A Phase II Randomized Controlled Screening Trial of Nivolumab with Image Guided, Stereotactic Body Radiotherapy (SBRT) versus Nivolumab Alone in Patients with Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC)

PROTOCOL FACE PAGE FOR
MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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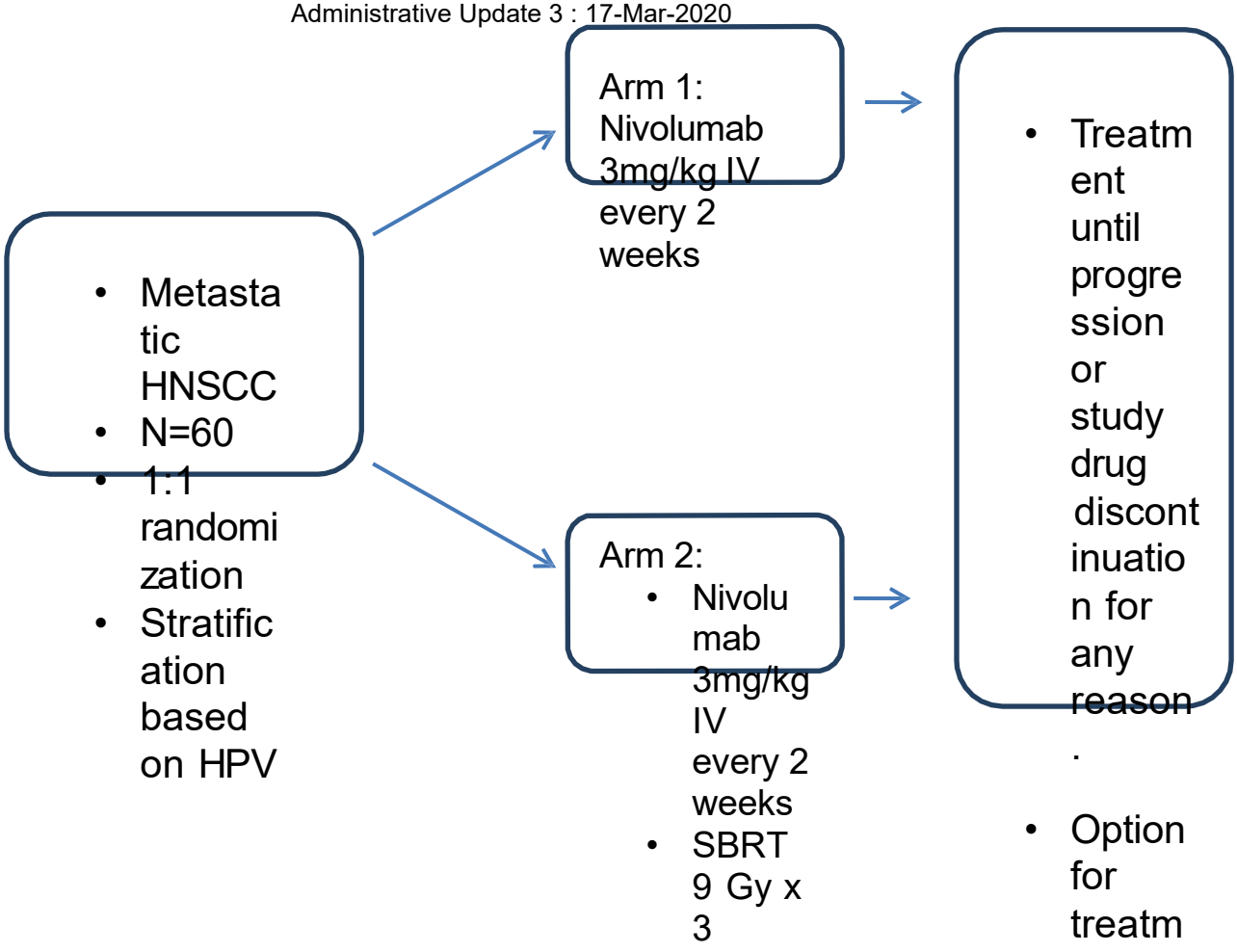
1.1 PROTOCOL SUMMARY AND/OR SCHEMA

Title: A Phase II Randomized Controlled Screening Trial of Nivolumab with Image Guided, Stereotactic Body Radiotherapy (SBRT) versus Nivolumab Alone in Patients with Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC).

