone or correspond with disease assessment visits or other scheduled visits
u. Free T3 & Free T4 if TSH not within normal limits

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4.4 Safety Assessments / Considerations

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include weight, height, Karnofsky Performance Status, BP, HR, and temperature. Baseline signs and symptoms are those that are assessed within 28 days prior to treatment. Concomitant medications will be collected from within 28 days prior to treatment.

Baseline local laboratory assessments should be done within 28 days prior to treatment to include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, albumin, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH, Free T4, Free T3, and Hep B and C testing (HBV sAg, HCV Ab or HCV RNA).

Pregnancy testing for WOCBP must be performed within 24 hours prior to the initial administration of study drug at baseline and then every 4 weeks during the treatment period and at the safety follow-up visits. After discontinuation from nivolumab these should be repeated at approximately 30 days and approximately 70 days [or more frequently if required by local standard]. If, following initiation of the investigational product, it is subsequently discovered that a study **subject is pregnant or may have been pregnant** at the time of investigational product exposure, including during at least 6 half lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). The investigator must immediately notify Worldwide Safety @BMS of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form [provided upon request from BMS].Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase. During the safety follow-up phase (6 weeks), toxicity assessments should be done. Once subjects reach the survival follow-up phase either in person or documented telephone calls to assess the

subject's status are acceptable. Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.0.

On-study weight and Karnofsky Performance status and vital signs should be assessed at each on-study visit. Vital signs should also be taken as per institutional standard of care prior to, during and after dosing. Oxygen saturation by pulse oximetry at rest and after exertion should be assessed at each on-study visit prior to dosing. The start and stop times of nivolumab and ipilimumab infusions should be documented. Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

On study local laboratory assessments should be done within 72 hours of dosing to include; CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3 on Day 1 of Weeks 1 and 4 for Cycles 1 and 2 and on Day 1 of Weeks 1 and 5 starting from Cycle 3. Additional measures including non-study required laboratory tests should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug inducted liver enzyme elevations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline or are deemed irreversible. In addition, LFTs should also be assessed prior to the second dose of each cycle. The results of these labs should be reviewed prior to dosing. Amylase, Lipase and thyroid tests must be drawn, but do not need to be resulted prior to infusion unless patient is symptomatic. The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

Oxygen saturation by pulse oximetry should be obtained prior to each dosing and at any time a subject has any new or worsening respiratory symptoms. A reading at rest

and on exertion should be obtained at each time point. The extent of the exertion should be based on the judgment of the investigator, but should remain consistent for each individual subject throughout the study. If the patient's status changes, the investigator can alter the extent of exertion based on their medical judgment. If a subject shows changes on pulse oximetry or other pulmonary related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary adverse events, the patient subject should be immediately evaluated to rule out **pulmonary toxicity.** An algorithm for the management of suspected pulmonary toxicity can be found in the appendix of the nivolumab Investigator's Brochure.
Some of the previously referred to assessments may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

Overdose: An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.
Other Safety Considerations: Any significant worsening noted during interim or final physical examinations, electrocardiograms, x rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

4.5 Imaging Assessment for the Study

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

4.5.1 CT/MRI

Both, contrast-enhanced Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) scans acquired on dedicated CT/MRI equipment are adequate imaging modalities for this study.
CT scans should be acquired with 5 mm slices with no intervening gap (contiguous). Subjects who cannot receive IV contrast at the start of study should be imaged by MRI

of abdomen/pelvis with IV contrast and CT of chest without contrast. MRIs should be acquired with 5 mm slices with no intervening gap (contiguous). Subsequent assessments should include chest, abdomen, and pelvis, and all known sites of disease and should use the same imaging method as was used at baseline. Patients initially imaged with CT of chest, abdomen, and pelvis with IV contrast who can no longer receive contrast can be monitored by CT of chest, abdomen, and pelvis without IV contrast. Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time.

4.5.2 MRI/CT Brain

MRI (preferred) or CT of brain (with contrast) is required at screening only when metastatic disease to the brain is suspected or known. MRI or CT brain scans during on-study treatment and follow up periods are required only if clinically indicated for new signs and symptoms that suggest CNS involvement or progression.

4.6 Efficacy Assessments

4.6.1 Baseline Assessments

Baseline assessments should be performed within 28 days prior to the initiation of study utilizing CT or MRI. In addition to chest, abdomen, pelvis, and brain, all known sites of disease should be assessed at baseline.

4.6.2 Response Criteria

Subjects will be evaluated for tumor response beginning *6 weeks weeks (± 1 wk) from treatment and continuing every 6 weeks (± 1 wk) for the first 13 months from treatment and every 12 weeks (± 1 wk) thereafter,* until disease progression is documented or treatment is discontinued (whichever occurs later).

4.6.3 Therapeutic Response

Tumor assessments for ongoing study treatment decisions will be completed by the investigator using RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria. Traditional measures of response reflect when a treatment is working and measures of progression indicate when a drug should be stopped.

