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Phase II Trial of Nivolumab and Stereotactic Ablative Radiation Therapy (SAbR) for Metastatic Clear Cell Renal Cell Carcinoma (mRCC)

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Signature Page

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

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

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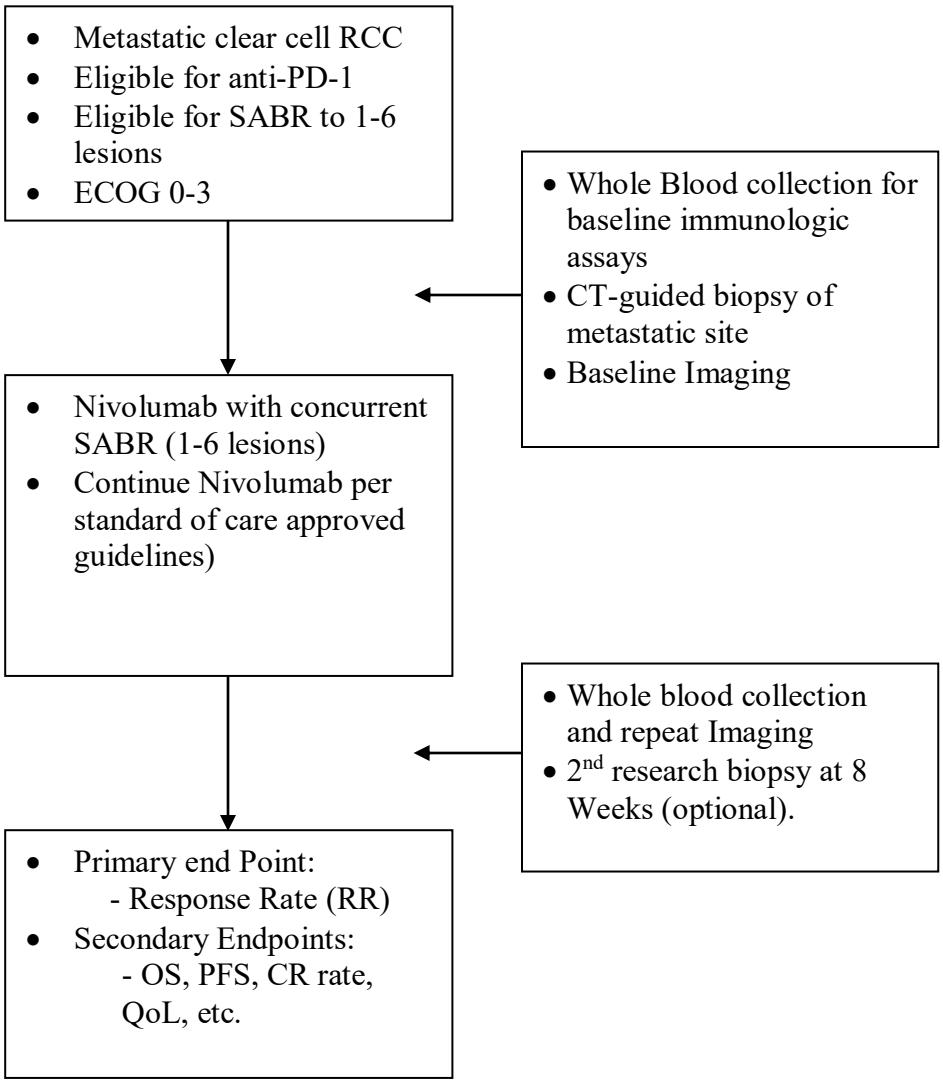
LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
BPI	Brief Pain Inventory
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
FACS	Florescence Activated Cell Sorting
H&P	History & Physical Exam
HRQOL	Health-related Quality of Life
HRPP	Human Research Protections Program
IHC	Immunohistochemistry
IV (or iv)	Intravenously
mRCC	Metastatic Renal Cell Cancer
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
p.o.	Per os/by mouth/orally
PR	Partial Response
PRN	“Pro re nata” or as needed
QoL	Quality of Life
RR	Response Rate
RT	Room Temperature
SAbR	Stereotactic Ablative Body Radiotherapy
SAE	Serious Adverse Event
SBRT	Stereotactic Body Radiation Therapy
SD	Stable Disease
VAS	Visual Acuity Score
WBC	White Blood Cells

STUDY SCHEMA



STUDY SUMMARY

Title	Phase II Trial of Nivolumab and Stereotactic Ablative Radiation Therapy (SAbR) for Metastatic Clear Cell Renal Cell Carcinoma (mRCC)
Short Title	Nivolumab and SABR for metastatic RCC
Protocol Number	STU 122015-052
Phase	Phase II
Methodology	Single arm
Study Duration	8 years (5 years for enrollment and 3 years for follow-up).
Study Center(s)	Single-center at UTSW
Objectives	To evaluate safety and response rate (RR) of mRCC after treatment with SAbR and Nivolumab
Number of Subjects	21 patients
Diagnosis and Main Inclusion Criteria	Metastatic Clear Cell Renal Cell Carcinoma patients who have failed one anti-angiogenic therapy
Study Product(s), Dose, Route, Regimen	Nivolumab (brand name Opdivo): Nivolumab administered per standard of care according to institutional guidelines. The standard FDA approved administration and indications of Nivolumab is listed in the FDA website: www.fda.gov or Package Insert https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125554s058lbl.pdf. ; SABR, dose variable, in 1-3 fractions.
Duration of administration	Nivolumab: Nivolumab administered per standard of care according to institutional guidelines. The standard FDA approved administration and indications of Nivolumab is listed in the FDA website: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125554s058lbl.pdf; SABR: 1-3 fractions over one week.
Reference therapy	Nivolumab alone from published historical control phase III study
Statistical Methodology	Exact binomial test will be used to investigate if the response rate of the treatment arm is significantly different from that of the historical control. One-sample log-rank tests will be conducted to examine if OS or PFS in the treatment arm is significantly different from that of the historical control.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

An estimated 64,770 cases of kidney cancer (RCC) will be diagnosed in the U.S. in 2012 with an estimated 13,570 deaths (SEER). There has been a steady 2-4% per year increase in the incidence of RCC since 1975 that is not explained by increased and improved imaging studies. Clear cell cancers are the most common variant of kidney cancers comprising up to 80% of RCC. The five-year survival rate for RCC patients is 70%, however, this is including the majority of patients with localized disease whose five-year survival is 91%. At the time of diagnosis approximately 30% of RCC patients have metastatic disease and another 30% of patients recur, whose five-year survival is less than 10%. Therefore, there remains a great need for improvement in the therapeutic management of metastatic clear cell RCC (mRCC).

RCC is a unique cancer that is well known for its immunogenicity. It is one of the first cancers in which immunostimulatory therapy, such as interferon and interleukin, has been shown to induce durable treatment response leading to FDA approval of HD IL-2 treatment for mRCC patients as early as 1992. A number of targeted therapies have been recently approved for the treatment of mRCC including vascular endothelial growth factor (VEGF) pathway inhibitors [1-3], mammalian target of rapamycin (mTOR) inhibitors [4], and most recently programmed death 1 (PD-1) inhibitor Nivolumab [5]. Complete response remains rare even with immunotherapies. Strategies for enhancing the percentage of patients exhibiting a CR may prove to be the only hope in offering a definitive treatment for this patient population.

1.2 Stereotactic Ablative Body Radiation (SABR)

Stereotactic ablative body radiation (SABR) is an emerging treatment paradigm defined in the American Society of Therapeutic Radiology and Oncology guidelines as a “treatment method to deliver a high dose of radiation to the target, utilizing either a single dose or a small number of fractions with a high degree of precision within the body” [6] . Potential indications for SABR include a broad spectrum of tumor types and locations. The safety and efficacy of SABR to multiple sites is excellent as documented in multiple studies [7-9].

Previous studies have demonstrated multiple immunogenic properties of radiation therapy, especially when given at high doses such as with SABR [10, 11]. Since SABR is a highly focused therapy, it does not inherently immunocompromise the host. In addition, as opposed to conventional radiation fields, SABR is a highly focused therapy that spares the surrounding lymph nodes which are vital for an effective immune response. By not surgically removing the tumor, the body retains the antigen depot (dying tumor cells) within the host. Furthermore, since SABR causes local inflammation, dendritic cells (DCs) are attracted into the tumor. The antigen-presenting properties and the induction of immunogenic cell death by SABR are well documented [12]. SABR-induced tumor cell death is primarily via mitotic catastrophy or necrosis, both of which are known to be immunogenic cell deaths as opposed to apoptosis, which is immunologically tolerogenic [13]. *In vivo* studies have shown that radiation induces release of damage (or danger)-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 DCs for antigen presentation [14-16]. 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 [17]. The 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 demonstrated [17, 18]. Furthermore, SABR causes a dose-dependent increase in MHC I tumor neo-antigen presentation by the tumor cells [19]. This, in conjunction with a demonstrated increase in FAS death receptors on the tumor cell surface in response to radiation, renders tumor cells particularly susceptible to CD8+ T cell-mediated cytotoxic attack [20, 21].

There is also evidence from both pre-clinical and clinical studies that radiation, specifically at ablative doses typical of SABR, initiates and augments an immune response and can synergize with immunotherapy [18, 22-25]. In the clinic, this effect of SABR has been documented by multiple case reports of the abscopal effect, where SABR to one site results in a systemic response with tumor regression at untreated metastatic sites [26-28] including that in

mRCC [29]. *In vivo* animal studies have demonstrated that this abscopal effect of SABR is immune-mediated [30]. The abscopal effect of SABR was shown most recently by Postow et. al. in their NEJM report demonstrating that the abscopal effect was due to an increase in tumor-specific T-lymphocytes and a decrease in MDSC following the combination treatment of SABR and CTLA-4 immunotherapy (Ipilimumab) in metastatic melanoma patients [28]. The team noted a temporal association of events with tumor shrinkage associated with antibody responses followed by changes in peripheral-blood immune cells, and a corresponding increase in antibody response to other antigens after radiation therapy.

1.3 PD-1 inhibitor (Nivolumab)

Although HD IL-2 remains a first-line therapy for clear cell mRCC patients, only a small minority of patients exhibits complete response (CR). Educating the immune system by the means of immune-stimulatory treatment to eradicate the primary as well as metastatic tumors may be a promising strategy for this patient population. Immunotherapy such as Nivolumab, which provide a non-specific immune stimulation by blocking immune checkpoints, have shown promise in early phase trials in inducing a cancer-specific immune response in certain metastatic cancer sites [31] and has recently been shown to improve overall survival in mRCC patients who have failed at least one prior anti-angiogenic therapy compared to Everolimus [5].

Nivolumab (BMS-936558; MDX-1106; commercial name Opdivo) is a fully human IgG4 programmed death receptor 1 (PD-1) immune checkpoint inhibitor antibody. It selectively blocks the interaction between PD-1, expressed on immune cells, and PD ligand 1 (PD-L1) and 2 (PD-L2), expressed on tumor cells and immune cells. Normally, this interaction leads to an inhibition in the activation of immune cells and thus would suppress the immune system. By blocking this interaction, Nivolumab activates the immune system. Multiple clinical trials have established the safety and efficacy of Nivolumab for the treatment of advanced or metastatic melanoma and/or renal cell carcinoma [5, 31]. Moreover, it has been recently FDA approved for patients with mRCC who have failed a prior anti-angiogenic therapy.

1.4 Rationale

The combination of Nivolumab immunotherapy and SABR for the treatment of mRCC can be explained by both immunological and clinical rationales.

1.4.1 Immunologic Rationale

Programmed death receptor 1 (PD-1) is a transmembrane protein of the immunoglobulin CD-28 family and is expressed on activated immune cells including macrophages, dendritic cells, activated B and T cells [32]. Two ligands specific for PD-1 have been identified: PD-L1 and PD-L2. PD-L1 is a member of the B7 family costimulatory molecules. Except for some immune cell lineages, human cells do not normally express PD-L1. In addition, while not commonly expressed in tumor cell lines *in vitro*, PD-L1 is widely expressed in various *in vivo* tumor tissues. Multiple studies have shown that interferon-gamma (IFN-γ) produced by activated T-cells induce the over expression of PD-L1 on tumor cells [33]. Tumor cells, induced by IFN-γ, can express high levels of PD-L1, which interacts with PD-1 on immune cells, and through PI3K/Akt inhibition, suppresses their immune response by inducing T cell apoptosis, anergy, exhaustion, dendritic cell suppression, IL-10 production and Treg induction. PD-L1 and PD-1 interaction also protect tumor cells from lysis by cytotoxic T lymphocytes [34]. Given the expression of PD-L1 on host immune cells, anti-body mediated PD-1 inhibition should work in both PD-L1 positive and PD-L1 negative tumors.

As discussed above, Nivolumab blocks the interaction between PD-1 and PD-L1, and thus activates the immune system in a non-specific manner. SABR should be able to provide a specific direction to the immune response by promoting antigen presentation. Recruited and activated by the DAMPs and other changes brought onto the tumor microenvironment by radiation therapy, the APCs migrate to the lymph node for antigen presentation and T-cell activation. RT also increases tumor infiltrating lymphocyte (TIL) trafficking within irradiated tumors [17, 25]. Typically, TILs produce IFN-γ which promotes antigen presentation but at the same time induces PD-L1 expression which is meant to prevent the propagation of the inflammatory

response and limit tissue damage. In the presence of PD-1 inhibitors, INF-γ will enhance antigen presentation and stimulate the immune response without the down-stream effects of PD-1/PD-L1 interaction [35]. Nonetheless, not all PD-L1 expression on tumor cells is IFN-γ-dependent. Certain tumors intrinsically express PD-L1 and certain cancer mutations can also upregulate PD-L1 expression [36, 37].

NK cells are part of the immune system's innate defense against cancer and were first discovered because of their anti-tumor activity [38]. In fact, *ex vivo* expansion and re-infusion of autologous NK cells has shown to induce long-term remission in cancer patients [39]. Specific destruction of cancer stem cells has been demonstrated by NK cells [40]. Radiation therapy increases expression of retinoic acid early inducible-1 (RAE-1) in carcinoma cells, which binds to the NKG2D receptor present in NK cells and CTLs and leads to their activation [25, 41]. Interestingly, NK cells also express PD-1 and it has been shown that PD-1 inhibition enhances NK cell response against multiple myeloma [42]. This suggests another possible synergistic interaction of Nivolumab and SABR in producing an anti-tumor effect mediated by NK cell activation.

Cytoreductive nephrectomy in mRCC has shown to occasionally induce regression of the metastatic foci [43]. It is hypothesized that this is secondary to an immune-mediated response. Two large randomized trials have demonstrated a survival benefit of nephrectomy followed by IFN-α in mRCC patients [44, 45]. In multiple settings, it has been demonstrated that a bulky tumor is able to produce immunosuppressants and induce proliferation of myloid-derived suppressor cells (MDSCs) leading to immune tolerance of the tumor [46, 47]. The cancer immune surveillance hypothesis states that a tumor is only able to survive and grow large when it has successfully evaded the immune system [48]. Therefore, surgical excision, or in this case ablative radiation of the bulky primary sites of disease can lead to decreased levels of MDSCs, immunostimulation and regression of metastatic foci. In the absence of PD-1/PD-L1 immune check point, a directed immune response against the cancer can flourish.

1.4.2 Clinical Rationale

As applied in concert with Nivolumab in the present study, SABR is intended not only as a systemic cytoreductive agent but also an immunostimulant by antigen presentation. By aggressively cytoreducing the tumor burden, the growth dynamics may be altered to render the remaining cells more susceptible to the immunotherapy, thereby converting more PR patients into CR. Therefore, the purpose of SABR would be three-fold: (1) It would irradiate sites of disease that are bulky and therefore resistant to immunotherapy and potentially serving as origins of further tumor spread and metastasis. (2) By decreasing the burden of disease below a threshold, SABR would reduce or eliminate immunosuppressive effects of tumor. (3) Simultaneously, SABR would act as an *in-situ* tumor vaccination by initiating antigen presentation and immunocyte infiltration, thereby acting synergistically with PD-1 inhibition in facilitating an effective immune response and eventually affecting PR, CR, disease progression and overall survival.