Brief Background: Nivolumab is a fully human monoclonal immunoglobulin G4 antibody that binds to programmed death-1 (PD-1) cell surface membrane receptor, a negative regulatory molecule expressed by activated T and B lymphocytes. Inhibition of the interaction between PD-1 and its ligands (e.g. PD-L1) promotes immune responses and antigen-specific T cell responses to both foreign antigens as well as self antigens.[1] In early phase clinical trials in a variety of malignancies, including HNSCC, anti-PD-1 antibodies have shown impressive objective response rates with a surprising number of patients experiencing durable, long-term complete or near complete remissions. Still, these sustained responses have only been seen in a distinct minority of patients with HNSCC (20%) [2]. Accumulating pre-clinical evidence suggests a role for relatively high-dose-per-fraction radiotherapy in up-regulating adaptive immune response against established malignancies. This can occur through a variety of mechanisms, including radiation-induced increases in tumor-antigen presentation by antigen presenting cells (ADCs), increases in tumor cell phagocytosis by dendritic cells, increases in secretion of "danger signals" such as HMGB1, and decreases in peripheral myeloid derived suppressor cells [3, 4]. Compared to conventional fractionated radiation therapy (1.8 Gy to 2 Gy per fraction), higher dose-per-fraction radiation therapy, delivered by conformal, image guided mechanisms has shown increased T- cell activity [5]. Even more tantalizing, recent evidence in patient-derived xenograft models have demonstrated potentially powerful synergy between high-dose radiotherapy and anti-PD-L1 antibody therapy (another mechanism of PD-1:PD-L1 signaling inhibition) [6]. The concomitant administration of radiation to a single metastasis and anti-PD-L1 therapy proved capable of dramatic reductions in non-irradiated metastases above and beyond the regression seen with anti-PD-L1 therapy alone. This radiation-induced regression of non-irradiated systemic disease is termed the *abscopal effect*. Multiple case reports have also now been published purportedly demonstrating the same phenomenon in patients who had initially progressed through checkpoint inhibitory therapy [7] .

Research Hypothesis: The concomitant administration of SBRT with Nivolumab will result in a significant increase in objective response rate above and beyond Nivolumab alone in patients with metastatic HNSCC.

Schema:


Metastatic HNSCC
N=60
1:1 randomization
Stratification based on HPV
Arm 1: Nivolumab 3mg/kg IV every 2 weeks
Arm 2:
Nivolumab 3mg/kg IV every 2 weeks
SBRT 9 Gy x 3
Treatment until progression or study drug discontinuation for any reason.
Option for treatment beyond progression in both arms.
Prim Endpoint: ORR per RECIST
Second Endpoint: PFS, OS, ORR

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective:

- To compare objective response rate (ORR) during the first 2 years of treatment as determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria between patients receiving Nivolumab and SBRT to those receiving Nivolumab alone. The ORR is defined as the number of patients randomized to a given arm with a best overall response (BOR) of complete response (CR) or partial response (PR) in non-irradiated lesions during the first 96 weeks after treatment initiation divided by the total number of patients randomized to the given arm.

Secondary Objectives:

- To compare Overall Survival (OS) of Nivolumab and SBRT to Nivolumab alone.
- To compare Progression Free Survival (PFS) of Nivolumab and SBRT to Nivolumab alone.
- To compare duration of response (DOR) between the Nivolumab alone arm and Nivolumab + SBRT arm.
- To compare treatment-related Adverse Events (tr-AE) of Nivolumab and SBRT to Nivolumab alone using Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v 4.0).
- To evaluate cancer-specific health related quality-of-life using the EORTC-QLQ C-30.

Exploratory Objectives:

- Evaluation of tumor tissue PDL1 expression via IHC and its correlation with response.
- Evaluate of peripheral blood mononuclear cell composition and its correlation with response
- Evaluation of soluble PD-1 and PD-L1 and its correlation to response.
- Evaluation of neo-antigen expression (optional) and its correlation to response.