Measurable disease

Following RECIST 1.1, tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Nonmeasurable disease

Following RECIST 1.1, all other lesions (or sites of disease) will be considered nonmeasurable disease. This includes small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan) and any of the following:

• bone lesions
• ascites
• pleural or pericardial effusion
• lymphangitis cutis or pulmonis
• abdominal masses that are not confirmed and followed by imaging techniques
• cystic lesions
• lesions occurring within a previously irradiated area unless they are documented as new lesions since the completion of radiation therapy

4.6.4 Evaluation of Target lesions

Following RECIST 1.1, progression in a nodal or visceral site (ie, liver and lung) is sufficient to document disease progression. The presence or absence of nodal and visceral disease before and after treatment should be recorded separately.

All measurable lesions (up to a maximum of 5 lesions per organ and 10 lesions in total) will be identified as target lesions to be measured and recorded at baseline. The target lesions should be representative of all involved organs. Target lesions will be selected

on the basis of size (ie, the largest area) and suitability for accurate, repeated measurements (either by imaging techniques or clinically). The sum of the longest diameter (LD) of all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as a reference by which to characterize the objective tumor response.

Because small lymph nodes are difficult to measure accurately and may not be malignant, the greatest diameter of a lymph node must measure at least 1.5 cm by spiral CT to be considered a target lesions.

Table 7. RECIST response criteria for target lesions

Response	Evaluation of Soft-Tissue Lesions
Complete response (CR)	The disappearance of clinical and radiological evidence of all target lesions and normalization of tumor marker levels
Partial response (PR)	A decrease from baseline ≥ 30% in the sum of the LD of all target lesions
Progressive disease (PD)	An increase ≥ 20% in the sum of the LD of all target lesions based on the smallest sum LD since treatment started or the appearance of one or more new lesions or the appearance of new lesions
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD based on the smallest sum LD recorded since treatment started

4.6.5 Special Notes on the Assessment of Target Lesions

Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very

small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

4.6.6 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Table 8. RECIST response criteria for non-target lesions

Response	**Evaluation of Soft-Tissue Lesions**
Complete response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10mm short axis)
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive disease (PD)	Unequivocal progression (see comments below) of existing non- target lesions. (Note: the appearance of one or more new lesions is also considered progression)

4.6.7. Special Notes on Assessment of Progression of Non-Target Disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a

change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

4.6.8 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

4.6.9 Evaluating best overall response

The best overall response is the best response recorded from the start of treatment until either disease progression or recurrence. The investigator's determination of best overall response will be based both on response criteria and on confirmation criteria. To be assigned a status of partial response or complete response, changes in tumor measurements must be confirmed by repeat assessment performed at least 6 weeks after the criteria for response are first met. To confirm stable disease, follow-up measurements must meet SD criteria at a minimum interval of 6 weeks after SD was first documented. Table 9 can be used as an assessment tool.

Table 9. Assessing Overall Response

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Patients with global deterioration of health status who require treatment to be discontinued without objective evidence of disease progression should be classified as having symptomatic deterioration. Every effort should be made to document their objective progression, even after discontinuing treatment.

Patients who do not have tumor response assessment due to rapid progression or toxicity will be considered non-responders, will be included in the denominator for the response rate, and will be classified into one of the categories listed below:

- death attributed to disease progression
- early discontinuation attributed to disease progression
- death attributed to drug toxicity
- early discontinuation attributed to drug toxicity

***Note**: If a patient receives subsequent therapy before tumor progression is documented, the reason for changing therapy must be reported. Reasons include clinical progression, drug toxicity, or secondary therapy for maintaining tumor response.*

4.6.10 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive repeat assessments that should be performed at least at 6 weeks after the criteria for response are first met. For this study, the next scheduled tumor assessment can meet this requirement.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive disease.

4.7 Correlatives Studies

A variety of factors that may impact the immunomodulatory properties and efficacy of nivolumab plus ipilimumab in combination with SBRT will be investigated in tumor tissue and in peripheral blood specimens taken from all subjects prior to and/or during treatment and/or progression as outlined in Table 10.

Table 10. Correlative studies

Analysis	Sample	Assay	Time Points
Tissue staining (PDL1, CD8 etc)	Archival and FFPE biopsy tissue	IHC/IF	Archival tissue, Baseline Biopsy, Week 7 Biopsy, Biopsy at time of progression
Soluble Factors/ Cytokines	Serum	Luminex xMAP, Immunology Core	Baseline Blood sample, Week 7 Blood sample, Blood sample at time of progression
Immune Gene Expression Mutational Analysis	FFPE biopsy tissue RNA Later	Nanostring nCounter, RNAseq Whole Exome seq	Baseline Biopsy, Week 7 Biopsy, Biopsy at time of progression
T-Cell receptor sequencing	Frozen tumor biopsy, PBMC	Adaptive Bio, Immunoseq	Baseline Biopsy/Blood, Week 7 Biopsy/Blood, Biopsy/Blood at time of progression
ELISPOT Assay	Frozen PBMC	Immunology Core	Baseline Biopsy, Week 7 Biopsy, Biopsy at time of progression
Humoral Immune Response	Plasma	Protoarray (Life Tech), Microarray Core UTSW Immunology Core	Baseline Blood sample, Blood sample at Week 7 Biopsy, Blood sample at time of progression
Cell Culture	Biopsy material	Hammers Lab	Baseline Biopsy

Optional research biopsy at week 7 Optional Tumor Biopsy:

A week 7 optional tumor biopsy will removal a small piece of your tumor for examination and correlative studies. The biopsy can usually be done with local anesthesia with or without sedation. Some side effects that patients may experience by havingthe biopsy performed may include pain, bruising, bleeding, redness, low blood pressure, swelling, infection at the site of the biopsy, and rarely, death. Additional risks my occur and would be explained by the doctors who conduct the biopsies. At the time of biopsy, a CT scan may be done to determine where the biopsy will be done (CT-guided biopsy) or the biopsy may be done via Ultra sound guidance.