Metastatic RCC can be seen as composed of bulky sites of disease and innumerable micrometastatic foci that are below the resolution limit of radiographic imaging. Systemic therapies like cytokine therapy or newly emerging targeted therapies including PD-1 inhibitors are often effective towards micrometastatic disease but less so to the bulky sites of metastasis which requires multimodality treatment. In a recently published phase 3 RCT comparing Nivolumab to Everolimus in advanced and metastatic RCC patients who have failed at least one anti-angiogenic therapy, the rate of pCR was 1% in the Nivolumab arm and <1% in the Everolimus arm. Therefore, systemic therapies can result in a response, rarely complete, and ultimately the tumors progress, resulting in declining quality of life and death from cancer. Historically, the use of local therapies such as surgical metastasectomy or conventional radiation for a purpose other than palliation was ineffective since the tumor distribution was systemic. RCC is one of the few cancer sites where NCCN guidelines recommend cytoreductive nephrectomy and metastasectomy in selected stage IV patients, not only for palliative purposes but also for potential survival benefit as well. Similarly, RCC is one of the few cancer sites that has demonstrated a survival benefit for metastasectomies. Multiple retrospective studies, and one recently published randomized trial, have demonstrated an overall survival benefit (five years at 32.5% versus 12.4%, $p<0.001$) of metastasectomy in RCC patients [49-51]. There is growing

evidence that this new, potent, highly focused, and convenient form of radiation called SABR can dramatically debulk and even eradicate bulky tumor deposits as effectively as surgical metastasectomy while being non-invasive [7, 52-54].

Since SABR is shown to be immunostimulatory, and tumor debulking in mRCC has shown to impart survival benefit, the combination of SABR and immunotherapy is expected to be synergistic for mRCC. A combination treatment that offers local control through eradication of bulky progressive sites and simultaneously synergizes with concurrent systemic immunotherapy to eliminate micrometastatic disease is expected to improve outcome dramatically by converting partial responders to complete responders and non-responders into partial responders.

The toxicities of Nivolumab are tolerable and well described. Given the multiple studies demonstrating excellent safety profile of SABR, including our own departmental experience, there are limited concerns for additional toxicity when they are administered sequentially [7-9]. No clinical trials combining SABR with PD-1 inhibitors are published and there is paucity of data regarding the side effect profile of the combination. However, preliminary data from our phase II trial of HD IL-2 (a form of immunotherapy with a serious toxicity profile) and SABR showed that the addition of SABR to immunotherapy did not increase toxicity (data unpublished). A phase I trial of HD IL-2 and SABR in melanoma and RCC patients has proven the safety and feasibility of this regimen [55]. In addition, we have already used SABR in five patients who are receiving Nivolumab for metastatic disease (4 with mRCC and 1 with metastatic melanoma – See table 7.3.1). Our preliminary acute toxicity data (See table 7.3.2), with a follow up ranging between 1 and 3 months, shows that the combination treatment is well tolerated with a favorable toxicity profile comparable to the published side effects of Nivolumab alone (Please see 7.2.2). Please note that the grade 4 toxicity in patient #1 was considered to be due to disease progression in the lung rather than due to the therapy itself.

Therefore, we propose a single institution, safety lead-in phase II trial with SAbR to multiple metastatic sites concurrently administered with Nivolumab for patients with metastatic clear cell renal cell cancer who have failed at least one anti-angiogenic therapy. This phase two trial tests the hypothesis that addition of SABR to Nivolumab is a durably effective means of potentiating the effects of PD-1 blockade in inducing higher objective response rate (RR) eventually leading to improvements in progression-free survival, complete response rate, overall survival without degrading quality of life in the mRCC patient population. As reported in prior trials, the RR for Nivolumab (dosing as per the institution guidelines, q 3 weeks until progression) in mRCC is 22%-25% [5, 56]. In the same trials, median OS was 25 months, and PFS was 4-4.6 months. The primary endpoint of this study is to measure improvement in response rate (RR) when SABR is added to Nivolumab compared to the RR in the reported historical control arm with Nivolumab alone. We will propose that the addition of SAbR to Nivolumab will increase the RR to 43.8% i.e. 75% increase compared to the historical RR with Nivolumab alone. In our current ongoing phase II clinical trial (STU 012013-041) with similar patient population and treatment strategy of SABR + immunotherapy using IL-2, we are noticing a 53% RR with the combination whereas the historically reported response rate of IL-2 alone treatment is 20% (1). Therefore, we have increased the RR by >150%. Therefore, in oncology clinical trials, it is not uncommon to see such increases since the baseline RR is often low. The secondary objectives of this trial will measure progression-free survival (PFS), overall survival (OS), time to progression (TTP), complete response rate (CRR), duration of treatment response, and health related quality of life outcomes (HR-QoL). In addition, the exploratory objectives will include correlation of the immune response to clinical outcome, evaluation of immunologic biomarkers to predict response and explore possible mechanism of immune resistance. This will help us identify patients who may be more responsive to this regimen. Given the high cost of Nivolumab, it would be also interesting to evaluate the cost-effectiveness of adding SABR upfront with the hope that it would have cost saving effects and improve the quality-adjusted life-years for patients.

1.5 Correlative Studies

The correlative studies will explore the mechanisms of possible immune enhancement by SABR. Activation of the immune response will be evaluated separately utilizing different assays. The humoral response will be evaluated using ELISA to measure the titer of tumor-specific

antibodies generated by SABR and Nivolumab against tumor tissue collected from the respective patients and established human renal cancer cell lines Caki-2 (clear cell) and ACHIN (adenocarcinoma). An overall increase in tumor antigen-specific antibody will be measured using immunoblotting with patient sera as a source of primary antibody.

Enhancements of increased cytotoxicity to renal cancer cells can be measured by cytotoxicity assays. Antibody-dependent cell-mediated cytotoxicity (ADCC) measures the cell-killing ability of certain lymphocytes that require the target cell to be marked by an antibody and thus measures the humeral response [57]. On the other hand, lymphocyte-mediated cytotoxicity assay will measure the formation of tumor-specific CTLs among the lymphocytes collected from patients before and after SABR and Nivolumab. Since it is not practical or feasible to obtain sufficient quantities of tumor cells from each patient to quantitatively assess cytotoxicity by these assays, established allogenic human renal cancer cell line Caki-2 and ACHIN will be used for this purpose. It is a generally accepted principle of tumor immunology that there will be many common tumor antigens between different patient tumors of same site origin, and therefore tumor cell lines as well [57]. In fact, the tumor antigens (PSA, CEA, CA 19-9 etc.) that are in clinical practice are reported to be present in a significant portions of patients of the respective tumor site. This concept of commonality of tumor antigens between allogenic tumor cell lines and patients is put into clinical practice by the GVAX anti-tumor vaccine which is currently in early phase clinical trials for pancreatic, melanoma and renal cancer [58, 59]. GVAX consists of multiple human tumor cell lines of the respective site that is modified to express GM-CSF, and killed with radiation prior to injection in patients. The presence of common tumor antigens in the cell lines and patient's tumors, leads to induction of an immune response. The LNCaP and PC-3 cell lines has been shown to express many of the common renal cancer antigens, and therefore, is an appropriate surrogate to be used instead of patient's own cells and has been used in similar *in vitro* cytotoxicity assays [60-64].

Cytokines are hormonal messengers responsible for most of the effects in the immune system such as activation of innate versus adaptive immune response, cellular versus humoral immune response [65, 66]. For example, an increased level of IL-2 and IFN-γ suggests activation of Th1 cells leading to activation of macrophages and suggests a cell-mediated adaptive immune response whereas IL-4 and IL-5 may indicate Th2 activation and induction of humoral immunity [57, 66]. An increase in IL-17 may suggest activation of autoimmune responses [67]. Therefore, measurements of serum cytokine levels have generally been used previously in clinical trials as surrogates to assess specific activation of immune pathways [68, 69]. Serum cytokines from this clinical trial before and after SABR and at different time-points of Nivolumab administration will be measured using an extensive array of cytokines to explore the specific immune pathways that are initiated/inhibited by our treatments. The planned array of cytokines will measure levels of the following cytokines at different time points for each patients: Th1/Th2/Th17 cytokines: IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12p70, IL-13, IL-17 TNF-α; pro-inflammatory cytokines: GM-CSF, IFN-γ, IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12p70, TNF-α; Chemokines: Eotaxin, MIP-1β, TARC, IP-10, IL-8, MCP-1, MCP-4, KC, and others including IL-6, IL-12, TGF-β and HMGB1.

Many surrogate markers for activated and proliferating lymphocytes have been described. Some of these markers include CD25, CD71, CD45RO, CD107a, CD54, CD69, Ki67 and ICOS/CD278 [70-73]. These markers are easily measured with specific antibodies tagged with a fluorophore utilizing FACS analysis. Also using FACS, activation markers such as CD80 and CD 86 on DCs, and inhibitory markers such as PD-1, can be measured as surrogates of immune activation or inhibition. These measurements from PBMCs collected from patients will give us further information regarding the intensity of the immune response.

The relative levels of different monocyte subpopulations in the tumor biopsy sample after treatment as well as in the peripheral circulation often dictate the overall outcome of an immune response, and has been reported in previous immunotherapy trials [55]. Exploration of possible mechanisms of treatment failure can be explored from this analysis as well. Therefore the following subpopulation of cells will be quantified in patient PBMCs (and in tumor biopsy samples where applicable) collected before and after treatment utilizing some of the listed markers specific for those cells:

Immune Cells	**Markers**

Lymphocytes	
Cytotoxic T Lympocyte (CTL)	CD3, CD8
NK	CD3-, CD8, CD16, CD56, CD11b
NKT	CD3, CD16, CD1d
Helper T Cells	CD3, CD4
Th1	IL-18 receptor α, CXCR3, T cell Ig domain, TIM-3, T-bet
Th2	T1/ST2, TIM-1, TIM-2, GATA-3
Th17	Unknown, differentiated by IL-17 production, ROR-γT
Treg	CD4+CD25+FoxP3+
Memory T Cells	CD45RO
TCM	CD4/CD8, CD62L, CCR7
TEM	CD4/CD8, CCR7−, CD45RA−, CD27
B Cells	CD19, mIg, FcR, CR, CD3-, HLA-DR
MDSC	CD14+, CD11b, CD33, CD 15, CD4, CD8-, HLA-DR-/low
Neutrophils	FcR, CR-,CD3-, HLA-DR-, GR-1^{+high}, CD11b, Ly6G
Macrophages	FcR, CR, HLA-DR, GR-1^{+mid}
DC	
Myeloid DC-1	CD11c, TLR2,TLR4
Myeloid DC-2	CD 141, TLR2,TLR4
Plasacytoid DC	CD303, TLR7,TLR9

Table 1: PBMC subpopulations and their markers.

Additionally, we plan to specifically quantify the expression of PD-L1 in all tumor samples from patients' pre-treatment tumor biopsies. Tumor PD-L1 membrane expression (≥1% vs. <1% and ≥5% vs. <5%) will be quantified in sections which have at least 100 tumor cells as assessed with immunohistochemical staining. It has been shown previously that tumors with higher PD-L1 expression have worse outcomes but it remains to be shown whether these tumors respond better to anti-PD-1 therapy. It would be very interesting to examine the correlation between PD-L1 expression and tumor response to the combination therapy.

1.6 Health-related Quality of Life (HRQOL) and Economic Analysis

In the United States, total national health expenditures (NHE) increased from $7.14 billion in 1990 to $2.23 trillion in 2007, which represents an average annual growth rate of 7.0%. In contrast, over the same period, U.S. gross domestic product (GDP) increased from $5.8 trillion in 1990 to $13.8 trillion, or average 5.2% annual growth rate. Given that national health expenditures have grown faster than GDP, the share of GDP devoted to health expenditures has increased from 12.3% in 1990 to 16.2% in 2007 [74]. Moreover, national health expenditure growth is expected to continue to outpace income growth, with total NHE reaching $4.35 trillion by 2018, accounting for 20.3% of GDP (CMS 2009). There is growing concern that these trends in health expenditures are not sustainable. For the Medicare program, current estimates of the present value of total unfunded liabilities through the year 2083 (the present value of the difference between projected future Medicare expenditures and Medicare revenues over the next 75 years under current Medicare policy) total $89 trillion, with Medicare's Hospital Insurance ("Part A") trust fund projected to be depleted by 2017 [75].

Prior studies have estimated that about half of the recent growth in health expenditures is attributable to advances in various forms of health technology, including new pharmaceutical products, surgical procedures, imaging modalities, and new biomarkers [75]. While almost all of these new technologies offer some potential to improve clinical outcomes, they also more often than not add to health expenditures. Within the context of unsustainable trends in health expenditures, a key policy question relates to whether the extent of improvement in outcomes associated with the use of a new technology is attained at a "reasonable" additional cost,

compared to existing technology. Indeed, the value offered by new technologies is being subjected to increasing scrutiny by reimbursement authorities in many health systems worldwide. For example, in the United Kingdom, the National Health Service bases payment policy decisions for new technologies on recommendations from the National Institute for Health and Clinical Excellence (NICE), which in turn are substantially influenced by cost-effectiveness analysis yielding an estimated additional "cost per quality-adjusted life-year (QALY) gained" via use of the new technology. Currently, NICE usually considers technologies offering improved outcomes at a cost less than £20,000 to £30,000 per QALY gained (about $33,000 - $50,000) acceptable, though exceptions are common[76].

Several recent studies have evaluated health-related quality of life (HRQoL) for biologics and targeted treatment for mRCC. In the Sunitinib versus INF-alpha trial, health-related quality of life was superior in the Sunitinib group as assessed by the FKSI-15, FACT-G, and EQ-5D [3][80]. In a review article regarding quality-of-life in patients with recent renal cell by Cella et al., it is clear that quality-of-life measures are increasingly being utilized within the clinical trial setting to assess quality adjusted life year expectancy [81]. Two recent trials evaluating health-related quality of life for Sorafenib utilizing the FACT-FKSI, FACT-G, and EQ-5D indicated that Sorafenib resulted in improvements in individual items related to registry function and quality of life compared with placebo [82]. Additionally, European trials evaluating temsirolimus in a phase 3 setting versus INF-alpha or both, showed quality adjusted survival favoring patients who received temsirolimus [83]. In a group of heavily pretreated metastatic renal cell cancer patients enrolled on a phase 3 trial comparing everolimus versus placebo, quality of life as measured by EORTC QLQ C30 and FKSI-DRS showed no changes between the two treatment groups showing stable quality-of-life as compared to placebo [84]. Additionally, there are ongoing studies evaluating QoL in patients receiving axitinib as well.

Due to the high cost of these new therapeutic agents several cost-effectiveness studies have evaluated the cost per quality adjusted life year of first-line therapeutic options of metastatic renal cell carcinoma. In an economic analysis of sunitinib versus INF-alpha and IL-2, Sunitinib was shown to be a cost-effective alternative to INF-alpha and IL-2 from a US societal perspective [85]. An economic analysis from the Chinese perspective was undertaken evaluating INF-alpha, IL-2, INF-alpha plus IL-2, sunitinib, and bevacizumab plus INF-alpha, and it showed that sunitinib was cost effective when the willingness to pay threshold was over $16,000 which would be appropriate for several developed regions within China [86]. Given the rising costs associated with the biologic and targeted therapies for metastatic renal cell carcinoma, the cost implications of this protocol warrant further study.

Therefore, we propose to evaluate patients' health related quality of life (HR-QoL) and health resources utilization in order to evaluate the economical consequence of using the treatment proposed in this study and its impact on quality adjusted survival. Based on the primary hypothesis of this study that response rates will be improved with the combination of SABR and Nivolumab, we further hypothesize that the addition of SABR will increase the durability of response or lengthen the time to progression, thus increasing the cost effectiveness of the combined therapies. Thus, we hypothesize that upfront SABR, while adding modestly to the total cost of the combined therapies, may be cost saving over the patient's entire treatment course compared to Nivolumab alone, making the combination a very attractive treatment for mRCC patients. Additionally, we hypothesize that combination therapy will increase the quality-adjusted life-years for mRCC cancer patients (compared to the prior reported chemotherapeutic, biologic, and targeted options for mRCC) at a reasonable incremental cost, as defined by generally accepted cost-effectiveness thresholds. The sample size would be prohibitively large should these secondary endpoints be analyzed beyond simple descriptive statistical purposes.