3.0 BACKGROUND AND RATIONALE

3.1 Overall Study Rationale

Substantial pre-clinical data has accumulated suggesting that higher-dose per fraction radiation therapy (SBRT) can enhance immune surveillance of extant tumors. Over the past several years, early phase clinical trials involving novel immunotherapies—specifically mono-clonal anti-body inhibitors of various immune checkpoints--have shown impressive tumor control outcomes. Herein we outline a randomized, open label, Phase 2

trial designed to determine whether clinically significant synergy exists between the immune checkpoint inhibitor Nivolumab and high dose per fraction, stereotactic body radiotherapy (SBRT) in patients with metastatic HNSCC.

3.2 Current Standard of Care in Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC)

HNSCC is currently the fifth most common incident cancer worldwide. Within the United States in 2013, 53,640 new cases of HNSCC were diagnosed, with approximately 11,500 deaths attributed to this disease. The specific anatomic locations that fall under the HNSCC diagnostic umbrella include oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, nasal cavity, and para-nasal sinuses [8]. Broadly speaking, HNSCC can be divided into tumors that arise from excessive toxic exposures, namely alcohol and tobacco, and those that arise as a result of viral infections, specifically the Epstein-Barr virus (EBV) in nasopharyngeal carcinoma, and the Human Papilloma Virus (HPV) in oropharynx cancer.

At initial diagnosis, approximately 10% of patients with HNSCC will have metastatic (Stage IV-C) disease. For patients with locally advanced, non-metastatic HNSCC at diagnosis (Stage III-IVA/B), approximately 50% treated with definitive surgery or concurrent chemo-radiotherapy will recur. In recurrent disease with a metastatic component, median progression free survival (PFS) is ≤ 6 months [9].

Treatment of metastatic disease typically consists of cytotoxic chemotherapies (e.g. methotrexate, organoplatinum compounds, 5-fluorouracil (5FU), or taxanes) oftentimes in combination with the monoclonal anti-body inhibitor of the epidermal growth factor receptor (EGFR), Cetuximab. Additionally, it is not uncommon for patients to undergo palliative radiation therapy to synchronous loco-regional disease because of the high potential morbidity of continued progression in the head and neck region. A Phase 3 trial by Vermorken, et al established the current chemotherapeutic standard of care for well performing patients with metastatic HNSCC [10]. Therein they found a significant improvement in overall survival (OS) comparing patients that received 5FU, a platinum agent, and Cetuximab to those who received 5FU and a platinum agent alone (10.1 months versus 7.4 months). A recent retrospective report on response rates to tri-modal treatment with 5FU, platinum, and cetuximab as a first line therapy in metastatic HNSCC showed an ORR of approximately 23.9% [11].

Tumor response rates in metastatic patients who have progressed through or recurred after a first-line platinum-containing therapy are even lower; a single arm, Phase 2 trial of Cetuximab monotherapy in patients who had failed a prior platinum-containing therapy showed an ORR of 13%. In examining multiple studies of patients in this cohort, median OS is approximately 3-4 months, with survival at 1 year of approximately 5% [12].

In sum, response rates in both the 1st line and 2nd line settings in metastatic HNSCC are underwhelming. More broadly, chemotherapeutic options in this disease are limited. The need for more potent therapies for these patients is clear.

3.3 Rationale for Use of Nivolumab in HNSCC

3.3.1 Immunosurveillance in HNSCC

Over the past decade, substantial evidence has accrued demonstrating the critical role that the immune system plays in the development and progression of HNSCC. The two primary pathways by which HNSCC develops—chemical carcinogenesis and human papilloma virus (HPV) infection—both involve a failure of immune surveillance; tumor cells escape cytotoxic T-lymphocyte-based adaptive immune destruction.

HNSCC employs multiple mechanisms of immune escape [13]. Despite that fact that immunogenic tumor antigens (TA) exist in HNSCC along with their cognate TA-specific cytotoxic T-lymphocytes (CTLs specific for EGFR, E7 HPV oncoprotein, etc), these TA-specific CTLs fail to eradicate their targets. One evasive maneuver used by HNSCC to accomplish this escape is the down-regulation of human leukocyte antigen (HLA) 1, the MHC molecule required for interaction between TA and TA-specific CTLs. Additionally, it has been shown by multiple groups that HNSCC has developed the ability to downregulate its own antigen processing machinery (APM). This deficiency also extends to nearby dendritic cells (DC), themselves critical intermediaries of antigen presentation.