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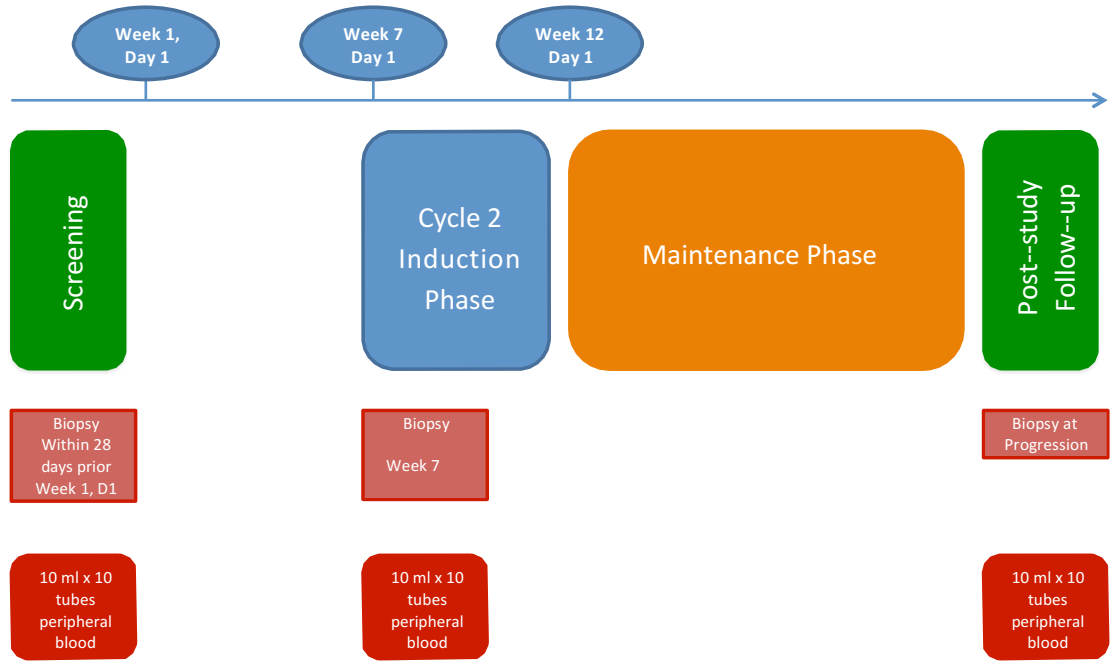
Flow diagram samples collection



4.7.1 Samples Collection and Banking

Please refer to laboratory manual.

5 ADVERSE EVENTS

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the

changes observed; or

- death.

5.1 Definition and Grade

Adverse Events will be reported as indicated by the appropriate following table (see below). An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam, imaging finding or clinically significant laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Acute Adverse Events

Adverse events occurring in the time period from the signing of the informed consent through 100 days post treatment will be considered acute adverse events.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE version 4) and version number specified in the protocol. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

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Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization [1,2] or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring >24 hour inpatient admission to the hospital would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

[1]Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery, that prolong the existing hospitalization, those events should be evaluated and/or reported as SAEs.

[2] NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should only be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example: a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

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5.2 Unanticipated Problems:

The phase "unanticipated problems involving risks to subjects or others " is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56. 108(b)(1) and 21 CFR 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- ***AND***
- Related or possibly related to participation in the research(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);
- ***AND***
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

5.3 Reporting SAEs and UPIRSOs to the Simmons Comprehensive Cancer Center(SCCC) Data Safety Monitoring Committee (DSMC)

All SAE/UPIRSOs at all sites, which occur in research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. All SAEs/UPIRSOs occurring during the protocol-specified monitoring period should be submitted to the SCCC DSMC within 5 business days of the PI or delegated study team members awareness of the event(s). In addition, for

participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events. .

The UTSW study team is responsible for submitting SAEs/UPIRSOs to the SCCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB Reportable Event report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE/UPIRSO documentation that is available are also submitted to the DSMC Chair who determines if further action is required

5.3.1 Reporting Unanticipated problems Involving Risks to Subjects or Others(UPIRSOs)

UT Southwestern reportable event guidance applies to all research conducted by or on behalf of UTSouthwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on non-UT Southwestern IRB.

According to UTSW HRPP/IRB policy, UPIRSOs are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure, protocol, or informed consent document),AND
2. Probably or definitely related to participation in the research, AND
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

For purposes of this policy, UPIRSOs include unanticipated adverse device effects (UADEs) and death or serious injury related to a humanitarian use device (HUD).

UPIRSOs must be promptly reported to the UTSW IRB within 5 working days of PI awareness.