2.0 STUDY OBJECTIVES

This study is a safety lead-in phase II single institution clinical trial using Nivolumab and concurrent SABR to 1-6 metastatic sites in patients with metastatic clear cell renal cell cancer (mccRCC) who have received at least one prior anti-angiogenic therapy. Nivolumab will be dosed intravenously as per the institution guidelines, until disease progression, unacceptable toxicity or other reasons specified in the protocol. No dose modifications for Nivolumab will be allowed. SABR will be administered to 1-6 sites of metastatic disease one week after the first dose of

Nivolumab with a single (24-27 Gy) or three (11-16 Gy/fraction) fractions. The sites of larger (bulky) disease and the sites of symptomatic disease will be prioritized for treatment at the discretion of the treating radiation oncologist.

2.1 Primary Objectives

The primary objective of the interim safety analysis of the trial (6 patients) is feasibility, safety and toxicity. The primary objective of the phase II portion of the trial will be to increase the historical RR of treatment with Nivolumab alone by 75% with the addition of SABR. The assessment of RR will be based on the evaluation of RECIST criteria and radiated lesions will be excluded from target lesions. The reported RR for Nivolumab for RCC is 25% [5, 31]; an increase of 100% will lead to a RR of about 50%. Therefore, the hypothesis of the phase II trial is that **concurrent administration of SABR will increase the RR of Nivolumab to 50% for mRCC in patients who have failed one prior anti-angiogenic therapy.**

Treatment with immuotherapies has been reported to cause a “tumor flare” which denotes the apparent radiographic increase in tumor burden or occurrence of new lesions before a true clinical response can be established. This “flare” is thought to be due to a transient increase in immune cell infiltration while the immune system is being primed. Therefore, RECIST criteria may fail to accurately report RR and some patients will be taken off therapy before a true response is measured. In the CheckMate 025 trial, 44% of patients who progressed per RECIST criteria were continued on Nivolumab if they were thought to have clinical benefit. In addition, in the phase II trial of Nivolumab dose escalation trial, treatment beyond first RECIST-criteria progression was allowed in patients who tolerated Nivolumab and exhibited investigator-assessed clinical benefit. 17%, 22% and 26% of patients in the 0.3, 2 and 10 mg/kg groups were treated beyond progression. Median number of doses received after RECIST progression was 4.5, 7.5 and 8.5 in the 0.3, 2 and 10 mg/kg groups. Median PFS was 2.7 mos, 4.0 mos and 4.2 mos in the 0.3, 2 and 10 mg/kg groups using the RECIST criteria but increased to 4.3, 5.4 and 6.9 mos respectively using immune-response PFS. In a subgroup analysis, 69% (25/36) of patients who received treatment beyond first progression, defined as patients receiving their last Nivolumab dose >6 weeks after RECIST-defined progression, demonstrated sustained reductions in tumor burden or lesion stabilization with an acceptable safety profile. Median OS for patients treated beyond first progression was 22 mos vs 12 mos for those not treated. Thus, patients will be allowed to stay on Nivolumab after their first RECIST-criteria progression per the treating physician. Data will be evaluated using the RECIST criteria for primary endpoint and ir-RECIST for secondary endpoint.

2.2 Secondary Objectives

2.2.1 RR based on ir-RECIST

2.2.2 To evaluate overall survival (OS), which is defined as the time between date of registration and the date of death due to any cause. In analyzing OS, we will take into account the MSKCC prognostic criteria for mRCC and compare our data to historical controls in the appropriate risk category

2.2.3 To evaluate progression free survival (PFS), which is defined as the time between date of registration and the first date of documented disease progression or date of death due to any cause

2.2.4 To evaluate complete response rate, which is defined as the percentage of patients who show complete response as per ir-RECIST criteria

2.2.5 To evaluate time to progression (TTP), which is defined as time between date of registration and date of documented progression.

2.2.6 To evaluate median response duration, which is defined as the time between the date a response (CR or PR) was first seen until date of progression

2.2.7 To evaluate the tolerability and toxicity as measured according to CTCAE v4.0.

2.2.8 To measure the improvement in health-related quality of life (HR-QoL)

2.3 Exploratory Objectives

2.3.1 To measure treatment-related tumor-specific immune response (immunogenicity).

2.3.2 To explore the immunological biomarkers (PD-L1 expression in tumor, DC-HIL expression in MDSC, TCR diversity and clonality, etc) as correlates or predictors for treatment response.

2.3.3 To evaluate the cost-effectiveness and cost-utility of the addition of SABR to Nivolumab in patients with mRCC

2.4 Endpoints

2.4.1 **Response:** Treatment response will be measured using both the RECIST and immune related RECIST criteria (ir-RECIST), a minor modification of RECIST 1.1 for immunotherapy [89]. Radiated lesions will be excluded from target lesions.

2.4.2 **Death:** Death due to any cause, although in mRCC patient population, the overwhelming majority is expected to be secondary to disease progression.

2.4.3 **Progression:** Progression will be defined according to the ir-RECIST criteria and verified by a second set of imaging at least 6 weeks apart.

2.4.4 **Immune Response:** Immune response will be measured using ELISpot assay, T-cell proliferation assay and ELISA.

2.4.5 **Toxicity:** Toxicity will be measured using CTAE v4.0

2.4.6 HR-QoL: HR-QoL will be measured using FACT-G, EQ-5D and FKSI questionnaires at baseline, and at different time-points during treatment and follow up

2.4.7 Cost-effectiveness analysis: Health care utilization data needed to assess costs will be obtained from patients' insurance claims during and after treatment. Markov modeling with probabilistic sensitivity analysis will be used to correlate quality-adjusted survival and cost.

3.0 Subject ELIGIBILITY

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.

3.1 Inclusion Criteria

3.1.1 At least 18 years of age

3.1.2 Willing and able to provide consent

3.1.3 Pathologic diagnosis of metastatic RCC with clear cell component with progression or intolerance to at least one prior systemic anti-angiogenic therapy

3.1.4 Measurable disease in at least 1 non-radiated sites.
3.1.5 Eligible for extra-CNS SAbR to 1-6 sites of disease

3.1.6 Must have received at least one prior anti-angiogenic therapy (or inability to tolerate, as above) in the advanced or metastatic setting. Prior cytokine therapy (eg, IL-2, IFN-α), vaccine therapy, or treatment with cytotoxics is also allowed but not any other drug specifically targeting T-cell co-stimulation or checkpoint pathways.

3.1.7 Previous treatment with surgery, radiation, chemotherapy, targeted agents (see above) are allowed provided that:

3.1.7.1 Chemotherapy/Major surgery was administered > 7 days before the start Nivolumab
3.1.7.2 Minor surgery, radiation, or any targeted agents were administered before the start of Nivolumab

3.1.8 Performance Status (ECOG 0 - 3 OR Karnofsky 100 - 30)

3.1.9 Women of child-bearing potential (WOCBP):

- A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:
  - Has not undergone a hysterectomy or bilateral oophorectomy; or
  - Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).
- WOCBP must have a negative serum or urine pregnancy test at screening and within 24 hours prior to the start of investigational product.
- Women must not be breastfeeding.
- WOCBP must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation and contraception should be continued for a period of 90 days plus

the time required for the investigational drug to undergo five half-lives. This is equivalent to 31 weeks after discontinuation of Nivolumab.

- Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.10 Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Contraception should be continued for a period of 90 days plus the time required for the investigational drug to undergo five half-lives. This is equivalent to 31 weeks after discontinuation of Nivolumab.

3.2 Exclusion Criteria

3.2.1 Subjects who have had major surgery (such as nephrectomy) or chemotherapy within7 days (or at the discretion of the treating medical oncologist)prior to first dose of drug

3.2.2 Subjects who have had radiation therapy within 1 week prior to first dose of drug

3.2.3 Uncontrolled adrenal insufficiency or active chronic liver disease

3.2.4 Any history of CNS metastases that is not adequately treated with surgery or SABR >14 days prior.

3.2.5 Prior treatment with any 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.

3.2.6 Any positive history for HIV/AIDS, HTLV, hepatitis B or hepatitis C virus indicating acute or chronic infection.

3.2.7 Any active known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

3.2.8 Any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to the first dose of study drug. Inhaled steroids and adrenal replacement steroid doses up to 10 mg daily prednisone equivalent are permitted (although not encouraged) in the absence of active autoimmune disease.

3.2.9 Subjects with life expectancy < 6 months

3.2.10 Subjects receiving any other investigational or standard antineoplastic agents.

3.2.11 Prior malignancies 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 prostate, cervix, breast, or etc.

3.2.12 Psychiatric illness/social situations that would limit consenting and compliance with study requirements.

3.2.13 Patients with history of hypersensitivity to monoclonal antibodies

3.2.14 Subjects who are pregnant or nursing due to the potential for congenital abnormalities and the potential of this regimen to harm nursing infants.

4.0 TREATMENT PLAN

4.1 SABR Dose and Techniques

Patients should have at least 1 measurable non-CNS lesions. Lesions receiving SABR will be called “radiated” lesions. “Target” lesions will be selected from non-treated lesions. In any case, there should be at least one (non-CNS) measurable lesion for effect measurement. Prior irradiated lesions (outside of the trial) will be excluded from target lesions. SABR will be administered to 1-6 sites of metastatic disease on the 2 weeks after the second dose of Nivolumab with a single (24-27 Gy) or three (11-16 Gy/fraction) fractions. The sites of larger (bulky) disease and the sites of symptomatic disease will be prioritized for treatment.

4.1.1 SABR Dose

The SABR dose and fractionation scheme is generated to deliver a potent dose to ablate the targeted lesions and at the same time maximize an immune response. Since multiple studies have shown an influx of lymphocytes and monocytes after tumor irradiation [12, 17, 18, 90] and since these cells play a critical role in antigen presentation and initiation of an adaptive immune response, multiple fraction irradiation which would kill these infiltrating immunocytes, is discouraged. Therefore a single fraction or a three fraction treatment regimen is allowed, and a single fraction treatment is preferred over three fractions. Due to normal organ toxicity and limits of dose constraints, sometimes a three fraction treatment must be undertaken and in those cases it is recommended that the treatment course is completed within 7-10 days (preferably 5 business days). Radiation dose-(immune) response studies have shown a linear increase in immune response with increased dose per fraction of radiation without demonstration of a plateau [17, 19, 90, 91]. Two studies comparing 15Gy x 1 vs 5Gy x3, and 20Gy x1 vs 5Gy x4 have shown a superior immune response generated by the single fraction radiation [17, 90]. Clinical experience with oligometastatic patients treated at 1-5 sites of disease has also showed an increase in progression free survival with the increasing radiation dose per fraction [92]. A dose of less than 7.5 Gy per fraction has demonstrated lower induction of systemic IFN-γ producing cells [91], and a previous phase II study of mRCC patients treated with HD IL-2 and singe fraction of 8Gy irradiation to a single lesion did not show an overall improvement in response rate [93]. Therefore 8Gy per fraction is the lowest permitted dose for this study and can be used only when administering the three fraction regimen as described in the prescription dose table below.

The SABR prescription dose will be delivered to the periphery of the planning target volume (PTV, see below for definitions). Investigators will have discretion in choosing from either of the biologically equivalent dose levels using one or three fractions, although a single fraction is preferred over three fraction treatments. Treating physician will have further discretion in selecting the number and location of sites to treat if multiple sites of disease are present. Maximum number of lesions treated is deemed as feasible per the treating radiation oncologist. Physicians will be **REQUIRED** to leave at least one site of disease for the purpose of measuring a radiographic response (see section 6) at a non-treated site, as this is part of the primary endpoint. If left untreated, this site can be treated once patient meets the definition of progressive disease (PD) (see section 6). To clarify the definition of “site”, each site is an area or organ with active extracranial disease (</=3 in the liver = one site and </=3 in the lung= one site) identified by CT scan, or PET/CT, within 4 weeks prior to initiation of SABR (up to 2 contiguous vertebral metastasis will be considered a single site of disease). For example: a patient with 4 right axillary lymph nodes, L1-L2 bone metastasis, 3 right lung lesions, 1 left lung lesion, 2 liver lesions, and

T2-T3 bone metastasis would be defined as having 6 sites of disease. Preference should be given to the largest feasible disease site, symptomatic sites and sites where palliative and preventative (i.e. to prevent a pathologic fracture in weight bearing bone, impending cord compression, impending SVC compression etc.) indications are applicable. The gross target/tumor volume (GTV) should be at least 2 cm^3 in size, corresponding to roughly a 1.5 cm diameter tumor. This is to ensure that adequate tumor volume and therefore adequate tumor cells (roughly 10^8 -10^9 cells/cm^3 [94]) are killed for antigen presentation. Treating physicians should choose their dose based on established planning guidelines at their center including their ability to respect normal tissue tolerance listed below. It is not required that all targets be treated with the same dose fractionation. A dose from the following table should be used:

Table 4.1.1 Prescription Dose

	Total Cumulative Dose Encompassing 95% of Planning Target Volume (Gy)		
Number of Fractions	Protocol Compliant	Minor Deviation *	Major Deviation
1	24-27 Gy	≥16 Gy, <24 Gy	<16 Gy
3	33-48 Gy	≥24.5 Gy, <33 Gy	<24 Gy

*This column is protocol compliant for tumors abutting the spinal cord (major deviation remain as listed)

Dose tolerance limits should be adhered to for all treatments. Protocol compliant dose should be used in all cases, if possible. When treating tumors abutting the spinal cord, tolerance limits should not be exceeded. To facilitate this requirement, minor deviation dose ranges listed above in the table will be considered fully compliant for tumors abutting the spinal cord.

4.1.2 Planning Constraints and Concerns

The tolerance dose of SABR to the gastrointestinal tract is not established, and patients with metastatic disease involving the esophagus, stomach, intestines, or mesenteric lymph nodes will be eligible only if no other sites of lesions are present that can be safely targeted, and the treating radiation oncologist feels that a sufficiently conservative dose constraints to these organs can be met. Patients with renal or adrenal metastases are potentially eligible if normal tissue constraints are otherwise met.

It is well established that for palliative effect for a painful bone metastasis, a single dose of 8 Gy is usually as effective as 30 Gy [95]. However, in this protocol the goal is not just to relieve pain within an osseous metastasis but also to dramatically debulk the tumor present and induce in immune response, and the higher dose is more likely to accomplish this goal given a higher biological potency [96]. Long term survival after bone metastasectomy has been reported [97]. Irradiation of non-spinal skeletal sites does not generally require specialized techniques of treatment. Metastases in major lower extremity weight-bearing bones should undergo surgical stabilization if there is plain film evidence of cortical erosion.

4.1.3 SABR Treatment Technique

4.1.3.1 Simulation, beam arrangements, tumor prescription dose

Treatment to skeletal lesions and paraspinous lesions may be accomplished with any 3D conformal radiotherapy or intensity-modulated radiotherapy (IMRT) technique suitable for this application with performance specifications adequate to provide proper tumor dose distribution and normal tissue sparing.

At the time of simulation for patients who will receive SABR to the lung and/or liver, the movement of the dome of the diaphragm (superior portion of the liver) is to be observed under fluoroscopy or other acceptable means to estimate respiratory movement during treatment if no

breathing control device is used. Patients will be assessed for suitability for tolerance of a respiratory control device using a breath-hold technique, respiratory gating, or abdominal compression to limit diaphragmatic excursion during respiration. Patients with severe lung disease and patients who cannot tolerate diaphragmatic or breathing control devices for other reasons will be treated without them. A larger margin to account for breathing related intra-fractional organ movement is required.

With the patient is immobilized in a vacuum-type or equivalent body mold, a planning CT scan with 2-5 mm slices is performed. Intravenous contrast is recommended for lesions near mediastinal structures and lesions within the liver. The form of respiratory control to be used during treatment should also be used during the simulation. Oral GI contrast to highlight the stomach and duodenum is recommended for patients with medial liver lesions or lesions of the caudate lobe.

The planning target volume (PTV) is constructed to account for the positional uncertainty of the GTV during treatment. The PTV for each contoured GTV should be at least 5mm larger than the GTV in the axial plane and 1.0 cm larger than the GTV in the cranio-caudal plane. Larger margins may be used in cases where greater motion of the hemi-diaphragm is observed in simulation despite standard maneuvers to diminish motion. For lung SABR the same principles apply; the entire lung volumes are contoured, as are each individual GTV within the lung.