However, it is not just failure to present CTLs with viable tumor-specific targets that cripples the adaptive immune response to HNSCC, it is also the de-activation of the CTLs themselves that compounds the degree of suppression. This deactivation occurs via an alteration in the balance of co-stimulatory (e.g. OX40 and 4-1BB) and co-inhibitory receptors (e.g. T-lymphocyte-associated antigen 4 (CTLA-4) and programmed-death 1 (PD-1)) expressed by CTLs and their paired ligands (PD-L1, B7,etc), expressed by CD4+ helper T cells, DCs, myeloid derived suppressor cells (MDSCs), and tumor cells. In the functioning immune system, expression of co-stimulatory receptors and ligands are requisite requirements for the successful activation of CTLs in the face of foreign antigen presentation. Once an infectious threat has been eliminated, the binding of CTL, membrane bound co-inhibitory receptors, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed-death 1, to their cognate ligands serves to dampen any further adaptive response and promote functional anergy. In addition to CTLs, PD-1 is also expressed by the immunosuppressive T-regulatory (Treg) cells where receptor engagement may be critical to the Treg cell's suppressive function. There is now mounting evidence that HNSCC has co-opted these co-signaling pathways in order to facilitate profound intra-tumoral immunosuppression [14, 15].

3.3.2 Programmed Cell Death 1 (PD-1) in HNSCC

The data demonstrating the PD-1:PD-L1 pathway as a major mechanism of immune escape in HNSCC have become increasingly robust over the last few years. A member of the CD28 family, PD-1 is a 55kD, type I transmembrane T-cell co-stimulatory receptor. The receptor contains an intracellular immunoreceptor inhibitor motif (ITIM) and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM). The two known ligands of PD-1 are PD-L1 and PD-L2 which, upon binding to PD-1, deactivate T cells. The down-regulation of T-cell activation is mediated via SHP-2 binding to the

phosphorylated tyrosine residue in the ITSM in the cytoplasmic region of PD-1. PD-1 deficient mice are prone to a variety of auto-immune ailments. Blockade of PD-1 with a mono-clonal antibody can bring about the same auto-immune phenotype.

Several studies have shown high levels of PD-L1 expression in 46%-100% of tumors in treatment naïve primary, recurrent, and metastatic HNSCC [16]. Moreover, there appears to be differential PD-L1 expression in HNSCC lesions depending upon etiology, with HPV-positive tumors having a statistically significant higher expression (49.2-65.2% vs 34.1%-40%). In addition to tumor cells themselves, there are data suggesting that peripheral blood MDSCs, in-part responsible for suppression of T cell activation and migration, show increased PD-L1 expression in HNSCC; this up-regulation of PD-L1 expression is also seen in intratumoral Tregs in HNSCC. This enhancement of PD-L1 on tumor cells, MDSCs, and Tregs is matched by a commensurate increase in PD-1 expression by both CD8+ T cells in the peripheral blood, and, to an even greater degree, CD8+ T cells in the tumors of HNSCC patients; this was seen in both HPV positive and negative patients. Moreover, in vitro blockade of PD-1 in these CD8+ T cells enhanced their adaptive function.

The above pre-clinical data argue that the PD-1:PD-L1 axis plays an important role in both HPV positive and HPV negative HNSCC pathogenesis. Because of the strength of the above pre-clinical data and the impressive results seen in other solid malignancies treated with anti-PD-1 therapy, Seiwert, et al devised, ran, and recently reported on a Phase Ib trial involving 60 recurrent/metastatic HNSCC patients with tumors positive for PD-L1 treated with Pembrolizumab, a humanized monoclonal IgG4 antibody directed against PD-1. They screened 104 patients for PD-L1 expression; 77.9% of patients were positive (defined as >=1% of cells in the tumor microenvironment staining for PD-L1); of the positive patients, sixty were eventually enrolled on the trial, 37 of which were HPV negative. In total, the best overall response rate was 20%, a percentage that was identical regardless of HPV status. Approximately 89% of the enrolled patients had undergone prior systemic treatment [2].