For research relying on a non-UT Southwestern IRB (external, central, or single IRB):
Investigators relying on an external IRB who are conducting research on behalf of UT Southwestern or its affiliates are responsible for submitting LOCAL UPIRSOs to the UT Southwestern IRB within 5 working days of PI awareness. Investigators much report to their relying IRB according to the relying IRBs policy. In addition, the external IRB's responses or determinations are these local events must be submitted to the UT Southwestern IRB within 10 working days of receipt.

Events not meeting UPIRSO criteria:
Events that do NOT meet UPIRSO criteria should be tracked, evaluated, summarized and

submitted to the UTSW HRPP/IRB at continuing review.
For more information on UTSW HRPP/IRB reportable event policy, see https://www.utsouthwestern.edu/research/research-administration/irb/assets/policies-combines.pdf.

4.

5.3.2 SAE

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Comprehensive Cancer Center, the DOT Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all SAEs/UPIRSOs upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Telephone reports to: PI: Hans Joerg Hammers, MD Email: hans.hammers@utsouthwestern.edu Lead Site Protocol Coordinator: Allison Beaver, RN Email: Allison.beaver@utsouthwestern.edu Phone: 214-645-8787
Written reports to: PI: Hans Joerg Hammers, MD Email: hans.hammers@utsouthwestern.edu Lead Site Protocol Coordinator: Allison Beaver, RN Email: Allison.beaver@utsouthwestern.edu Fax: 214-645-8767 UTSW SCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu Fax: 214-648-5949 or deliver to BLB.306 UTSW Institutional Review Board (IRB) Submit via eIRB with a copy of the final sponsor report as attached supporting documentation

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5.4 Steps to Determine If an Adverse Event Requires Expedited Reporting to the SCC DSMC and/or HRPP

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2: Grade the adverse event using the NCI CTCAE v4.

Step 3: Determine whether the adverse event is related to the protocol therapy

Attribution categories are 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 may NOT be related to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 100days of the last dose of protocol treatment. Any event that occurs more than100days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure
- the study agent(s)/therapies background and associated known toxicities section of this protocol

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5.5 Other Events of Special Interest that require Expedited Reporting

- Potential drug induced liver injury (DILI) is also considered an important medical event.
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.
- Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

5.6 Nonserious Adverse Event Collection and Reporting

A nonserious adverse event is an AE not classified as serious. The collection of nonserious AE information should begin at initiation of study drug. All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

5.7 Handling of Expedited Safety Reports

In accordance with local regulations, BMS and the IND Sponsor will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). Investigator notification of these events will be in the form of an expedited safety report (ESR).

- Other important findings which may be reported by the as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant

safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
- In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by the Principal Investigator to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

5.8 Reporting:

All AEs (both expected and unexpected) will be captured on the appropriate study-specific CRFs.

5.9 Nonserious Adverse Event

- Nonserious Adverse Events are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g. IND US trial] as part of an annual reporting requirement.
- The collection of nonserious AE information should begin at initiation of study drug. All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

5.10 Laboratory Test Abnormalities

- All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such.
- The following laboratory abnormalities should be documented and reported appropriately:
- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

5.11 Pregnancy

- Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

5.12 Overdose

- An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

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5.13 Other Safety Considerations

- Any significant worsening noted during interim or final physical examinations, electrocardiograms, x rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

5.14 Seven Calendar-Day Telephone or Fax Report:

The IND Sponsor is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the investigational agent. Such reports are to be telephoned or faxed (214-645-8766) to the FDA within seven calendar days of first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

5.15 15 Calendar-Day Written Report:

The IND Sponsor is required to notify the FDA of any SAE that is unexpected and related to the investigational agent in a written IND Safety Report.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous related reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA within 15 calendar days of first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

SAEs should be reported on MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/.

MedWatch SAE forms should be sent to the FDA at:
MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

All SAEs should simultaneously be faxed or e-mailed to BMS at:
Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 100 days of discontinuation of dosing.

All SAEs must be collected that occur during the screening period. If applicable, SAEs must be collected that relate to any protocol-specified procedure (eg, a follow-up skin biopsy). The investigator should report any SAE that occurs after these time periods that is believed to be related to study drug or protocol-specified procedure.
SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on BMS or an approved form; pregnancies must be recorded on a Pregnancy Surveillance Form.
SAE Email Address: Worldwide.Safety@BMS.com
SAE Facsimile Number: 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours

to the BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

The Sponsor/Investigator will ensure that all SAEs in the clinical database are reported to BMS and any applicable health authority during the conduct of the study. This reconciliation will occur at least quarterly and be initiated by the sponsor/investigator.

Sponsor/investigator will request a reconciliation report from: aepbusinessprocess@bms.com. During reconciliation, any events found to not be reported previously to BMS must be sent to Worldwide.Safety@BMS.com.

6 ETHICAL CONSIDERATIONS

6.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to Principal Investigator (Dr. Hans Hammers). A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

6.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The principal investigator should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The principal investigator should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

6.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

The informed consent form will include all elements required by Registration of Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP) and applicable regulatory requirements and will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1. Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2. Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3. Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.

4. Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5. If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6. Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that investigators and regulatory authorities have direct access to subject records. The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

6.4 Multicenter Guidelines

The Protocol Chair

The Protocol Chair, Hans-Joerg Hammers, MD PhD, is responsible for performing the following Tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments
- Assuring that all participating institutions are using the current IRB approved version of the protocol
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study
- Reviewing and ensuring reporting of Serious Adverse Events (SAEs)

from all sites

- Reviewing all study data from all sites

6.5 Coordinating Center Responsibilities (UTSW)

Coordinating Centers must:

- Verify that each participating institution has a Federal Wide Assurance (FWA) number.
- Confirm that IRB approval has been obtained at each participating site prior to their first patient registration
- Maintain copies of IRB approvals from each site
- Implement central patient registration
- Prepare all submitted data for review by the Protocol Chair (Hans-Joerg Hammers, MD PhD
- Establish procedures for documentation, reporting, and submitting of adverse events to the Protocol Chair (Hans-Joerg Hammers, MD PhD) and all applicable parties
- Facilitate audits by securing selected source documents and research records from participating sites for audit, or by conducting audits at participating sites.

6.6 Participating Sites Responsibilities

Participating sites are responsible for performing the following tasks:

6.6.1 Follow the protocol as written and conduct the study within the guidelines of Good Clinical Practice

6.6.2 Required Documentation (for multi-site studies)

Before the study can be initiated at any site, the following documentation must be provided to the Department of Urology {Research Office}.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list or Federal wide Assurance letter
- 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 {institution} holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

7 Data Management, Monitoring/Auditing and Reporting Requirements

REDCap is the UTSW SCC institutional choice for the electronic data capture of case report forms for SCC Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with Simmons Cancer Center requirements as appropriate for the projectIn order to facilitate remote source to case report form verification, the Simmons Comprehensive Cancer Center study team will require other institutions participating in this trial as sub-sites to enter data into the selected EDC system and upload selected de-identified source materials when instructed

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the DOT, and/or the CRO Multi-Center IIT Monitor. This review includes but is not limited to accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

For further information, refer to the UTSW SCCC IIT Management manual.

Toxicity reviews will be performed after the first 6 patients have been enrolled and then on a quarterly basis These reviews will be documented in the form of short summaries after investigator discussions. The principle investigators of all accruing

sites are required to participate.The UTSW Simmons Cancer Center (SCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and unanticipated problems in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

8 STUDY MANAGEMENT

8.1 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

8.2 Emergency Exceptions(also called single-subject exceptions or single-subject waivers)

These include any departure from IRB-approved research that is *not due to an emergency* and is:

- intentional on part of the investigator; or
- in the investigator's control; or
- not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria)

➢ **Reporting requirement**: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation.

Emergency Deviations: include any departure from IRB-approved research that is necessary to:

- avoid immediate apparent harm, or
- protect the life or physical well-being of subjects or others

Reporting requirement: Emergency deviations must be promptly reported to the IRB within (5) working days of the occurrence.

8.3 Major Deviations/ (also called violations): include any departure from IRB-approved research that:

- Harmed or placed subjects(s) or others at risk of harm (e., did or has the potential to negatively affect the safety, rights or welfare of subjects or others), or
- Affect data quality (e.g., the completeness, accuracy, reliability, o validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

➢ **Reporting requirement**: Major deviations must be promptly reported to the IRB within 5 working days of PI awareness.

8.3.1 Minor Deviations: include any departure from the IRB approved research that:

- Did not harm or place subjects(s) or others at risk of harm (i.e., did not or did not have the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Did not affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

➢ **Reporting requirement**: Major deviations must be promptly reported to the IRB within 5 working days of PI awareness.

- Harmed or placed subject(s) or Others at risk of harm (i.e., did or has the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

➢ **Reporting requirement**: Major deviations must be promptly reported to
the IRB within 5 working days of PI awareness.

8.4 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

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8.5 Case Report Form Submission

Data required by the study will be collected in Case Report Forms provided by the Coordinating Center (SKCCC). The participating site will be required to complete a paper Eligibility Checklist case report form (CRF) at the time of patient registration. All other data will be collected on the electronic case report forms (eCRFs) in CRMS. Site staff access to CRMS will be initiated at the time of the site activation.

8.5.1 Case Report Forms

Case report forms (e-CRF) will be generated by Staff at the Lead Site Coordinating Center at UTSW for the collection of all study data. Investigators will be responsible for ensuring that the CRFs are kept up-to-date.

8.5.2 Case Report Form Completion

The paper Eligibility Checklist CRF must be completed using black ink. Any errors must be crossed out so that the original entry is still visible, the correction clearly indicated and then initialed and dated by the individual making the correction.

eCRFs(REDCAP) will be completed within 2 weeks of the patient coming to the clinic and all relevant supporting documentation such as scans, progress notes, nursing notes, blood work, pathology reports, etc., will be submitted to the Coordinating Center (UTSW) via email at Allison.Beaver@utsouthwestern.edu to the Lead Center Program Coordinator, Allison Beaver. All patient names or other identifying information will be removed prior to being sent to the Coordinating Center (UTSW) or non- redacted source documents can be sent via a password ¬-protected/ secured document transfer based on each institution's guidelines.

Authorized representatives of the Coordinating Center (UTSW) may be performing audits or inspections, including source data verification. The purpose of these audits or inspections is to systematically and independently examine all trial-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), and any applicable regulatory requirements.