The prescription dose for each lesion is listed in the table in section 4.1.1, prescribed to the periphery of the PTV. There is no restriction on the dose "hotspot" except that it must be located within the PTV. A Linear Accelerator with effective photon energies of ≥ 6 MV is required. The use of a multi-leaf collimator (MLC) or custom blocks are acceptable. A stereotactic relocalization system that relies upon stereoscopic radiographs, implanted fiducials, or near real-time CT based verification will be used. The PTV may be treated with any combination of coplanar or non-coplanar three-dimensional conformal fields, shaped to deliver the specified dose while restricting the dose to the normal tissues. Field arrangements will be determined by the planning system to produce the optimal conformal plan in accordance with volume definitions.

4.1.3.2 Normal Tissue Dose Constraints

In accordance with prior Phase I studies [98], certain normal tissue dose constraints must be respected. The possibility that SABR-induced fibrosis might cause occlusion of large central airways, thus impeding ventilation distal to the occlusion has been well considered [99]. An adjustment to the fractionation scheme may be made if, in the opinion of the treating radiation oncologist, the following conditions apply: (1) the location of a lung lesion is close enough to a large proximal bronchial airway such that occlusion might occur, and (2) compromised ventilation to the segment(s) of lung potentially affected would cause clinically significant adverse consequences. In such a case, the treating radiation oncologist should discuss any proposed dose modifications with the PI to decide whether a regimen of similar biological potency can be safely given.

The same special condition applies in the setting of a patient whose primary disease has been irradiated previously and is present as a site of disease. Since re-irradiation toxicity is a concern, these patients will be considered by the PI on a case-by-case basis and SABR to a site previously irradiated with conventional fractionation within two years is not recommended. Re-irradiation to a site that has received previous SABR is not allowed. Deviations from the intended dose regimen will be documented, with calculations of the BED of the applied regimen included in the patient's research chart along with documentation of the discussions pertaining to the idiosyncrasies of the case.

The following table lists the specific organ and dose fractionation constraints on normal tissues.

For One Fraction:

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose	Endpoint (≥Grade 3)

			(Gy)**	
Optic Pathway	<0.2 cc	8 Gy	10 Gy	neuritis
Cochlea			9 Gy	hearing loss
Brainstem (not medulla)	<0.5 cc	10 Gy	15 Gy	cranial neuropathy
Spinal Cord and medulla	<0.35 cc <1.2 cc	10 Gy 8 Gy	14 Gy	myelitis
Spinal Cord Subvolume (5-6 mm above and below level treated per Ryu)	<10% of subvolume	10 Gy	14 Gy	myelitis
Cauda Equina	<5 cc	14 Gy	16 Gy	neuritis
Sacral Plexus	<5 cc	14.4 Gy	16 Gy	neuropathy
Esophagus*	<5 cc	11.9 Gy	15.4 Gy	stenosis/fistula
Brachial Plexus	<3 cc	13.6 Gy	16.4 Gy	neuropathy
Heart/Pericardium	<15 cc	16 Gy	22 Gy	pericarditis
Great vessels	<10 cc	31 Gy	37 Gy	aneurysm
Trachea and Large Bronchus*	<4 cc	17.4 Gy	20.2 Gy	stenosis/fistula
Bronchus- smaller airways	<0.5 cc	12.4 Gy	13.3 Gy	stenosis with atelectasis
Rib	<5 cc	28 Gy	33 Gy	Pain or fracture
Skin	<10 cc	25.5 Gy	27.5 Gy	ulceration
Stomach	<5 cc	17.4 Gy	22 Gy	ulceration/fistula
Bile duct			30 Gy	stenosis
Duodenum*	<5 cc <10 cc	11.2 Gy 9 Gy	17 Gy	ulceration
Jejunum/Ileum*	<30 cc	12.5 Gy	22 Gy	enteritis/obstruction
Colon*	<20 cc	18 Gy	29.2 Gy	colitis/fistula
Rectum*	<3.5 cc <20 cc	39 Gy 22 Gy	44.2 Gy	proctitis/fistula
Ureter			35 Gy	stenosis
Bladder wall	<15 cc	12 Gy	25 Gy	cystitis/fistula
Penile bulb	<3 cc	16 Gy		impotence
Femoral Heads	<10 cc	15 Gy		necrosis
Renal hilum/vascular trunk	15 cc	14 Gy		malignant hypertension
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**		**Endpoint (≥Grade 3)**
Lung (Right & Left)	1500 cc	7 Gy		Basic Lung Function
Lung (Right & Left)	1000 cc	7.6 Gy	V-8Gy <37%	Pneumonitis
Liver	700 cc	11 Gy		Basic Liver Function
Renal cortex (Right & Left)	200 cc	9.5 Gy		Basic renal function

For Three Fractions:

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)**	Endpoint (≥Grade 3)
Optic Pathway	<0.2 cc	15.3 Gy	17.4 Gy	neuritis
Cochlea			14.4 Gy	hearing loss
Brainstem (not medulla)	<0.5 cc	15.9 Gy	23.1 Gy	cranial neuropathy
Spinal Cord and medulla	<0.35 cc <1.2 cc	15.9 Gy 13 Gy	22.5 Gy	myelitis
Spinal Cord Subvolume (5-6 mm above and below level	<10% of subvolume	18 Gy	22.5 Gy	myelitis

treated per Ryu)				
Cauda Equina	<5 cc	21.9 Gy	25.5 Gy	neuritis
Sacral Plexus	<5 cc	22.5 Gy	24 Gy	neuropathy
Esophagus*	<5 cc	17.7 Gy	25.2 Gy	stenosis/fistula
Brachial Plexus	<3 cc	22 Gy	26 Gy	neuropathy
Heart/Pericardium	<15 cc	24 Gy	30 Gy	pericarditis
Great vessels	<10 cc	39 Gy	45 Gy	aneurysm
Trachea and Large Bronchus*	<5 cc	25.8 Gy	30 Gy	stenosis/fistula
Bronchus- smaller airways	<0.5 cc	18.9 Gy	23.1 Gy	stenosis with atelectasis
Rib	<5 cc	40 Gy	50 Gy	Pain or fracture
Skin	<10 cc	31 Gy	33 Gy	ulceration
Stomach	<5 cc	22.5 Gy	30 Gy	ulceration/fistula
Bile duct			36 Gy	stenosis
Duodenum*	<5 cc <10 cc	15.6 Gy 12.9 Gy	22.2 Gy	ulceration
Jejunum/Ileum*	<30 cc	17.4 Gy	27 Gy	enteritis/obstruction
Colon*	<20 cc	24 Gy	34.5 Gy	colitis/fistula
Rectum*	<3.5 cc <20 cc	45 Gy 27.5 Gy	49.5 Gy	proctitis/fistula
Ureter			40 Gy	stenosis
Bladder wall	<15 cc	17 Gy	33 Gy	cystitis/fistula
Penile bulb	<3 cc	25 Gy		impotence
Femoral Heads	<10 cc	24 Gy		necrosis
Renal hilum/vascular trunk	15 cc	19.5 Gy		malignant hypertension
Parallel Tissue	**Critical Volume (cc)**	**Critical Volume Dose Max (Gy)**		**Endpoint (≥Grade 3)**
Lung (Right & Left)	1500 cc	10.5 Gy		Basic Lung Function
Lung (Right & Left)	1000 cc	11.4 Gy	V-11Gy<37%	Pneumonitis
Liver	700 cc	17.1 Gy		Basic Liver Function
Renal cortex (Right & Left)	200 cc	15 Gy		Basic renal function

*Avoid circumferential irradiation.
** “point” defined as 0.035cc or less
Exceeding these dose tolerances by more than 2.5% constitutes a minor protocol violation.
Exceeding these dose tolerances by more than 5% constitutes a major protocol violation.

4.1.4 Radiation Therapy Quality Assurance

Dr. Timmerman or Dr. Hannan will perform a RT Quality Assurance Review after complete data for the first 20 cases enrolled has been received at the University of Texas Southwestern. Dr. Timmerman or Dr. Hannan will perform the final review after complete data for the subsequent 15 cases enrolled at the University of Texas Southwestern. These cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received, whichever occurs first.

4.2 Nivolumab

4.2.1 Treatment Dosage and Administration

Nivolumab administered per standard of care according to institutional guidelines at the discretion of the treating medical oncologist. The standard FDA approved administration and indications of Nivolumab is listed in the FDA website: www.fda.gov or Package Insert https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125554s058lbl.pdf. Nivolumab may be administered in a community practice setting as long as the treating study oncologist assumes responsibility for all reporting and follow-up requirements.

If Nivolumab dosing is delayed for a drug-related adverse event, treatment may resume when the event has resolved to Grade 1 or baseline. If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except in cases where the delay is due to the need for a prolonged steroid taper to manage drug-related adverse events or the delay is not drug related.

4.2.1.1 Toxicities and Dosing Delays/Dose Modifications

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events table (5.4). Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0. No dose modifications for Nivolumab will be allowed. Treatment with Nivolumab will be modified by withholding doses rather than continuing therapy at a reduced dose. We recommend to follow the FDA institutional guidelines or at the discretion of the treating medical oncologist for any dose delay criteria, criteria to resume treatment with Nivolumab and/or discontinuation for nivolumab.

Treatment of Nivolumab Related Infusion Reactions

Since Nivolumab contains only human immunoglobulin protein sequences, it 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, pruritus, 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 infusion, 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 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 case report form (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 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 ventilator support indicated) Immediately discontinue infusion of Nivolumab. 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 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 pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

Continued Treatment Beyond Progression of Disease
As indicated above, we will use the RECIST and ir-RECIST criteria for tumor measurement and RR determination. Accordingly, an initial progression on the first set of scans should be verified by a second set of scans before considering it as disease progression and before the decision to discontinue treatment is made. If progression is confirmed on the second set of scans, the first date will be used in evaluations of PFS. (Scans are collected at the time points listed in the study procedures)

In addition, accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit from continued treatment despite initial evidence of progressive disease. For this reason, subjects will be permitted to continue study therapy beyond initial investigator-assessed ir-RECIST) progression as long as they meet the 2 criteria listed below at the discretion of the treating medical oncologist:
- Investigator-assessed clinical benefit,
and
- Subject is tolerating study drug.

Subjects should discontinue study therapy upon evidence of further progression at the discretion of the treating medical oncologist, defined as an additional 10% or greater increase in tumor burden 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). <u>For statistical analyses that include the investigator-assessed progression date, subjects who continue treatment beyond initial investigator-assessed, ir-RECIST 1.1-defined progression will be</u>

considered to have investigator-assessed progressive disease at the time of the initial progression event.

4.3 Duration of Therapy

Nivolumab will be dosed per standard of care approved guidelines. Nivolumab administration will be repeated, at the discretion of the treating medical oncologist until [5]:

- Disease progression as per the ir-RECIST criteria
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the subject unacceptable for further treatment in the judgment of the principal investigator or medical oncologist.

SABR will be performed after the second Nivolumab dose but before the fourth dose (i.e. before the second Nivolumab cycles).

4.4 Duration of Follow Up

For patients who respond to treatment, subjects will be followed for five years or until death (although findings will be analyzed and reported at a median follow up of 2-4 years), whichever occurs first. For these patients, follow-up will be every 8 - 12 weeks from study registration with imaging studies and physical exam (recommended) every 8-12 weeks for the first year, then every 8-12 weeks for the second year, then every four-six months thereafter for a total of five years.

Subjects who show progressive disease will be followed for survival and will no longer strictly adhere to study calendar requirements.

Subjects removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

4.5 Removal of Subjects from Protocol Therapy

Subjects will be removed from therapy when any of the criteria listed in Section 5.5 apply, however will continue to be followed up as per protocol described above. Study coordinators will notify the Principal Investigator, and document the reason for study removal and the date the subject was removed in the Case Report Form.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed strictly for research purposes will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively for research purposes) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 8 weeks prior to registration unless otherwise stated. If patients remain eligible after the screening occurs, they will be registered. The screening procedures include:

5.1.1 *Informed Consent*

5.1.2 *Medical history*

Complete medical and surgical history, history of infections and pulmonary risk factors

5.1.3 ***Demographics***

Age, gender, race, ethnicity

5.1.4 ***Review subject eligibility criteria***

5.1.5 ***Review previous and concomitant medications***

5.1.6 ***Physical exam (recommended) including vital signs, height and weight***

Vital signs (temperature, pulse, respirations, blood pressure, O2 saturation), height, weight: should be done at screening and prior to first dose of Nivolumab

5.1.7 ***Performance status***

Performance status evaluated prior to study entry according to Appendix A.

5.1.8 ***Adverse event assessment***

Baseline adverse events will be assessed. See section 7 for Adverse Event monitoring and reporting.

5.1.9 ***Hematology (within 14 days of registration)***

Recommended

5.1.10 ***Blood draw for correlative studies***

Must be done 0-28 days prior to first dose. See Section 9.0 for details.

5.1.11 ***Serum/urine chemistries (within 14 days of registration)***

Recommended

5.1.12 ***Pregnancy test (for females of child bearing potential)***

Per standard of care at the discretion of the treating medical oncologist.

5.1.13 ***Radiographic Imaging***

5.1.13.1 CT chest, abdomen and pelvis (recommended with IV contrast) must be done within 6 weeks of registration. MRI can replace CT at the discretion of the treating physician.
5.1.13.2Brain MRI is allowed up to 3 months prior to registration.

5.1.14 ***Biopsy of metastatic lesion***

5.1.14.1 Pre-treatment biopsy:

A CT-guided biopsy of a tumor lesion will be performed prior to study registration, unless previous biopsy of metastatic site exists in which case a pretreatment biopsy is not required.

5.1.14.2 Post-treatment elective biopsy:

An elective post-treatment biopsy will be performed at 8 weeks (+/- 2 weeks, >4weeks after SABR) (first follow up visit) and for this biopsy, any site other than a lymph node and a treated site is acceptable. In case of CR no lesions may remain to be biopsied.

5.1.15 QoL Questionnaires

FACT-G, EQ-5D, FKSI, Cost Effectiveness questionnaire: These forms will be referred to collectively as QoL Questionnaires and will be collected prior to first Nivolumab dose and at specific time-points as indicated in section 5.4

5.1.16 Tumor assessment

To be performed on CT or MRI from 5.1.13.

5.2 Procedures During Treatment

SABR treatment requires one week for planning and one week for delivery of the 1 or 3 fractionation schemes. Thus, CT simulation and treatment planning will take place any time before the radiation. SABR will be performed after 1st cycle of Nivolumab infusion. Vital Signs, AE Assessment, Medication Review and Laboratory Review may be performed by a Nurse or Physician.

5.2.1 Prior to first Nivolumab dose (0-28 days prior)

- Focused physical exam (recommended)
- Vital Signs
- Performance Status (recommended)
- AE Assessment
-
- For WOCBP, pregnancy test within 24 hours of first dose of Nivolumab
- Blood draws for immunologic studies
- FACT-G, EQ-5D, FKSI, Cost-Assessment questionnaires

5.2.2 Day 1 of Nivolumab cycle

- Focused PE (recommended)
-
- All labs (except corollary blood collections) will be done per standard of care at the discretion of treating medical oncologist.
- First Nivolumab infusion cycle administered
- Blood draws for immunologic studies at baseline, follow up q 8-12 weeks (until discontinued or within first year of enrollment, whichever is first)and at 1 year (if discontinued before 1 year).

5.2.3 Pre-RT

- CT simulation for SABR planning
-

5.2.4 Radiation Treatment

- AE assessment
- Vital Signs
- SABR treatments will be performed after 1st cycle of Nivolumab infusion.

These cycles will continue (without SABR) until patient is discontinued from Nivolumab as discussed above.