Although in the aforementioned study, patients were selected for inclusion only if their tumors expressed PD-L1, data from melanoma, non-small cell lung cancer, and renal cell carcinoma shows the potential for a still robust response in PD-L1 negative patients [17]. Therefore, in our own trial, we have chosen to include patients regardless of PD-L1 expression status.

3.3.3 Nivolumab Efficacy and Safety

In our own trial, we will use Nivolumab as the anti-PD-1 agent. Nivolumab is a fully human monoclonal immunoglobulin IgG4 antibody that binds to PD-1 cell surface membrane receptor. A recently reported on Phase I open label, multiple dose escalation study investigated the safety and efficacy of Nivolumab in 304 patients with melanoma, renal cell carcinoma, non-small cell lung carcinoma (NSCLC), colorectal cancer, or hormone refractory prostate cancer [18]. Squamous NSCLC is the histology most biologically similar to HNSCC. For NSCLC, the most active doses were 3 and 10 mg/kg, with a reported ORR of between 19% and 26%, with durable responses observed in both

squamous and non-squamous subtypes. There was no maximally tolerated dose identified in the above Phase I trial. Drug-related adverse events occurring in >5% of subjects included, in order of most frequent to least frequent: fatigue, rash, diarrhea, pruritus, nausea, decreased appetite, decreased hemoglobin, and pyrexia. Approximately 15% of patients experienced Grade 3 or 4 adverse events. Those occurring in greater than >1% of research subjects included: fatigue (1.6%), lymphopenia (1.3%), abdominal pain (1%), diarrhea (1%), hypophosphatemia (1%) and pneumonitis (1%). Approximately 49% of patients on the Phase I study experienced a severe adverse event (SAE); 7.6% of patients experienced a Grade 3-4 SAE. Drug-related SAEs occurred in 11.5% of patients. Grade 3-4 SAEs that occurred in 2 or more study subjects included: diarrhea (1%), pneumonitis (1%), pneumonia (0.7%), and increased lipase (0.7%). Only 5.9% of patients had their treatment discontinued because of an SAE. These SAEs included pneumonitis (4 subjects) and hepatitis (2 subjects). There were 3 treatment-related deaths (1%), all related to pneumonitis.

Siewert, et al recently updated their experience with Pembrolizumab (MK-3475) in an unselected group (both PDL1 positive and negative) of patients with recurrent/metastatic HNSCC. In this expansion cohort of KEYNOTE 012, ORR (confirmed and unconfirmed) per RECIST 1.1 was 18.2% (95% CI, 11.1-27.2) [19].

3.4 Rationale for and Safety of Combining Nivolumab with Stereotactic Body Radiation Therapy (SBRT)

The data examining the immune-modulatory effects of radiation are substantial. Several groups have reported an up-regulation of pro-inflammatory cytokines in response to ionizing radiation, namely TNF, IL-1alpha, and IL-1beta [20]. These inflammatory cytokines in turn promote the expression of critical leukocyte adhesion molecules (e.g. ICAM-1, VCAM-1, and E-selectin). Given the above biology, it is not surprising that irradiation has been shown to enhance T-cell infiltration into the tumor microenvironment. Once intercalated into the microenvironment, radiation also serves to promote T-cell activation by increasing the expression of both tumor antigens and MHC Class I and II molecules [21]. In addition, several studies have demonstrated that radiation tends to results in immunogenic tumor cell death via necrosis and mitotic catastrophe [22]. The release of endogenous danger signals, such as HMGB1 and ATP, that accompany these types of tumor cell kill lead to the engagement of the innate immune system via the Toll-Like Receptors (e.g. TLR4) found on antigen presenting cells (APCs). Activated APCs serve to further enhance anti-tumor T-cell response.

Radiation-related induction of T-cell activity is not just incidental to but rather necessary for the anti-tumor effect of radiotherapy [23]. Indeed, several studies have shown that depletion of CD8+ T cells significantly hampers radiation-related retardation of local tumor growth. But radiation alone rarely generates a systemic, immune-mediated anti-tumor response—the so called “abscopal effect”. There has thus been great interest in combining radiotherapy with immune modulatory agents like Nivolumab in the hope that the synergy between the two therapies would result in substantial enhancement of anti-tumor immunity and subsequent regression of metastatic disease outside of the irradiated

field. The abscopal effect would predict that this systemic disease response to radiation and Nivolumab at unirradiated sites should be in excess of the systemic response seen with Nivolumab monotherapy.