9 Statistical Considerations

9.1 Study Design

This is a multi-institution, open-label, single-arm Phase II study to determine the safety and efficacy of SBRT followed by nivolumab in combination with ipilimumab in patients with metastatic RCC. The primary endpoints of safety evaluated by the level of G3/4 treatment related adverse events and the need for corticosteroids in this patient population and ORR assessed by RECIST criteria. Secondary endpoints include TTP, DOR, PFS, OS and local control of irradiated lesion. Simon's minimax two-stage design will be used to allow for early termination of the study if addition of SBRT to nivolumab in combination with ipilumumab is unlikely to be promising. A safety run-in phase will be included in the first 6 patients, and safety will be monitored continuously after this safety run-in phase using a Bayesian posterior probability approach.

9.2 Safety Run-in Phase

There is no previous experience with SBRT used concurrently with nivolumab plus ipilimumab in this study population. Therefore, to ensure that the combination is safe, the first six patients enrolled will be treated with a combination regimen consisting in nivolumab 3 mg/kg IV combined with ipilimumab 1 mg/kg IV and SBRT within 3 weeks after the initiation of this combination regimen. Safety will be evaluated using standard safety assessments every 21 days for 4 cycles and then every 2 weeks. If 4 out of the first 6 patients experience Grade 3/4 toxicity during the safety run-in observation period (defined as the first 4-cycles, 12 weeks), enrollment will cease and the study will be halted until further safety analysis of the combination regimen can be performed. If less than 4 out of the first 6 patients experience Grade 3/4 toxicities or require steroids, we will proceed with additional accrual with this regimen to complete a total of 15 patients for Stage 1 interim analysis.

9.3 Justification for the Sample Size

The point estimate of the ORR with nivolumab in combination with ipilumumab in this patient population is 40%, based on the Phase I presented at ASCO meeting which is chosen as the reference rate (P0) in the study proposed. The response rate where the regimen would be considered promising to pursue further is 70% (P1). In the first stage,

responses will be evaluated on the first 15 subjects treated. If 6 or fewer responses are observed after 6-18 weeks of follow-up, the study will be terminated for futility. Otherwise, 10 additional subjects will be accrued to target a total of 25 treated subjects. During the evaluation of response in the first stage, we will continue the recruitment and treatment of subjects. This design has at least a 90% chance (power) of concluding the combination therapy is effective when the true response rate is 70% and a 5% chance (Type I error) of concluding the treatment is effective when the true response rate is 40% or less. The probability of stopping early is 61% if the true response rate is 40% or less and 1.5% if the true response rate is 70%. The null hypothesis will be rejected and the regimen will be declared a success if at the end of the study 17 or more responses are observed in 25 treated subjects. The anticipated accrual rate for this group of patients is expected to be 2 patients per month.

Early Stopping Guidelines for Safety: The safety profile of the combination of SBRT with dual immune checkpoint inhibition using nivolumab and ipilimumab is not yet established, and therefore we will conduct continuous toxicity monitoring after safety run-in to ensure this combination is safe. If the risk of Grade 3/4 adverse events convincingly exceeds 50%, a threshold we are comfortable given the potential benefit of the regimen as well as our experience in managing the side effects in this patient population, we will temporarily halt the study and carefully review the available data at that point in order to suggest potential modification of the combination regimen. Specifically, a Bayesian toxicity monitoring rule will suggest suspending enrollment if the posterior probability of risk being larger than 0.50 is 75% or higher. The prior for this monitoring rule is beta (1, 2), representing the risk of DLT has mean of 33% and there is 90% probability that this risk is between 2.5% and 78%. The stopping rules for safety and the operating characteristics based on 5000 simulations are as below.

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No. patients experiencing G3/4 AE/steroid needs	6	7	8	9	10	11	12	13	14	15
Out of	7-8	9-10	11-12	13-14	15-16	17	18-19	20-21	22-23	24-25

True risk of AE	Prob. declaring regimen too toxic	Avg. sample size
0.30	2.1%	24.7
0.40	12.8%	23.3
0.50	38.5%	20.1
0.60	71.3%	15.6
0.65	85.3%	13.2
0.70	94.6%	10.9

9.4 Statistical Analyses of Primary Endpoint

Safety analyses will be performed in all treated subjects. Adverse events will be tabulated and presented with frequencies and percentages using NCI CTCAE version 4.0. Safety population consists of all subjects who receive at least one does of study medication. The ORR will be estimated as the proportion of subjects who achieve a response (CR/PR) assessed by RECIST. The corresponding two-sided 95% exact confidence interval will be calculated assuming a binomial distribution. The efficacy evaluable population includes all subjects who receive at least one dose of study drug, have an adequate baseline disease assessment and at least one post-baseline response assessment.

9.5 Statistical Analyses of Secondary Endpoints

Clinical Endpoints: Time-to-event outcomes (e.g., TTP, DOR, PFS, OS, local control of irradiated lesion) will be described using the Kaplan-Meier method. Median values will also be estimated with 95% confidence intervals.

Exploratory Correlative studies: Optional biopsies will be performed in all subjects at baseline (within 28 days prior to combination therapy) and during week 7 on therapy. Immune related biomarkers at baseline and post-therapy will be summarized with descriptive statistics and graphically displayed by exploratory plots. Frequencies and percentages will be presented for categorical variables. Changes will be estimated as a ratio change (post/pre) and data will be log transformed as appropriate to induce symmetry and stabilize the variability.