5.3 Follow-up Procedures

- <u>For patients who are still receiving Nivolumab:</u>

Subject will be followed every 8-12 weeks starting from the date of registration for the first two years. , then every four-six months thereafter for five years or death, whichever comes first. The following procedures will be performed at each follow up:

- Physical exam (recommended), Performance Status (recommended), Vital Signs, Medication Review, AE assessment
- HR-QoL questionnaire at baseline, and then at six month intervals until patient meets primary endpoint
- Blood collection for correlative immunologic studies (see section 9.0): In total, all patients will get blood draws for correlative studies at baseline, follow up q 8-12 weeks (until discontinued or within first year of enrollment, whichever is first) and at 1 year (if discontinued before 1 year).
- Radiographic imaging: Tumor assessments will be completed by the investigator using the RECIST and ir-RECIST criteria as above.
  - CT chest, abdomen and pelvis with IV contrast (contrast recommended), if allowable by renal function. MRI with contrast (contrast recommended) can replace CT.
  - MRI, if necessary to confirm CT findings, at the discretion of physician

- For patients who have been discontinued from Nivolumab (See Section 4.3):

Subject will be followed within 3 months from last dose ((+/- 2 months), or may be on date of discontinuation).
The following procedures will be performed:

- Physical exam (recommended), Performance Status (recommended), Vital Signs, Medication Review, AE ssessment
- Subsequent anti-cancer treatment/s
- Blood samples for correlation immunologic studies

After that, survival visits/phone calls continue annually to include Survival Status, AE Assessment, and Subsequent anti-cancer treatment/s.

5.4 Time and Events Table

The above recommended labs are listed in the following table but investigators in the various participating institutions may obtain labs per their standard of care to assess suitability for treatment.

	Pre-study	Cycle Day 1 Infusion	Pre-RT	Radiation Treatment		Follow Up Schedule for Patients who respond to treatment (for other patients refer to Section 5.3)		
						Months 1-12: q8-12 Weeks	Months 13-24: q8-12 Weeks	Months 25-60: q16-24 Weeks
Informed Consent	X							
Vital Signs	X	X		X		X	X	X
Medical History	X					X	X	X
Physical Exam (recommended)	X	X				X	X	X
Performance Status (recommended)	X					X	X	X
AE Assessment	X	X		X		X	X	X

Medication Review		X				X	X	X
CT Chest, Abd**, pelvis w/ Contrast	X					X	X	X
MRI Brain w/contrast	X							
Tumor Assessment	X							
Biopsy of metastatic lesion	X^					X@		
CT Simulation			X					
SABR Treatment				X				
Blood Draw for Correlative Studies (Section 9.0)	X#	X#		X#		X#		
QOL Questionnaires	X					X%	X%	X%
Cost-Effectiveness Questionnaire	X					X^^		
Tumor assessment	X							

** MRI should be considered, in place of CT, on an individual basis if felt to be better by the radiation or medical oncologist.

[1] For cycle 1, no need to repeat blood tests at day 1

Immunologic blood collection is needed at baseline, follow up q 8-12 weeks (until discontinued or within first year of enrollment, whichever is first) and at 1 year (if discontinued before 1 year).

^ if previous biopsy of metastatic site with adequate review of slides is not available.

^^ Cost Effectiveness Questionnaire administered at Baseline, 8 week follow up and 6 month follow up.

@ Biopsy is optional at 8 weeks

% QoLs will be done at baseline and then at 6 month intervals

5.5 Removal of Subjects from Study Treatment or Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.5.1 Subject voluntarily withdraws from treatment (follow-up permitted);

5.5.2 Subject withdraws consent (termination of treatment and follow-up);

5.5.3 Subject is unable to comply with protocol requirements; patients must be withdrawn from the trial and replaced if they failed to receive the SABR treatment. Any patient with at least one cycle of Nivolumab and SABR will be included in the analysis.

5.5.4 Subject demonstrates disease progression (unless continued treatment with Nivolumab is deemed appropriate at the discretion of the medical oncologist);

5.5.5 Subject experiences toxicity that makes continuation in the protocol unsafe;

5.5.6 Treating physician judges' continuation on the study would not be in the subject's best interest;

5.5.7 Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

5.5.8 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

5.5.9 Lost to follow-up. If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented .

5.6. Subject Replacement: Subject replacements are allowed in the following situations:

5.6.1 If the subjects decide to withdraw from the study without finishing the course of SAbR

5.6.2 If the subjects decide to withdraw from the study or lost to follow up (for reasons of death from other causes, moving to other state etc.) or refuse follow up scans leading to <2 follow-up scans (making it impossible to assess the primary endpoint of the trial)

6.0 Measurement of Effect

6.1 Antitumor Effect

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. The only change from RECIST v.1.1 being implemented in this study is a confirmation of new lesions or progressive disease (PD) by a second scan >6 weeks apart, based on the immune RECIST (ir-RECIST) criteria proposed by Wolchok. *et. al* that is appropriate for immune-related treatment response [89]. This is primarily because immune response often can take longer time as compared to chemotherapy before producing a radiographic response and during this time new lesions may arise which will eventually regress. If it were not for a second confirmation, these patients would be labeled to have failed therapy. Additional criteria for bone lesions and clinical endpoints of pathologic fracture and cord compression are added to this study (see Section 6.1.4). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria outlined in http://www.recist.com/. The primary endpoint will be evaluated using RECIST v1.1 and secondary endpoint will be ir-RECIST.

6.1.1 Definitions

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their registration.

Evaluable for objective response. Only those subjects who have undergone SABR and 1 cycle of Nivolumab and have had their disease re-evaluated at least at two occasions will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below.

6.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded)

as ≥10 mm with spiral (Helical) CT scan (CT/MRI scan slice thickness should be no greater than 5 mm). All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). For 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). At baseline and in follow-up, only the short axis will be measured and followed. Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan) and lymph nodes <15 mm, are considered non-measurable disease. Leptomeningeal disease (patients excluded), ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable. Blastic bone lesions are non-measurable. Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Note: Lesions receiving SABR will be called "radiated lesion" which should not be confused with "target lesions" defined here for the for the purpose of radiographic measurement. Radiated lesions and target lesions are mutually exclusive lesions. Therefore, radiated lesions will not be used as target lesions for evaluating response. At least 2 non-CNS measurable lesions are required for enrollment.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 6 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.1.3 Methods for Evaluation of Measurable Disease

All measurements will be done digitally on the PACs system. All baseline evaluations should be performed as closely as possible to the beginning of treatment.

Whenever possible, the same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up using appropriate radiologic imaging.

MRI Brain, and CT scan or MRI with IV contrast (whenever possible) will be performed at baseline. Since bone scan is not reliable for RCC, it will only be used to evaluate overall response when positive in baseline scan, and any new lesions found on bone scan must be verified with a CT. Bone scans will not be used for measuring lesion size.

Spiral CT and MRI. All CT scans will be Spiral CT and should be performed using a 5 mm contiguous reconstruction algorithm.

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted no less than 4 weeks apart. Any pathological lymph nodes must have reduction in short axis to < 10 mm. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions verified by a second scan > 6 weeks apart. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

6.1.4.2 Evaluation of Non-Target 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 (< 10 mm short axis).

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

6.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subjects' best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

6.1.4.4 Evaluation of Bone Lesions:

Bone lesions will be evaluated either by CT or MRI, whichever is deemed to be better suited by baseline studies. Since the size of the lesion is difficult to measure in a bone scan, particularly if it is not well visible in CT, the following guideline will be used. Any ambiguity will require MRI for resolution:

6.1.4.4.1 Progression of bone lesions will be defined as follows:

- Appearance of 1 or more new bone lesion in CT scan, confirmed by a repeat scan in ≥6 weeks.

6.1.4.4.2 Response of bone lesions in CT scan will be defined by either a complete resolution (CR) at the metastatic sites or partial resolution (PR) of radiotracer uptake by a radiologist.

6.1.4.5 Evaluation of Pathologic Fracture:

Any clinical suspicion of pathologic fracture will prompt radiologic evaluation with plain film, CT or MRI as appropriate and if confirmed by a radiologist, will constitute progression, unless it is at a treated site, in which case a treatment-related toxicity will be considered. In that case, patients will be referred for orthopedics specialist evaluation.

6.1.4.6 Evaluation of spinal cord Compression or Cauda Equina compression:

Any clinical suspicion of cord or cauda equina compression will prompt radiologic evaluation with MRI (CT myelography if patient is not eligible for MRI) as appropriate and if confirmed by a radiologist, will constitute progression.

6.1.5 Response Rate:

Response rate (RR) is defined by combining CR and PR.

6.1.6 Duration of Response

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

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the study registration until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

6.1.7 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from the date of registration to time of progression or date of death due to any cause.

6.2 Safety/tolerability

Analyses will be performed for all subjects having received at least one fraction of SABR and one cycle of Nivolumab. The study will use the CTCAE version 4.0 for reporting of non-hematologic adverse events (http://ctep.cancer.gov/reporting/ctc.html) and modified criteria for hematologic adverse events.

6.3 Quality of Life (QoL)

6.3.1 Functional Assessment of Cancer Therapy-P (FACT-G) and Kidney Symptom Index (FKSI)

Patient-reported functional status will be assessed the Functional Assessment of Cancer Therapy-General (FACT-G) (See appendix E). The FACT-G is a 28-item questionnaire that uses 5-point Likert-type response choices (0 = not at all; 1 = a little bit; 2 =somewhat; 3 = quite a bit; 4 = very much). It will take less than 10 minutes to complete the questionnaire. The Trial Outcome Indices (TOI) also will be utilized to measure the summed functional well-being, and physical well-being [102, 103]. A 5-point deterioration in the FACT-G TOI between pre-treatment and at post treatment or at year 1 will be considered clinically significant [104].

The FKSI is a 15 question validated symptom index for kidney cancer patients which has been used in several metastatic renal cell cancer studies [105]. This scale focuses on symptoms predominantly related to kidney cancer such as energy, fatigue, pain, bone pain, weight loss, shortness of breath, cough, fever, hematuria. This subscale of the FKSI-DRS was validated in another study as well [106]. The FACT-G and FKSI will

be collected prior to first Nivolumab dose (baseline), and at every subsequent follow up appointment until the patient meets primary endpoint [105][3][82].

The first analysis of change in QOL from baseline to 8 weeks will only be performed on patients who are still alive at 8 weeks. Changes in QOL will be also analyzed using all available data at baseline, 2, 4, 6, 8, 10 and 12 months with semiparametric generalized estimating equations (GEE).

Additionally, similarly we will also compare the percentage of patients with an effect size for the change in FKSI (FKSI) scores between pre-treatment and post treatment which will allow us to compare the percentage of patients whose functional status remains more similar to baseline levels.

6.3.2 EQ-5D

The EQ-5D is a patient self-administrated questionnaire that takes approximately 5 minutes to complete (See appendix D). The first part consists of 5 items covering 5 dimensions including: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on 5 levels. Health states are defined by the combination of the leveled responses to the 5 dimensions, generating 243 health states to which unconsciousness and death are added.

The 5-item index score is transformed into a utility score between 0, “Worst health state,” and 1, “Best health state.” The index score or the cost-utility equation can be used in the quality adjusted survival analysis depending on the health state(s) of interest.

Additionally the EQ 5D is utilized to establish health state utility which is used in cost-effectiveness analysis to calculate quality adjusted life years. This is the recommended health state utility form used in the United Kingdom and approved by the National Institute for Clinical Excellence (NICE) and has been used to establish health state utility and metastatic renal cell cancer patients. The EQ 5D will be given at baseline and at follow ups. The EQ-5D will also be available in the Spanish language.

The EQ-5D also includes a visual analog scale (VAS), a validated measure of general well-being, scored on a scale of 0-100. These data will be analyzed over time in a similar manner as the FACT-G and FKSI. EQ-5D will be collected prior to first Nivolumab dose (baseline), and at every subsequent follow up appointment until the patient meets primary endpoint.

6.4 Cost effectiveness data collection:

Healthcare utilization data needed to assess costs will be obtained from insurance claims and medical records. Also the cost effectiveness questionnaire will be completed by the patients at baseline, 8 week follow up and 6 months follow up (see Appendix G). These costs will be divided into the following domains:

Hospitalizations: For hospitalizations with physician billing records, impatient physician costs will be estimated by applying Medicare payment rates under the RBRVS-based Medicare Fee Schedule to billed procedures in the physician billing records.

Radiation Treatment Cost: Direct costs of radiation treatment including consultation, simulation, treatment planning, and treatment delivery. Patient bills related to treatment will be obtained and estimated by total billed charges adjusted by facility-specific cost-to-charge ration from Medicare cost reports as described above.

Emergency Room visits: The date of ER visit and name of the facility, and whether the ER visit resulted in a hospital admission. ER costs will be estimated using

Medicare average payment rates for facility and physician charges, using the merged MEDPAR and MBS data as described above.

Physician and Clinic Visits: The date of the visit, the name of the physician or physician clinic, and the service provided (physician exam, lab test, physical therapy, etc.). Costs for physician and clinic visits will be calculated based on billing records obtained for such visits, using Medicare payment rates for procedures indicated in the clinic billing records.

Medications: Nivolumab is a new generation immunotherapy drug and is very costly (over $100,000 per year). Nivolumab drug cost will depend greatly on the number of cycles received. Prescription drugs used, including information about name, dose, and frequency of all, will be recorded. The medications used by the study patients will be assigned an NDC drug code. Unit costs for these drugs will be estimated as the "AWP" price published in the Red Book less 15%. Outpatient drug costs will be calculated by multiplying unit cost by the number of pills used per day times the length of time the patient received the medication. Note that costs of drugs administered through a clinic (e.g., reimbursed under Medicare Part B) are included under "clinic visit costs" and impatient drug costs are included under "inpatient facility costs."

7.0 ADVERSE EVENTS

7.1 SABR

The contraindications and adverse events for SABR are mostly related to the treatment site and its radiation dose tolerance, as discussed in detail in section 4.1

7.1.1 Contraindications:

Treatment of patients who have received conventional radiation therapy at same site of new metastasis is at the discretion of the radiation oncologist. Treatment of patients who have received SABR at same site of new metastasis is contra-indicated. Treatment of patients with scleroderma or active Lupus is at the discretion of the radiation oncologist.

7.1.2 Special Warnings and Precautions for Use: N/A

7.1.3 Interaction with other medications: None

7.1.4 Adverse Reactions: Sites-specific. Please see section 4.1

7.2 Nivolumab

7.2.1 Contraindications

None

7.2.2 Special Warnings and Precautions for Use

See 7.2.4

7.2.3 Drug Interactions

No formal pharmacokinetic drug-drug interaction studies have been conducted with Nivolumab.

7.2.4 Adverse Reactions

In CA209001 (n = 39), in which subjects received a single dose of Nivolumab (BMS-936558) with possible retreatment at 3 months, the most frequent AEs were fatigue (56%), nausea (44%), proteinuria (38%), constipation (33%), back pain (33%), dry mouth

(28%), vomiting (28%), rash (26%), and dyspnea (26%). There was no clear or consistent relationship between the incidence or severity of AEs and the Nivolumab (BMS-936558) dose level (0.3, 1, 3, or 10 mg/kg IV single dose, with possible retreatment at 3 months). Of 39 (100%) subjects who had at least one AE, 32 (82%) had Grade 3 or 4 AEs regardless of causality. Three treatment-related SAEs were reported: hypothyroidism (Grade 2), colitis (Grade 3), and anemia (Grade 2). Among 12 deaths, none were considered drug-related.
In CA209003 (n = 296), as of the database lock date of 24-Feb-2012, BMS-936558-related AEs of any grade occurred in 70% of subjects. The most frequent drug-related AEs occurring in ≥5% of subjects included fatigue (24%), rash (12%), diarrhea (11%), pruritus (10%), nausea (8%), decreased appetite (8%), hemoglobin decreased (6%) and pyrexia (5%). The majority of events were low grade, with Grade 3/4 drug-related AEs observed in 14% of subjects. The most common Grade 3/4 drug-related AEs occurring in ≥1% of subjects were fatigue (2%), pneumonitis (1%), hypoxia (1%), diarrhea (1%), colitis (1%), abdominal pain (1%), AST/ALT increased (1% each), blood alkaline phosphatase increased (1%), lipase increased (1%), pneumonia (1%), hypophosphatemia (1%), and lymphopenia (1%). Drug-related serious AEs (SAEs) occurred in 11% of subjects. Grade 3/4 drug-related SAEs occurring in ≥1% of subjects were: pneumonitis (1%), pneumonia (1%), lipase increased (1%), and diarrhea (1%). The spectrum, frequency, and severity of BMS-936558-related AEs were generally similar across dose levels and histological subtypes. Other drug-related AEs included vitiligo, hepatitis, hypophysitis, and thyroiditis. Hepatic or gastrointestinal events were managed with treatment interruption and administration of corticosteroids, and were generally completely reversible. Endocrine events were managed with replacement therapy. Several subjects in these categories successfully reinitiated treatment with BMS-936558. Drug-related pneumonitis occurred in 3% of subjects; Grade ≥3 pneumonitis developed in 3 subjects (1%). No clear relationship between the occurrence of pneumonitis and tumor type, dose level, or the number of doses received was noted. Early-grade pneumonitis was generally reversible with treatment discontinuation and corticosteroid administration. In three subjects, infliximab and/or mycophenolate were utilized for additional immunosuppression, with unclear effectiveness. There were three (1%) drug-related deaths due to pneumonitis. In two of these cases, the subject did not receive the early and aggressive intervention (including systemic corticosteroid therapy) that is likely key in the management of this toxicity, while in the third case, other anti-cancer agents (erlotinib and vinorelbine) may have contributed to the fatal event. Preliminary new non-clinical safety findings of adverse pregnancy outcomes and infant losses in the absence of overt maternal toxicity have been reported. The findings of increased late stage pregnancy loss and early infant deaths/euthanasia in Nivolumab exposed pregnant monkeys suggest a potential risk to human pregnancy if there is continued treatment with Nivolumab during pregnancy.