Pre-clinical data and several case reports have hinted at the ability of such a combinatorial strategy to accomplish this. Deng, et al reported that 12Gy of ionizing radiation delivered to a mammary carcinoma established on the flank of a mouse in combination with an anti-PD-L1 antibody led to the sustained regression of tumors implanted on the contralateral flank of the animal, whereas no such contralateral responses were elicited when the animals were treated with either radiation or anti-PD-L1 alone [6]. A recently completed Phase I study combined SBRT (20 Gy per fraction) with IL-2, an older, established immune-modulatory agent, in patients with metastatic renal cell or melanoma. They reported CRs or PRs in 66.6% of patients, rates far in excess of those expected with IL-2 alone [24]. More pertinent to our own study, Postow, et al, reported on a melanoma patient who, having had progressive disease while on Ipilimumab, a mono-clonal antibody directed against the checkpoint inhibitor CTLA-4, demonstrated dramatic tumor regression after receiving SBRT (8.5 Gy x 3) concurrent with Ipilimumab at both the irradiated site and multiple metastatic sites four months after irradiation [25]. A further, and perhaps more dramatic demonstration of synergy was reported by Golden, et al in a patient with metastatic lung adenocarcinoma, a histology that had demonstrated relatively unimpressive responses to single agent Ipilimumab. In their case report, a patient with widespread metastases received SBRT (6 Gy x 5) to a liver lesion with infusion of Ipilimumab the day after the first fraction and continuing for 3 additional cycles. At 2.5 months post-treatment, dramatic regression was seen in both the irradiated lesion and in multiple osseous and hepatic metastases [26, 27].

Little data exists with regard to the safety of combined immunologic checkpoint inhibition and radiotherapy. However, Barker, et al recently reported on the Memorial Sloan Kettering institutional experience with Ipilimumab and non-brain radiotherapy [27]. They found no evidence of increased adverse effects compared to Ipilimumab alone. Many of the patients included in this retrospective report received SBRT with various dosing schemas.

3.4.1 Rationale for Radiation Dose and Fractionation in Combination with Nivolumab

Data with regards to appropriate dose per fraction is somewhat limited. Reits, et al examined MHC-1 up-regulation in response to variety of single dose radiation regimens [28]. They found that 1 Gy resulted in no increased expression, 4 Gy a slight increase, and 10 Gy and 25 Gy a two-fold increase, with the 25 Gy dose resulting in a faster rate of increase. This increase in MHC-1 expression persisted for up to 11 days. Schaue, et al showed that doses of greater than 15 Gy per fraction resulted in dramatic increase in the immunosuppressive Treg population. Conversely, doses of 5 Gy or less failed to induce tumor-specific T-cells. They concluded that doses of 7.5 Gy per fraction were best able to generate anti-tumor immunity without increasing the proportion of T-regulatory cells.

Addressing specifically the optimal fractionation in combination with checkpoint inhibitors, Dewan, et al evaluated three dose schemes [29]: 20 Gy x 1, 8 Gy x 3, and 6 Gy x 5. They found that the two fractionated regimens (8 Gy x 3 and 6 Gy x 5) resulted in more dramatic reductions in non-irradiated systemic disease compared to the single fraction dose in mouse

models of both breast and colorectal carcinoma. The 8 Gy x 3 regimen proved most effective, causing regression in 40% of tumors outside the irradiated field. This was nearly the same fractionation scheme used by Postow, et al in their seminal report.

Given the above data, we have chosen a dose fractionation of 9 Gy x 3 for our study.

3.4.2 Rationale for Timing of Radiotherapy and Nivolumab

Although not completely analogous, Witek, et al reported on timing of radiotherapy relative to the administration of an adenoviral-mediated vaccine against the colorectal cancer antigen GUCY2C in a murine subcutaneous tumor model using mouse CT26 colon cancer cells [30]. They found that T cell responses were enhanced and tumor eradication maximized when RT was administered prior to the vaccine.