Difference between pre- and post-therapy will be explored using paired t-tests or nonparametric Wilcoxon signed rank tests for continuous variables and McNemar's test for dichotomous or categorical variables (e.g., proportion of subjects with marker-positive at pre- and post-therapy). Distributions of immune parameters across clinical responders and non-responders will be evaluated and graphically displayed using box plots. Differences of baseline and change in these parameters across tumor response groups will be explored using Jonckheere-Terpstra trend test, Wilcoxon rank sum test as well as logistic regression where appropriate.

10 Record Retention

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11 Obligations of Investigators

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13 APPENDIX 1 INTERNATIONAL METASTATIC RCC DATABASE CONSORTIUM (IMDC) PROGNOSTIC CRITERIA

Adverse Prognostic Factors
Clinical
KPS < 80% Time from diagnosis to treatment < 1 year
Laboratory
Hemoglobin < LLN Corrected calcium > ULN Absolute neutrophil count > ULN Platelet count > ULN

LLN = Lower limit of normal
ULN = Upper limit of normal

Corrected calcium (mg/dL) = measured total Ca (mg/dL) + 0.8 (4.0 - serum albumin[g/dL]), where 4.0 represents the average albumin level in g/dL.

Corrected calcium (mmol/L) = measured total Ca (mmol/L) + 0.02 (40 - serum albumin[g/L]), where 40 represents the average albumin level in g/L

Risk Group Based on Number of Adverse Prognostic Factors	
Number of Adverse Prognostic Factors Present	**Risk Group**
0	Favorable
1-2	Intermediate
3-6	Poor

14 APPENDIX 2 MANAGEMENT ALGORITHMS FOR IMMUNO-ONCOLOGY AGENTS

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

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GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade (G) 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hours (hrs); not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with activities of daily living (ADL) Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV 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 > 3-5 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

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > upper limit of normal (ULN) and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	<u>If returns to baseline</u>: •Resume routine creatinine monitoring per protocol <u>If worsens:</u> •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy	<u>If returns to Grade 1:</u> •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol <u>If elevations persist > 7 days or worsen:</u> •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	<u>If returns to Grade 1</u> : Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and Infectious Disease (ID) consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression (e.g. infliximab, cyclophosphamide, intravenous immunoglobulin (IVIG), or mycophenolate mofetil)

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin (T. bili) > ULN - 1.5 x ULN	• Continue I-O therapy per protocol	• Continue liver function tests (LFT) monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 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 I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN and /or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 gram (g) twice daily (BID) • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.**