Opportunistic Infections Related to Immunosuppression

As of 03-Apr-2013, three subjects on Nivolumab (BMS-936558) clinical trials have developed opportunistic infections (2 cases of Aspergillus, and 1 case of Pneumocystis jiroveci) after receiving prolonged treatment with high dose steroids for Nivolumab-related adverse events without antifungal prophylaxis. Details of these cases are available in the BMS-936558 Investigator Brochure. Because of the potential for opportunistic infections with prolonged high dose corticosteroid administrations, the following recommendations should be considered for subjects with inflammatory events expected to require more than 4 weeks of corticosteroids or other immunosuppresants:

- Antimicrobial/antifungal prophylaxis per institutional guidelines to prevent opportunistic infections such as Pneumocystis jiroveci, bacterial and fungal infections.
- Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate.

- In addition, a concomitant opportunistic infection should be considered in the differential diagnosis when patients develop recurrent adverse events in the setting of ongoing or prior immunosuppressive use.

7.3 Combination Nivolumab and SABR: preliminary experience

Currently, there are no published studies reporting the toxicity of combination Nivolumab and SABR. However, either treatment alone is well tolerable with a favorable toxicity profile as seen above.

In our experience, we have already used SABR in five patients who are receiving Nivolumab for metastatic diseases (4 with mRCC and 1 with metastatic melanoma- See table 7.3.1).

Patient	Age/ Gender	Diagnosis	Surgery	Prior Chemotherapy/Immunotherapy	Prior Radiation	Peri-Nivolumab SBRT	Nivolumab
1	69, M	CC RCC	No	Pazopanib, Axitinib	SBRT liver on 05/2015	40 Gy in 5 fractions to L lung lesion and 40Gy in 5 fractions to L shoulder between 02/05/2016 and 02/19/2016.	1/20/2016; 2/2/2016; 2/15/2016.
2	65, M	CC RCC	Yes	Sunitinib, Axitinib, Everolimus, Pazopanib,	None	30 Gy in 3 fractions to R parotid between 3/14/16 and 3/18/16	2/15/16; 3/7/16; 3/21/16; 4/4/2016; 4/18/2016; 5/2/2016.
3	62, M	CC RCC	Yes	IL-2, Sunitinib, Axitinib, Everolimus, Pazopanib, Temsirolimus, Sorafenib	Multiple rounds of radiation for bone metastasis including SBRT	50 Gy in 5 fractions to L femur between 02/02/2016 and 02/16/2016.	2/19/2016; 03/xx/2016; 3/18/2016; 4/1/2016.
4	62, M	CC RCC with sarcomatoid features	Yes	Axitinib	SBRT for bone and visceral metastasis and GK x2 for multiple brain metastasis	36 Gy in 3 fractions to R clavicle and 33 Gy in 3 fractions to R chest wall between 4/4/16 and 4/8/16	3/21/16; 4/4/2016; 4/18/2016.
5	66, M	Melanoma	-	Ipilimumab	None	45 Gy in 3 fractions to L lung lesion between 3/2/16 and 3/7/16	2/12/16; 2/26/16; 3/11/16; 3/25/16; 4/8/16; 4/22/16.

Abbreviations: SBRT: stereotactic body radiation therapy; M: male; F: female; CC RCC: clear cell renal cell carcinoma; IL-2: Interleukin-2; Gy: Gray; GK: Gamma Knife; L: left; R: right

Table 7.3.1. Patients' characteristics and prior/current treatments

Our preliminary acute toxicity data (See table 7.3.2), with a follow up ranging between 1 and 3 months, shows that the combination treatment is well tolerated with a favorable toxicity profile comparable to the published side effects of Nivolumab alone. The majority

of events were low grade, with only one Grade 3/4 that was considered to be related to disease progression rather than the treatment itself. Grade 1 fatigue was seen in 3/5 patients. There was one grade 4 fatigue that was due to disease progression in the lung causing dyspnea. Grade 1/2 nausea, low appetite and anemia were seen in 2/5 patients. Grade1/2 dyspnea was seen in 2/5 patients, one of which was considered due to exacerbation of congestive heart failure. There was one grade 4 dyspnea that was due to disease progression in the lung. Peripheral edema was seen in 2/5 patients, one of which was due to disease progression causing lymphatic obstruction.

	1	2	3	4	5
Fatigue	YES, Grade 3	YES, Grade 1	X	Yes, Grade 1	Yes, Grade 1
Nausea	YES, Grade 3	X	YES, Grade 1	YES, Grade 1	X
Pruritus	X	X	X	X	X
Diarrhea	X	X	X	X	X
Decreased appetite	YES	YES	X	X	X
Rash	X	X	X	X	X
Cough	Grade 4 (due to tumor progression)	X	X	X	YES, Grade 2
Anemia	Grade 1	Grade 1	X	X	X
Dyspnea	Grade 4 (due to tumor progression)	YES, grade 2 (due to CHF)	X	X	YES, Grade 2
Peripheral edema	X	YES	Yes	X	X
Pneumonitis	X	X	X	X	Yes, Grade 2
Mucosal inflammation	X	X	X	X	X
Dysgeusia	X	X	X	X	X
Hyperglycemia	X	X	X	X	X
Stomatitis	X	X	X	X	X
Hypertriglyceridemia	-	X	-	-	-
Epistaxis	X	X	X	X	X
Oral Thrush	YES, Grade 2	X	X	X	X

Abbreviations: Hg: Hemoglobin; CHF: congestive heart failure; X: none; - no data available
Based on the NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 7.3.2. Summary of side effects with combined SBRT and Nivolumab treatments.

7.4 Adverse Event Monitoring

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 subjects' 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.

7.3.1 Definitions

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

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 or 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 occurring through the time period of the start of treatment through the first follow up occuring 12 weeks post treatment will be considered acute adverse events. All acute adverse events will be assessed and reported as per below.

Late Adverse Events

Adverse effects occurring in the time period from the end of acute monitoring, to 3 years post treatment for progression or death (whichever comes first), will be defined as late adverse events. These events will include all adverse events reported directly to a member of the study team and will be captured, assessed, graded and reported as appropriate.
In addition, the study team will review encounters in a select specialty category relevant to study endpoints. These select specialties include hospitalizations, medical oncology, and radiation oncology records and will be limited in scope based on categorization of events (GU/GI) and also the type of records that will be queried (hospitalizations, medical oncology, and radiation oncology).

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.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) 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

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 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.

7.4.2 Unanticipated Problems Involving Risks to Subjects or Other (UPIRSOs)

The phrase "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.

7.5 Reporting SAEs and UPIRSOs to the Simmon's 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. *(See Appendix III of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized when a sponsor form is unavailable and SAE submission to the eIRB is not required).*

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.

The following instructions section may be modified as needed to ensure clear guidance for institutions participating in the trial who will not report directly to the UTSW Institutional Review Board. If needed, this reporting may be facilitated by the UTSW study team for:

Telephone reports to: Investigator: Dr. Raquibul Hannan study team: Satish Veerla Phone No: 214-648-1895 or Fax: 214-645-8913
Written reports to: UTSW Radiation Oncology Study Coordinator or Clinical Research Manager Email: sarmistha.sen@utsouthwestern.edu Fax: 214-645-8913 UTSW SCCC 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

Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) to the UTSW HRPP/IRB

UTSW reportable event guidance applies to all research conducted by or on behalf of UT Southwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on a 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 must report to their relying IRB according to the relying IRB's policy. In addition, the external IRB's responses or determinations on 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-combined.pdf.

For further guidance for Investigators regarding safety reporting requirements for INDs and BA/BE studies, refer to FDA Draft Guidance document: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

7.6 Steps to Determine If an Adverse Event Requires Expedited Reporting

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 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days 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 (if applicable);
- the current Investigator's Brochure (if applicable);
- the Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities section of this protocol.

7.7 Reporting Requirements for Adverse Events

7.7.1 Expedited Reporting

- The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.
- If necessary, suspected adverse reactions will also be reported to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

- The IRB must be notified within 10 business days of “any unanticipated problems involving risk to subjects or others” (UPR/UPIRSO).

  The following events meet the definition of UPR:

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

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

7.7.2 Routine Reporting

- All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

7.8 Stopping Rules

The study will be stopped if the combination treatment of SAbR and Nivolumab resulted in >50% of increased Grade 3-5 toxicity as compared to those reported in the literature for patients receiving Nivolumab alone in the first 6 patients assigned to the experimental arm and the regimen is deemed to be unsafe by the Data Safety Monitoring Committee.

8.0 DRUG INFORMATION

8.1 Nivolumab

- Other names for the drug(s): Opdivo

- Classification - type of agent: Monoclonal antibody, Antineoplastic Agent, Immunotherapy, PD-1 inhibitor, Miscellaneous; Biological Response Modulator

- Mode of action: Immune-stimulator; Binds to PD-1 receptor on immune cells and prevents the interaction of PD-1 with PD-L1 on cancer cells. By inhibiting this interaction (which inhibits the immune response), Nivolumab is thought to activate the immune response in a non-specific manner

- Storage and stability: Nivolumab vials must be stored at a temperature of 2ºC to 8ºC and should be protected from light. If stored in a glass front refrigerator, vials should

be stored in the carton. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between Nivolumab and polyvinyl chloride (PVC), non-PVC/non-DEHP (di(2-ethylhexyl)phthalate) IV components, or glass bottles have been observed.

- Protocol dose: Per standard of care approved guidelines.
- Preparation: BMS-936558 (Nivolumab) 100 mg (10 mg/mL) will be packaged in an open-label fashion. Ten BMS-936558 10 mL vials will be packaged within a carton.

  Route of administration for this study: Nivolumab administered per standard of care according to institutional guidelines. The standard FDA approved administration and indications of Nivolumab is listed in the FDA website: www.fda.gov or Package Insert https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125554s058lbl.pdf.
- Incompatibility: None
- Availability: Commercially available from Bristol-Myers Squibb.
- Side effects: See 7.2.4
- Nursing implications: As dictated by clinical course
- Nivolumab may be administered in a community practice setting as long as the treating study oncologist assumes responsibility for all reporting and follow-up requirements.

9.0 CORRELATIVES/SPECIAL STUDIES

The goal of the planned laboratory correlative studies is to measure the induced immune response to patient's pre-treatment tumor tissue antigens (see section 1.5 for detail). In addition, the correlative studies will evaluate the immune response generated by the regimen. The submission of collected whole blood is mandatory and will be performed at baseline, follow up q 8-12 weeks (until discontinued or within first year of enrollment, whichever is first) and at 1 year (if discontinued before 1 year).

9.1 Sample Collection Guidelines

Samples will be labeled with the subject's de-identified study number and collection date and delivered for analysis during regular business hours to: NC7: 208; Attn Dr. Raquibul Hannan

9.1.1 Whole blood sample: Patient's whole blood will be collected in EDTA (Lavender top) tubes for ~ 40-50 ml. In addition, ~10 ml will be collected in anti-coagulant-free tubes (Red top) for the collection of sera. The blood will immediately be processed (within 2 hours) by centrifugation (1000 g, 15 min, 4^{o}C), collecting the supernatant and freezing at -80^{o}C in 5 aliquots for future experiments. The pellet will be re-suspended in PBS and PBMC will be isolated using standard protocol. Briefly, the cell suspension will be carefully placed on 10ml polystyrene tube containing 1ml ficoll and centrifuged (400g, 30min, RT). PBMC region will be collected from the ficoll and washed 3x with PBS. Cells will be counted and frozen in 5 aliquots with 10% DMSO, 90% FBS at -80^{o}C.

9.1.2 Tumor Biopsy Sample: A CT-guided biopsy of tumor lesion consisting of 4-5 18G needle cores is recommended at the time of registration of the patients to

the study unless a biopsy has been done in the previous 12 months (See 5.1.15). A second biopsy at 8 weeks (+/- 2 week) is elective.

9.1.2.1

Initial required biopsy: 3-4 core biopsies will be processed as routine diagnostic specimens by Pathology for the purpose of diagnosis and immumo-histochemistry (IHC). After on site adequacy check using touch imprint slides, the cores will be fixed in 10% buffered formalin for up to 8 hours and processed routinely to obtain formalin fixed paraffin embedded blocks. Eight, 3-micron thick sections will be cut. The first and last sections will be stained with hematoxylin and eosin (H&E) stain to evaluate the presence, extent, and grade of renal carcinoma. The remaining sections will be used to perform immunohistochemical staining if needed (see section 9.2 for IHC detail). **Two additional cores** will be placed in normal saline on wet ice and brought to NC9.208 (Dr. Raquibul Hannan) for generation of tumor lysates to be used as a source of antigen in the immunoassays. The biopsy cores will be chopped into minute pieces. Small volume of normal saline is added and the mixture is passed through a 19G needle, attached to a 5 ml syringe, several times, until the passage of the mixture occurred without difficulty. The process is repeated with 21G, 23G, and if possible 25G needle. The entire mixture is placed in liquid nitrogen until frozen, and then thawed in a water bath at 42°C. The freezing and thawing is repeated for a total of five times. The sample is passed through another 23G or 25G needle to disperse any clumps. The sample is then centrifuged at high speed, the supernatant collected, protein concentration measured using NanoDrop2000 and frozen at -80 °C in 5 aliquots.

9.1.2.2

8 week Elective Biopsy: One core from the biopsy will be processed by pathology to generate slides for histology and IHC. The second and third core will be placed in normal saline on wet ice and brought to NC9.208 (Dr. Raquibul Hannan) for processing for flow cytometry of cells. The tumor tissue is first cut into small pieces and incubated in PBS containing DNAse I 1mg/ml (Roche Diagnostics, Indianapolis, IN) and Collagenase 2mg/ml (Fisher Scientific, Pittsburgh, PA) for 1h at 37oC. The lysate is then passed through cell strainer in PBS and washed 2x in 10ml of PBS followed by RBC lysis buffer. The cells are then frozen in 4 aliquots with 10%DMSO 90%FBS in -80°C for future flow cytometry analysis.

9.2 Assay Methodology

9.2.1 **Elispot:** IFN-γ ELISpot assays will be performed according to manufacturer's protocol using a commercial ELISpot kit (MabTECH). Briefly, 96 well plates are coated overnight with 0.015 mg/ml of an anti-human IFN-g monoclonal antibody. PBMC from patients will be incubated in triplicates wells and stimulated in the presence of either PA2024 (10µg/ml), protein lysate from patient biopsy (50µg/ml) or 5 ng/ml PMA and 0.5 ng/ml ionomycin as positive control and albumin as negative control. For ELISPOT assays, plates are incubated for 48 hours, washed, probed with biotinylated anti-IFNg, further washed, and then incubated with streptavidin alkaline phosphatase. Spot development is achieved with 5-bromo-4-chloro-3-indolyl phosphate/nitroblue tetrazolium (BCIP/NBT; Invitrogen) and spots are enumerated by an automatic ELISpot reader.