Deng, et al, in their study of anti-PD-L1 antibody in combination with RT delivered the therapies on the same day or with anti-PD-L1 given 1 day prior to RT administration. Golden, et al, in their report of an abscopal effect seen with the combination of Ipilimumab and radiation NSCLC-adenocarcinoma, delivered the RT one day prior to the Ipilimumab.

Recognizing the paucity of data, but based on the aforementioned reports, this study will involve the administration of the first dose of Nivolumab one day ***before*** the first fraction of radiation.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a randomized (1:1), open label Phase 2 screening trial in subjects ≥ 18 years old with metastatic HNSCC. Subjects will stratified based on viral status (p16+ OPC/EBER+ NPC vs others) and then randomized to either Nivolumab with interdigitated SBRT or Nivolumab alone.

Subjects must undergo screening evaluations to determine eligibility within 28 days prior to randomization.

Sixty (60) subjects will be randomized to one of the following arms:

- Arm 1: Nivolumab 3mg/kg IV every 2 weeks
- Arm 2:
    - Image Guided, Stereotactic Body Radiotherapy (27 Gy over 3 fractions given every other day) to a single lesion to start by study day 14 (study day 1 is day of first dose of Nivolumab).
    - Nivolumab 3mg/kg IV starting day 1and then every 2 weeks thereafter.
- Treatment with Nivolumab will continue until progression or unacceptable toxicity.

<u>Key Inclusion Criteria:</u>

1) Males and females ≥ 18 years of age.
2) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
3) Histologically confirmed metastatic HNSCC, including nasopharynx WHO Type I-III histologies; patients can have simultaneous loco-regional disease.
4) Subjects must have at least two lesions:
    - One lesion must be safely amenable to irradiation in the opinion of the treating radiation oncologist. This can be a lesion that was previously irradiated as long as prior radiation preceded projected first fraction of SBRT by at least 6 months.
    - At least one, not-to-be-irradiated lesion measurable by CT or MRI per RECIST 1.1 criteria.
5) Available formalin fixed, paraffin-embedded (FFPE) tumor tissue block with unstained slides of tumor sample obtained via excisional, incisional, or core needle biopsy from a loco-regionally recurrent or metastatic lesion; FFPE tumor tissue block with unstained slides from the primary disease is acceptable with approval of principal investigator.
6) Documentation of tumor viral status (p16 testing for oropharynx, EBER for nasopharynx). Tests done on primary tumor specimens at outside institutions are sufficient to meet this criterion.
7) Prior palliative or curative radiotherapy must be completed at least 14 days prior to randomization.

<u>Key Exclusion Criteria:</u>

1) Active brain metastases or leptomeningeal metastases are not allowed.
2) Non-squamous histologies are not allowed; an exception is made for WHO Type I-III nasopharynx histologies.
3) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2 antibody.
4) Prior active malignancy within the previous 3 years except for locally curable cancers such as basal or squamous skin cancer, superficial bladder, low risk prostate cancer, breast, or cervix cancer. If other prior malignancy was active within prior 3 years, enrollment requires approval of a principal investigator.
5) Subjects with active, known or suspected auto-immune disease. Subjects with vitiligo, type 1 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 eligible to enroll.
6) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses >10mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

Based upon an estimated ORR of 15% in the Nivolumab alone arm in a PD-L1 unselected population and an ORR of 45% in the Nivolumab and SBRT arm, the enrollment of 54 patients will provide a one-sided alpha of 0.10 and a power of 0.80. Assuming a 10% drop-out rate, we will seek to enroll 60 patients. Patients will be randomized to the two

treatment arms in a 1:1 ratio (30 subjects in Arm 1 and 30 subjects in Arm 2). Patients will be stratified based upon viral status (HPV/EBV+ vs not). ORR will be assessed by the investigator using RECIST 1.1 criteria. Treatment with Nivolumab will continue until RECIST 1.1-defined progression, unacceptable toxicity, or withdrawal of consent. Nivolumab dose reductions will not be allowed.