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

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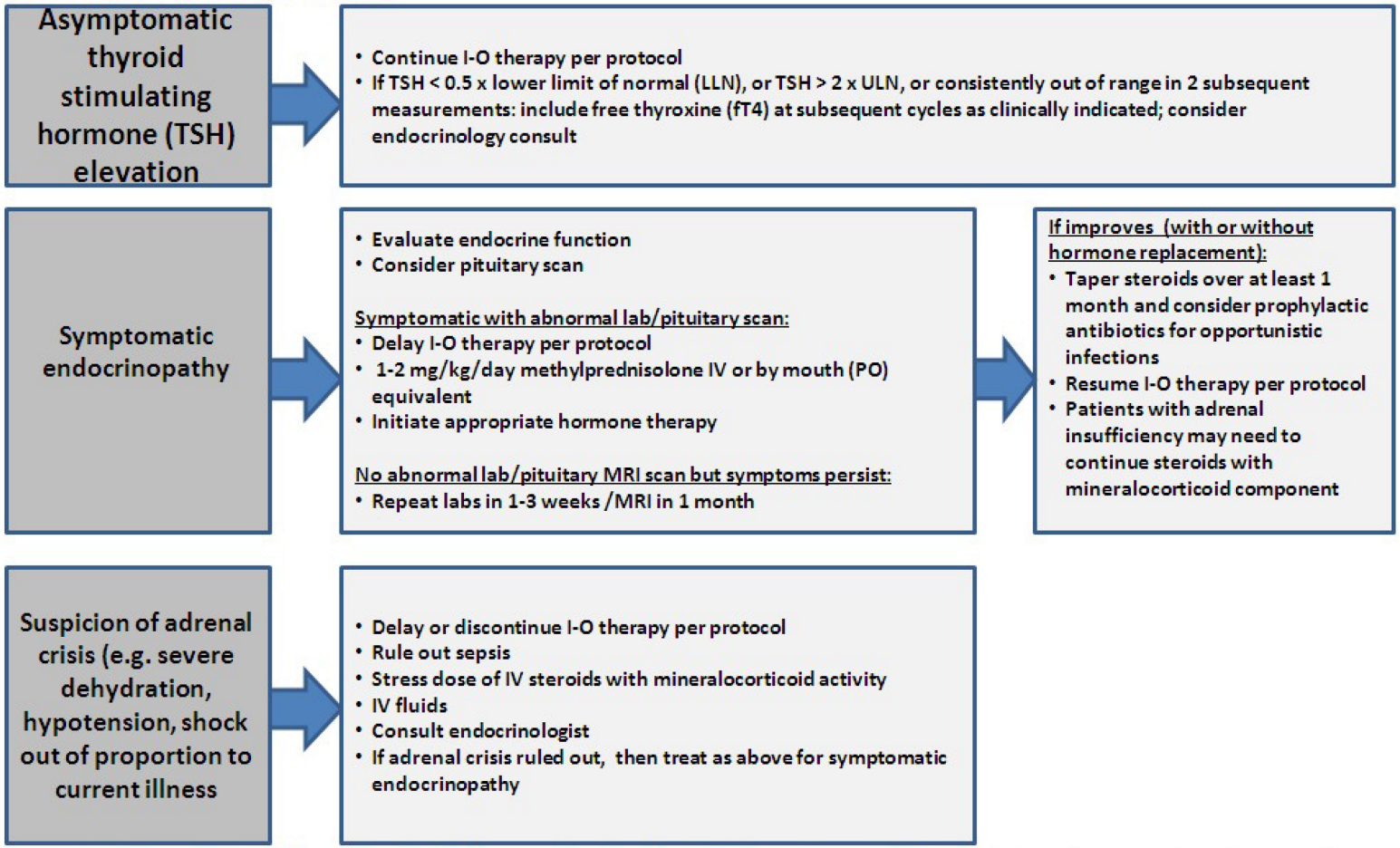
Endocrinopathy Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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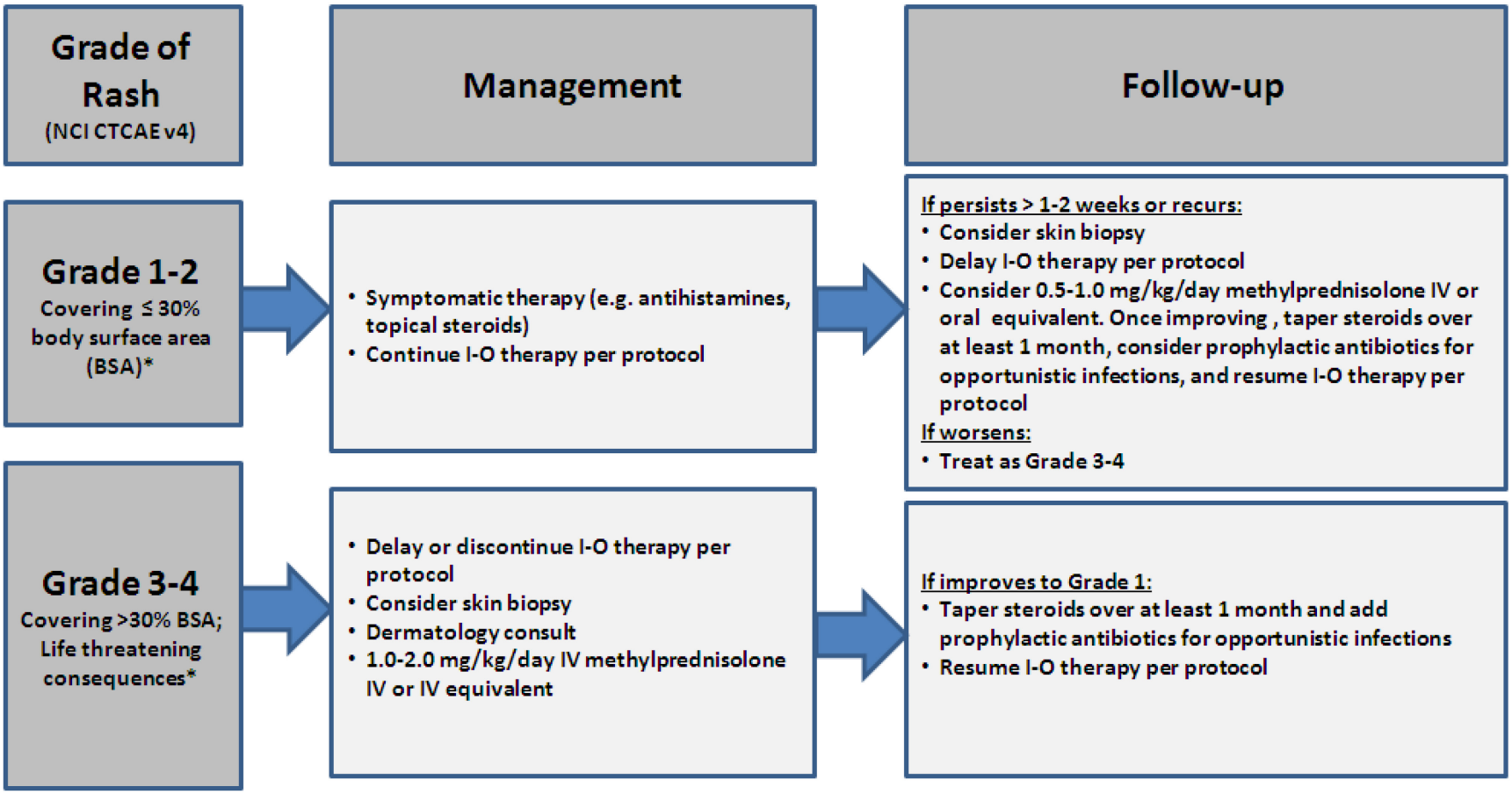
Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

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Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.