9.2.2 **ELISA**: In this procedure, patient tumor tissue lysate is first adsorbed to an EIA 96 well microplate (Fischer). Patient plasma is then added to each well as a source

of primary antibody and serially diluted. After extensive washes, detection enzyme (HRP)-linked anti-human mAb is then added to each well and allowed to bind. Appropriate substrate is then added to each well and color development occurs within 5-60 min. UV Microplate Reader will be used to read the plates

9.2.3 **^{3}H-thymidine Proliferation Assay:** PBMC from patients will be incubated in a similar manner as above for five days at 37 ºC then overnight with 0.5 mCi tritiated ^{3}H-thymidine, harvested onto a glass-fiber filter using a 96-well FilterMate cell harvester. The radioactivity of the ^{3}H-thymidine is detected by a direct betaplate counter. The degree of antigen-specific clonal T cell expansion will be expressed as a stimulation index (SI) of the ratio of ^{3}H-thymidine incorporation by cells incubated with patient tumor lysate compared with media controls. An alternate method utilizing FACS analysis with carboxy fluorescein diacetate succinimidyl ester (CFSE) is also available [107].

9.2.4 **Chromium Release Cytotoxicity Assays**: For cell-mediated cytotoxicity analysis, A 50 µl sample of ^{51}Cr-labeled target cells (Caki-2 and ACHIN human renal cancer cells) is mixed with 100µl of effector cells (patient PBMC) at various target to effector ratio (E:T ratios). After centrifugation at 100 X G, the cells are incubated for 2 hr at 37°C. The radioactivity of culture supernatant is measured using a gamma counter and percentage of cytotoxicity is calculated. For antibody-dependent cytotoxicity analysis this procedure will be performed with patient's plasma instead of PBMC and the percentage of cytotoxicity is calculated in similar manner. An alternate and non-radioactive labeling method utilizes GAPDH enzyme release from lysed cells called Bioluminescence Non-Radioactive Cytotoxicity Assay (aCella-TOX, T Cell Technology, INC) [108, 109].

9.2.5 **Flow cytometric analysis (FACS):** For FACS analysis of cell-surface molecules, the cell samples are stained with fluorescent dye – conjugated monoclonal antibodies against the selected markers on ice followed by fixation with 4% paraformaldahyde. Data are acquired on a LSRII (BD Biosciences) and analyzed using FACSDiva software (BD Biosciences). The PBMC of each patient before and after treatment will be analyzed to identify the relative sub-population of CTLs, regulatory T-Cells, effector memory T cells, MDSCs, neutrophils and NK cells utilizing appropriate cell surface markers.

9.2.6 **Immunohistochemical staining (IHC):** Standard immunohistochemistry staining procedure for will be performed using the Benchmark XT automated stainer (Ventana) for both antibodies. Briefly, formalin-fixed, paraffin-embedded tissue sections will be cut at 3-4 micron and air-dried overnight. The sections will be deparaffinized, rehydrated, and subjected to heat-induced epitope retrieval. Sections will then be incubated with appropriate primary antibody. For signal detection, ultraView universal detection system (Ventana) will be used. The slides will be developed using 3-3'-diaminobenzidine chromogen and counterstained with hematoxylin. Appropriate positive and negative controls will be utilized for each run of immunostains. The evaluation of the immunostaining will be carried out by a genitourinary pathologist without knowledge of any clinicopathologic data. Only nuclear reactivity will be considered positive. An H score will be assigned as the product of average intensity of staining (0 for negative, 1 for weakly positive, 2 for moderately positive, and 3 for strongly positive) and extent of immunoexpression (0-100% percentage of cells staining). In addition, Dual-antibody ISH will be performed to identify and analyze TILs, CTL (CD3+,CD8+), Tregs (CD4+FoxP3), DC (CD11c) , NK/T (CD3+, CD1d), neutrophils (CD11b, Ly6G} and MDSC (CD14+,CD11b) in the tumor tissue before and after treatment, when available. PD-L1 expression will be quantified from biopsies of tumors prior to treatment.

9.2.7 Serum Cytokine Analysis: Multiplex cytokine analysis in patient's plasma will be performed in precoated 96 well plates (Human TH1/TH2 10 plex ultrasensitive assay, Meso Scale Discovery – MSD, Maryland, USA) according to manufacturer's instructions. 25 µL of diluent 2 is dispersed into each well. The plate is sealed and incubated by vigorous horizontal shaking for 30 minutes at RT.

25 µL of the patient plasma is added per well and all samples measured in triplicates. Plates are sealed and incubated by vigorous horizontal shaking for two hours at RT. Plates are washed three times with 0.05% Tween 20 in PBS . 25 µL of 1× detection antibody solution is placed per well and sealed plates are incubated by vigorous horizontal shaking for two hours at RT. Plates are washed three times with 0.05% Tween 20 in PBS. 150 µL of 2× Read Buffer T is added to each well. Plates are analysed using the MSD SECTOR Imager 2400 and Discovery Workbench 3.0 software (both from Meso Scale Discovery, USA). The mean value of two wells is taken as the recorded reading, provided that the coefficient of variation (CV) was less than 10%. Concentrations recorded lower than the standard curve are kept as absolute values. For purposes of logarithmic analysis, readings of 0 are adjusted to 0.01 pg/ml. The following cytokines will be measured before and after treatment for each patients: Th1/Th2/Th17 cytokines, IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-8, IL-10, IL-12p70, IL-13, IL-17 TNF-α; pro-inflammatory cytokines: GM-CSF, IFN-γ, IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12p70, TNF-α; Chemokines: Eotaxin, MIP-1β, TARC, IP-10, IL-8, MCP-1, MCP-4 and others including IL-6, TGF-β and HMGB1 (see section 1.5).

9.2.8 Western-blot/Immuno-blot: Caki-2 and ACHIN human renal cancer cells lysate will be used to perform immune-blott using plasma collected from patients before and after treatment. The Caki-2 and ACHIN cell 10^6 cells/mL will be lysed in immunoprecipitation assay buffer on ice for 30 min. Standard western blott methodology will be utilized. Briefly, 400 µg of protein will be separated using pre-made gradient 4% to 12% Bis-Tris gels (Invitrogen, Burlington, ON, Canada) and transferred to nitrocellulose. Patient sera/plasma will be diluted 1/500 in Blotto (5% dry milk powder; 0.1% Tween 20; 50 mmol/L Tris; 150 mmol/L NaCl) and incubated with nitrocellulose membranes for 1 h at room temperature using a multichannel immuoblotting device (Mini Protean II Multiscreen, Bio-Rad, Missassauga, ON, Canada). The membrane will then incubated for 1 h at room temperature with horseradish peroxidase–conjugated goat anti-human IgG (H+L; Jackson ImmunoResearch, West Grove, PA) diluted 1/10,000 in Blotto and visualized by enhanced chemiluminescence**.**

9.3 Specimen Banking

Subject samples collected for this study will be retained at the department of pathology and at the lab of Dr. Hannan (NC7. 208). Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the subject, best efforts will be made to stop any additional studies and to destroy the specimens.

As outlined in the consent form, the protocol also gives the study personnel access to patient's tumor tissue available at current or outside institutions that has been performed previously or will be done in the future. These may have been collected during prior surgery or as part of other IRB approved protocol such as the GU tissue registry study of (032011-187), PDX tissues and cancer center's tissue repository.

Raquibul Hannan will be responsible for reviewing and approving requests for clinical specimen from potential research collaborators outside of UTSW. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge

agreement) that states specimens will only be released for use in disclosed research. Any data obtained from the use of clinical specimen will be the property of UTSW for publication and any licensing agreement will be strictly adhered to.

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by UTSW, the investigator or a collaborating researcher or entity.

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

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

10.0 QUALITY OF LIFE AND COST-EFFECTIVENESS

10.1 Health-Related Quality of Life (HRQOL) Analysis

The study design is to prospectively analyze the HRQOL among patients with mRCC treated with SABR and Nivolumab. While hypofractionation is hypothesized to yield greater tumor cell kill, it may also increase the normal tissue toxicity, in which case there may be a decrease in HRQOL. The primary normal tissue toxicities in patients receiving radiation depend on the location of the treatment. Prior studies have demonstrated that the most sensitive and clinically meaningful method for accurately capturing the normal tissue toxicities is via patients reported outcomes (PROs), such as HRQOL. A review of patient reported outcomes and health-related quality of life studies in the modern era of metastatic renal cell carcinoma is available highlighting the great need to assess patient reported outcomes in this patient population [81].

In this trial, we plan to assess the HR-QoL questionnaires at specific time points to minimize patient burden: baseline (pretreatment), and at subsequent follow ups. FACT-G is a measure that sums the functional well being (FWB), physical well being (PWB), the social/family well-being (S/FWB), and emotional well being (EMB). The FACT-G has been validated as well and has been used in other studies evaluating treatment options for patients with mRCC [105]. It takes about 5-10 minutes to complete and has been written at the 6th grade level. FACT has been translated into 26 languages and is available free of charge to institutions with the completion of an agreement to share data, accessible at http://www.facit.org/translation/licensure.aspx.

FKSI adds to the FACT–G (27 items) by including 15 items specific to kidney cancer patients. In a HRQOL study focused on patient with mRCC, a symptoms subscale questionnaire was developed and will also be administered in this study. It is 15 questions and should take less than 5 minutes to complete. This form focuses on symptoms frequently experienced by renal cell carcinoma patients and has been used in several recent mRCC studies [111]

In addition, the EQ-5D is a standardized instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. The US version of the EQ-5D will be used, to enable mapping of general HR-QoL scores from EQ-5D scores into health state utility scores (ranging from 0 to 1) for the US population. These utility scores are needed for cost-utility analysis (estimates of costs per “quality adjusted” life-year gained) [112, 113].

There is little reported on the effect on HRQOL for patients treated with Nivolumab. However, there are several detailed reports evaluating quality of life for sunitinib, sorafanib, temsirolimus, everolimus, pazopanib [114]. Thus, we propose utilizing the FACT-G, FKSI, and EQ-5D in the

patients enrolled on this study for descriptive purposes given the lack of HR-QoL data for either Nivolumab, SABR or Nivolumab+SABR in this patient population [115].

10.2 Cost-Effectiveness Analysis (CEA)

For the primary CEA analysis, we will estimate cost accumulated within 1 year after enrollment. A larger limit is possible if we have a reasonable number of people surviving at that time.

Since patients are enrolled into the study over time and some patients are still alive at the end of the study, their survival time and costs are censored. Due to censoring, we cannot use a simple average of the patients' total costs, a simple average of the patients' costs for those with complete cost information, or a Kaplan-Meier estimator on censored costs, since these all produce biased estimators of the mean costs [112]. Instead, we will use the inverse-probability weighting method to calculate average costs [113, 117]. The assumption used in this method is that censoring is independent of the survival time, or cost collection process, which is often satisfied in well-conducted clinical trials. If the new treatment can both extend patients' survival time (or quality-adjusted survival time), and save costs at the same time, the new treatment will be preferred to the current standard treatment under any willingness to pay threshold. However, if the new treatment extends survival time but costs more, cost-effectiveness analysis provides an estimate of the incremental cost of greater incremental effectiveness. For traditional cost-effectiveness analysis, treatment effectiveness is measured simply as survival time. The incremental cost-effectiveness ratio indicates the additional cost required to attain one additional year of survival. For cost-utility analysis, treatment effectiveness is measured as quality-adjusted survival time (which accounts for the impact of treatment on both mortality and morbidity, including any differences in adverse effects of treatment affecting HR-QoL). For cost-utility analysis, the incremental cost-effectiveness ratio indicates the additional cost required to attain one additional year of quality adjusted survival.

10.2.1 Projection Model and Sensitivity Analysis

If the new treatment is implemented in usual practice, some of its potential benefits to patients may extend beyond the time horizon of the clinical trial. We will explore the potential to use results from the clinical trial based cost-effectiveness analysis, augmented with information from secondary sources, to develop a model to project costs and effectiveness beyond the time horizon included in the clinical trial. Any such model projections would be subjected to probabilistic sensitivity analysis, to assess the impact of parameter uncertainty on estimated cost effectiveness results. This is typically done via Markov Modeling with probabilistic sensitivity analysis.

10.3 Quality adjusted survival time

The quality-adjusted survival time estimates need to account for the presence of censoring. Due to the induced informative censoring problem, the ordinary survival method (e.g., Kaplan-Meier estimator) cannot be applied in this case [113, 117, 118]. Accordingly, we will use the inverse-probability weighted method of Zhao and Tsiatis to carry out the survival time analysis [113, 117]. To estimate quality adjusted survival time, data from EQ-5D will first be translated into utility measures. These measures are obtained at discrete time points, so they will be interpolated into the time intervals between the visits. The quality-adjusted survival time is just an integration of the utility measures over a patient's survival time, or until the time limit similar as the cost calculation, whichever occurs earlier.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design/Study Endpoints

This is a safety lead-in phase II clinical trial using SAbR of multiple metastatic sites concurrently administered with PD-1 blocking antibody Nivolumab for patients with metastatic clear cell renal cell cancer (RCC) who have failed at least one anti-angiogenic treatment. The primary endpoint is

RR, while the secondary endpoints include in OS, PFS, CR rate, immunologic response, toxicity and quality of life (Please see endpoint details above).

11.2 Sample Size and Accrual

The first six patients assigned will be assessed for feasibility, safety, and toxicity for interim safety of the trial 8 weeks post-registration. If more than 3 patients experience ≥Grade 3 SAE attributed to the SAbR+Nivolumab out of 6 patients, the study will be held until approval from DSMC.

The previous studies show that the maximum RR for mRCC patients treated with Nivolumab is 25%. We expect that the addition of SAbR to Nivolumab will increase the RR to 50% i.e. a 100% increase compared to the historical RR to Nivolumab alone. In our current ongoing phase II clinical trial (STU 012013-041) with similar patient population and treatment strategy of SABR + immunotherapy using IL-2, we are noticing a 53% RR with the combination whereas the historically reported response rate of IL-2 alone treatment is 20% (1). Therefore, we have increased the RR by >150%. Therefore, in oncology clinical trials, it is not uncommon to see such increases since the baseline RR is often low.

The calculation of the sample size is based on the RR. In this phase II trial, we will recruit a total of 19 patients including the 6 patients that will be used for interim safety analysis. A total sample size of 19 achieves 80% power to detect 25% absolute difference in RR (25% vs. 50%) using an exact binomial test at a 0.2 two-sided significance level. To allow for potential subject dropouts, the accrual goal will be increased by an additional 2 patients for a total of 21 patients. The sample size was estimated using a sample size software PASS 14 ("Hintze, J. (2015). PASS 14. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com.")

11.3 Data Analyses Plans

Exact binomial method will be used to calculate the response rate, toxicity rate, CR rate, and the corresponding 95% confidence interval. Exact binomial test will be used to investigate if the response rate of the treatment arm is significantly different from that of historical control.
PFS and OS will be estimated using the Kaplan-Meier approach along with the 95% confidence interval using Greenwood's formula.
One sample log-rank tests will be conducted to investigate if OS or PFS in the treatment arm is significantly different from that of historical control.

Generalized estimating equation (GEE) analysis will be conducted to investigate if there are significant changes in surrogate makers such as CD25, CD71, CD45RO, CD107a, CD54, CD69, Ki67, ICOS/CD278 and PBMC over time.
HRQol, CEA and quality adjusted survival time analysis is described in Section 10.

12.0 STUDY MANAGEMENT

12.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the principal investigator. All investigators will follow the University conflict of interest policy.

12.2 Institutional Review Board (IRB) Approval and Consent

The IRB must approve the consent form and protocol. In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki. Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will

be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form. Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

12.3 Required Documentation (for multi-site studies) – N/A

12.4 Registration Procedures

All subjects must be registered with the Clinical Research Office, Department of Radiation Oncology, UTSW, before enrollment to study.
New subjects will receive a 3-digit number. The first subject enrolled receives the number 101, the second subject enrolled receives the number 102, etc.

Each newly consented subject should be numbered using the schema provided above. Upon registration, the registrar will assign the additional registration 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.

12.5 Data Management and Monitoring/Auditing

All subjects consenting to participate in any aspect of the trial must be registered on REDCap before initiating protocol activities. All research data will be recorded and entered into Case Report Forms using REDCap. Toxicity will be reviewed on an ongoing basis and will be reported per SCCC-DSMC guidelines.

The monitoring activities are designed to provide safety monitoring, data quality assurance, and oversight of protocols for study progress. The Radiation Oncology Clinical Research Office (CRO) reports serious adverse events (SAEs) to Radiation Oncology Safety Assurance Committee (ROSAC) monthly. These SAEs are also reported to the University of Texas Southwestern Medical Center (UTSW) IRB and Simmons Cancer Center DSMC. SCCC-DSMC will audit in accordance with the DSMC plan guidelines. The purpose of the Radiation Oncology Data and Safety Monitoring Plan is to ensure that clinical trial data is accurate and valid and to ensure the safety of trial participants. The plan complies with the Simmons Cancer Center (SCC) Data Safety Monitoring Plan and the University of Texas Southwestern Medical Center (UTSW) IRB guidelines.

ROSAC is in charged with developing, implementing, and maintaining the Data and Safety Monitoring Plan. The membership consists of a Medical Director of Clinical Research as well as representation from the following groups: clinical research, nursing, regulatory, pharmacy, physicists, radiation therapists, and faculty. Ad hoc members are contacted to participate as needed.

Clinical trials are assessed for safety on a continual basis throughout the life of the trial. All SAE's and any AEs that are unexpected and possibly/likely related to study participation are reported to UTSW IRB through an electronic research system per UTSW IRB guidelines. SAEs are reported to the sponsor per specific sponsor requirements. These SAEs are reported to the SCC DSMC on a real time basis. All local SAEs will be reported to the SCCC DSMC. SAE reports can be either scanned/emailed to the coordinator of SCC DSMC or sent through interoffice mail.

REDCap is the UTSW SCCC institutional choice for the electronic data capture of case report forms for SCCC Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with Simmons Comprehensive Cancer Center requirements, as appropriate for the project

In 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.

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and UPIRSOs 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 SCCC 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.

12.6 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.

12.6.1 Exceptions (also called single-subject exceptions or single-subject waivers): 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.

12.6.2 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 occurrence.

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

- 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.

12.6.4 Minor Deviations: include any departure from IRB-approved research that:

- Did not harm or place subject(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**: Minor deviations should be tracked and summarized in the progress report at the next IRB continuing review.

12.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. 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.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

12.8 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

12.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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14.0 APPENDICES

14.1 Appendix A: ECOG Performance Status

ECOG/ZUBROD PERFORMANCE SCALE

0	*Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).*
1	*Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).*
2	*Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).*
3	*Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).*
4	*Completely disabled. Cannot carry on self-care. Totally confined to bed or (Karnofsky 10-20).*
5	*Death (Karnofsky 0).*

KARNOFSKY PERFORMANCE SCALE

100	*Normal; no complaints; no evidence of disease*
90	*Able to carry on normal activity; minor signs or symptoms of disease*
80	*Normal activity with effort; some sign or symptoms of disease*
70	*Cares for self; unable to carry on normal activity or do active work*
60	*Requires occasional assistance, but is able to care for most personal needs*
50	*Requires considerable assistance and frequent medical care*
40	*Disabled; requires special care and assistance*
30	*Severely disabled; hospitalization is indicated, although death not imminent*
20	*Very sick; hospitalization necessary; active support treatment is necessary*
10	*Moribund; fatal processes progressing rapidly*
0	*Dead*

14.2 Appendix B: MSKCC prognostic classification for mRCC patients who have been treated previously

Determination of Prognostic Score in Previously Treated Patients

Parameter	Risk Factor	Criteria Value	Subject Value	If subject value meets criteria value, enter 1
KPS	Low KPS	< 80%		
Corrected Calcium*	High Corrected Calcium	≥ 10 mg/dL		
Hemoglobin	Low Hemoglobin	Males: ≤ 13 g/dL Females: ≤ 11.5 g/dL		
				Sum total of above = MSKCC Prognostic Score:

*Corrected Calcium = ([4 - serum albumin in g/dL] x 0.8 + serum calcium)

Risk Group Based on MSKCC Prognostic Score

Risk Group	MSKCC Prognostic Score
Favorable-Risk	0
Intermediate-Risk	1
Poor-Risk	2 or 3

14.3 Appendix C: CYP3A4 and PGP inhibitors and inducers

APPENDIX 4 CYP3A4 AND PGP INHIBITORS AND INDUCERS

Strong CYP3A4 Inhibitors • Ketoconazole • Itraconazole • Posaconazole • Voriconazole • Clarithromycin • Telithromycin • Nefazodone • Saquinavir • Ritonavir • Atazanavir • Darunavir • Indinavir • Nelfinavir
Moderate CYP3A4 and/or PGP Inhibitors • Amprenavir • Fosamprenavir • Aprepitant • Erythromycin • Fluconazole • Verapamil • Diltiazem • Cyclosporine oral
Strong CYP3A4 Inducers • Phenytoin • Carbamazepine • Rifampin • Rifabutin • Rifapentine • Phenobarbital • Corticosteroids (eg, dexamethasone, prednisone, prednisolone) • Efavirenz • Nevirapine

Notes:

Grapefruit, grapefruit juice and other foods that are known to inhibit CYP3A4 and PgP activity should be avoided during treatment.

St. John's Wort (*Hypericum perforatum*) is known to be an inducer of CYP3A4 and should be avoided during treatment.

14.4 Appendix D: US EQ-5D-5L

Figure 1: EQ-5D-5L (UK English sample version)

Under each heading, please tick the **ONE** box that best describes your health TODAY

MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

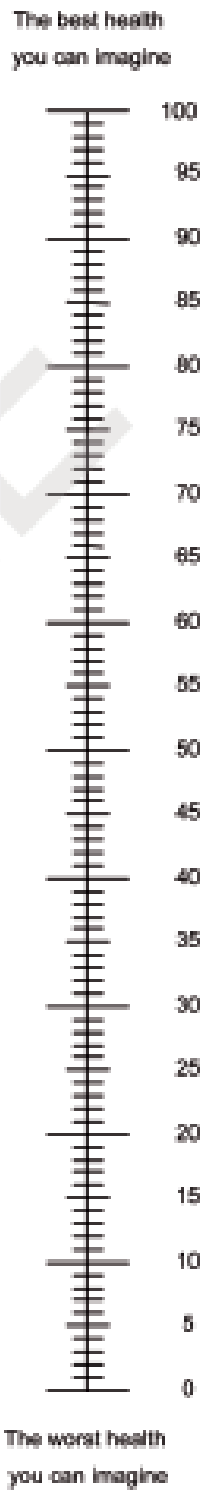
ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

Patient ID: _____
Time Point:_____
Date:_____

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



14.5 Appendix E: FACT-G

Below is a list of statements that other people with your illness have said are important. **Please circ**
or mark one number per line to indicate your response as it applies to the past 7 days.

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

14.6 Appendix F: FKSI

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
C 2	I am losing weight	0	1	2	3	4
BP1	I have bone pain	0	1	2	3	4
H17	I feel fatigued	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
B 1	I have been short of breath	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4
C 6	I have a good appetite	0	1	2	3	4
L 2	I have been coughing	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
GF1	I am able to work (include work at home)	0	1	2	3	4
RCC2	I have had blood in my urine	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4

Patient ID: _____
Time Point:_____
Date:_____

14.7 Appendix G – Patient Perspective Cost and Convenience of Care Questionnaire

We would like to ask you about your health coverage and the "out-of-pocket" costs you have had related to your cancer treatment.

1. Do you have any coverage that helps pay for your medicines, when you are **NOT** in the hospital: (Check **ALL** that apply)
   - ❑ Yes by Government (e.g. ,Medicare Part D,Tricare, etc.)
   - ❑ Yes by private or employer-paid health insurance (supplemental)
   - ❑ No coverage
   - ❑ Don't Know

2. Do you have any coverage that helps pay for home or community care, when you are **NOT** in the hospital (i.e. nursing, physiotherapy, cleaning, etc.): (Check **ALL** that apply)
   - ❑ Yes by Government (Medicare, Medicaid, Tricare)
   - ❑ Yes by private or employer-paid health insurance
   - ❑ No coverage
   - ❑ Don't Know

If you do NOT have private or employer paid health insurance ☞ Go to Question 4

3. If you have Private/Employer-paid health insurance, please describe your coverage for each type of service: (For each service, check the box that best describes your level of coverage.)

TYPE OF SERVICE	✓*Don't Know*	✓*Not Covered*	✓*Partial* **Coverage**	✓*Full* **Coverage**
Hospital supplemental charges (e.g. Private room, telephone, TV, etc.)				
Prescription drugs (e.g. Antibiotics, pain medication, etc.)				
In home healthcare (e.g. nursing, physiotherapist, etc.)				
Homemaking services (e.g. cleaning, cooking, etc.)				
Alternate Therapy (e.g. Homeopathy, Chinese medicine, over the counter drugs, etc.)				
Other (Specify) _____ _____				

Patient ID: _____
Time Point:_____
Date:_____

☞**Proceed**

4. Please supply the following details regarding your "out-of-pocket" costs for trips to and from your treatments and family doctor visits **related to your cancer** *in the last 30 days*.

Type of Visit	**Number of trips in the last 30 days**	**Distance <u>ONE WAY</u> OR** origin and destination points	**Method of transport (car, taxi, bus, train etc.)**	**Parking or Fare**	**Paid for by Insurance/ Government (circle one)**
Cancer Clinic/ Radiation Facility		Miles		$	None – Partial - Full
Hospital		Miles		$	None – Partial - Full
Family Doctor		Miles		$	None – Partial - Full
Other (Specify, i.e. 2nd Hospital or 2nd Doctor, ER) _____		Miles		$	None – Partial - Full

5. For questions listed below indicate if you had cancer related costs, paid by yourself, private insurance or government programs (e.g. Home Oxygen, Homecare, etc.) *during the last 30 days*. If you do not know the exact amount make your **best estimate,** rounded to the nearest dollar.

a) **Copays**

❑ No	❑ Yes (Check all that apply and fill in related estimate of dollar amount)		
	❑ paid by yourself	❑ paid by private insurance	❑ paid by government
	Amount (if known):		
	$ _____	N/A	N/A

b) **Prescription Drugs**

❑ No	❑ Yes (Check all that apply and fill in related estimate of dollar amount)		
	❑ paid by yourself	❑ paid by private insurance	❑ paid by government
	nount (if known):		
	$ _____	$ _____	$ _____

c) **In home healthcare (nursing, physical therapy, respiratory therapy, etc.)**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)
❑ paid by yourself ❑ paid by private insurance ❑ paid by government
Amount (if known):
$ _____ $ _____ $ _____

d) **Homemaking (cleaning, cooking, etc.)**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)
❑ paid by yourself ❑ paid by private insurance ❑ paid by government
Amount (if known):
$ _____ $ _____ $ _____

e) **Complementary and Alternative Therapy (homeopathy, massage, acupuncture, counseling, etc.)**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)
❑ paid by yourself ❑ paid by private insurance ❑ paid by government
Amount (if known):
$ _____ $ _____ $ _____

f) **Vitamins and Supplements including special diets**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)
❑ paid by yourself ❑ paid by private insurance ❑ paid by government
Amount (if known):
$ _____ $ _____ $ _____

g) **Family Care (child or elder)**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dol
❑ paid by yourself ❑ paid by private insurance ❑ paid b
Amount (if known):
$ _____ $ _____ $ _____

Patient ID: _____
Time Point:_____
Date:_____

h) **Accommodation/Meals**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)
❑ paid by yourself ❑ paid by private insurance ❑ paid by government
Amount (if known):
$ _____ $ _____ $ _____

i) **Devices or Equipment (<u>home oxygen</u>, wheelchair, walker, etc.)**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)
❑ paid by yourself ❑ paid by private insurance ❑ paid by government
Amount (if known):
$ _____ $ _____ $ _____

j) **Other (telephone costs, pagers, etc..)**

❑ No

❑ Yes (Check all that apply and fill in related estimate of dollar amount)
❑ paid by yourself ❑ paid by private insurance ❑ paid by government
Amount (if known):
$ _____ $ _____ $ _____

6. Would you say this last month your "out-of-pocket" expenses related to your cancer were:

❑ More than other months ❑ Typical ❑ Less than other months ❑ Don't Know

We would like to ask you some questions about your healthcare visits related to this cancer as well as the impact these visits have had on your work.

7. Since you finished radiation, have you had: (Check all that apply)
NOTE: We will ask you specific questions about these in a separate form.

❑ Doctor visits
❑ Emergency room visits
❑ Overnight hospitalization – indicate duration ❑ one
❑ Home nursing services
❑ Respiratory/ Physiotherapists/ Occupational Therapy services
❑ Medication changes
❑ Started oxygen treatment

Patient ID: _____
Time Point:_____
Date:_____

8. How much time over the *last 30 days* did you take off work to receive treatment related to your cancer

❑ Unemployed ❑ No time off work ❑ _____ days ❑ Don't Know
❑ Retired

9. Was this time away from work: (Check ALL that apply)

❑Not Applicable (not working) ❑Vacation ❑Time off **with** pay ❑Time off **without** pay

10. Did friends or family take time away from work in the *last 30 days* related to your treatment

❑ No time off work **OR** ❑ _____ days

We would now like to ask you a little bit about you, your work and your education:

11. Year of Birth _____

12. Sex: ❑ Male ❑ Female

13. Marital Status:

❑ Married ❑ Common Law ❑ Single (never married)
❑ Widowed ❑ Separated ❑ Divorced

14. How many other people do you share your home with (do not include people who are only visiting):

❑ Live alone (☒ **Go to Question 16**) ❑ Myself and one other
❑ 2 others ❑ 3 others ❑ More than 3 others

15. Are these people you share your home with:

❑ Family ❑ Friends ❑ Both Family and Friends

Patient ID: _____
Time Point:_____
Date:_____

16. City or Town where you live _____

17. How would you rate your current health?

❑ **Excellent** ❑ **Very good** ❑ **Good** ❑ **Fair** ❑ **Poor**

18. What do you do for a living:

❑ *Full time work : Specify* _____ ❑ *Part time work: Specify* _____

❑ *Retired* ❑ *Homemaker* ❑ *Unemployed* ❑ *Student*

19. What is the highest level of schooling you have completed?

❑ No schooling, some elementary school, or completed elementary school
❑ Some high school
❑ Completed high school
❑ Some university or community college
❑ Completed university or community college
❑ Post Graduate (MSc/MBA/PhD) or professional training (MD/LLB/DDS)

20. What was your total family income before taxes in the last year.
(include wages, salaries and self-employment earnings)

❑Less than $5,000
❑$5,000- $9,999
❑$10,000- $14,999
❑$15,000- $19,999
❑$20,000-$29,999
❑$30,000-$39,999
❑$40,000-$49,999
❑$50,000-$59,999
❑$60,000-$79,999
❑More than $80,000
❑Don't Know

21. How much of a financial burden are these out-of-pocket expenses listed in Q 4 & 5:

❑Not a burden at all
❑Only a slight burden
❑Somewhat of a burden
❑Significant burden, but manageable
❑Unmanageable burden

Patient ID: _____
Time Point:_____
Date:_____

24. What treatments or services that are **not** currently available would you like to see paid for through government or private insurance:

_____

_____

25. Was this questionnaire completed by:

❑ The patient ❑ A caregiver ❑ Both the patient and a caregiver

We would like to learn more about your personal reactions to the treatment and the impact it had on your typical activities:

26. To what extent has your treatment **disrupted** your normal daily activities?

0	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***

27. To what extent has your treatment **disrupted** your normal recreation activities?

0	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***

28. To what extent has your treatment **disrupted** your normal activities with your family and friends?

0	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***

29. To what extent has your treatment **disrupted** your sleep pattern?

0	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***

30. To what extent has your treatment **disrupted** your enjoyment of life?

0	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***

31. How **satisfied** are you with the length of time your treatment has taken to this point of time?

0	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***

32. How **disruptive** has your treatment been to the other important people in your life (example: family, spouse, close friends, coworkers)?

0	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***

Additional Comments

_____

_____ Patient ID: _____

_____ Time Point:_____

_____ Date:_____

_____

Thank you *for helping us with our survey. If you have completed all sections please place the survey in the envelope, seal it, and return it to the attending clinic staff*