Because the toxicity of Nivolumab combined with SBRT is unclear, we have included an interim toxicity analysis for Arm 2 to occur after the first 20 patients have been randomized to this arm. Using data from recently reported early phase trials of Nivolumab in NSCLC, we view 14% as an acceptable rate of acute (within 3 months of study initiation) >= Grade 3 treatment-related adverse events; an unacceptable rate of acute >= Grade 3 treatment-related adverse events is 30%. If more than 5 (e.g. 6 or more) of the first 20 patients experience an acute >= Grade 3 treatment-related adverse event, the trial will be stopped early. If the true toxicity rate is 30%, the above boundary assures a 58% probability of stopping the trial at interim analysis; if the true toxicity rate is 40%, there is an 87% chance of stopping the trial early. If the true toxicity rate is 14%, the above boundary has only a 5% probability of stopping the trial early. Of note, for radiation dermatitis, only Grade 4 treatment-related events will be included in the interim analysis of toxicity.

Study mandated follow-up for tumor assessment will conclude 96 weeks after the final patient is enrolled.

The primary endpoint of the trial is the ORR as defined by RECIST 1.1 criteria. Analysis of ORR will occur 96 weeks after randomization of the final subject.

The maximal total duration of the study from start of randomization to final analysis of ORR is expected to be 44 months, assuming an accrual of 3 patients per month. Sample size estimate is 60 patients.

4.2 Intervention

The study will consist of three phases: screening, treatment, and follow-up.

Screening Phase:

- Establishment of initial eligibility and signing of the informed consent.
- Confirmation that tumor tissue from a metastatic or loco-regionally recurrent lesion is available for biomarker analysis; if none is available and biopsy not an option, with the permission of the principal investigator, tumor tissue from the primary site at initial diagnosis is acceptable.
- HPV status will be determined via p16 IHC staining or HPV ISH or PCR for all oropharynx primaries. The p16 staining will be interpreted as positive if >70% strong and diffuse nuclear and cytoplasmic staining is specific to tumor cells. Status will be reported dichotomously as positive or negative. EBER staining will be reported as well for patients with nasopharynx cancer. For non-oropharynx and non-nasopharynx primaries, these tests are not required. Tests previously

performed on primary tumor specimens from oropharynx or nasopharynx lesions at time of diagnosis are sufficient to meet this criterion.

- Baseline tumor assessments will be performed within 28 days of randomization.
- Eligibility assessment per timeframe outlined.
- The screening phase will conclude with either randomization of the subject or with confirmation that the subject is a screen failure.

Treatment Phase:

- Nivolumab should begin within 14 days (+/-4 days) of randomization. The first day of Nivolumab is designated as study Day 1.
- Radiation will be delivered over 3 treatments (9 Gy per treatment) to a single lesion. The first fraction must be administered by study day 14. The remaining 2 radiation treatments will be delivered over 10 business days at a frequency no greater than every other day.
- All of the laboratories and vital signs will be collected prior to study drug dosing at the time points specified.
- Adverse events will be documented at the time points specified.
- Biomarker and immunogenicity samples will be obtained according to the outlined schedules.
- EORTC QLQ-C-30: will be completed by Day 1 of treatment, and then, starting at week 8 (+/- 2 weeks), every 8 weeks (+/-2 weeks) for the first 48 weeks and every 12 weeks (+/- 2 weeks) until either week 96 or disease progression (whichever occurs first).
- Nivolumab is administered as an IV infusion every 14 days (+/- 2 days) until disease progression (or until discontinuation of Nivolumab in subjects receiving beyond progression), unacceptable toxicity, or withdrawal of consent.
- Response is evaluated using RECIST 1.1 criteria.

The first tumor assessment of non-irradiated lesions will occur at week 8 (+/- 2 weeks) after treatment initiation and then every 8 weeks (+/-2 weeks) for the first 48 weeks and then every 12 weeks (+/-2 weeks) until documented progression or week 96 whichever occurs first. CT or MRI images of chest, abdomen, pelvis, head, neck, and all known sites of disease should be obtained. The same imaging modality that was used as baseline should be used at all subsequent evaluations.

- After week 96 of treatment, patients will be contacted every 3 months for survival. This can be done by phone if the patient is unable to come into clinic for routine follow-up.
- Treatment phase will conclude at the time of study drug discontinuation.
- Imaging can continue per institutional preference past 96 weeks, however, RECIST reads are not required.

Follow-Up Phase

- Begins at the conclusion of Nivolumab therapy.

- Subjects will have one follow-up visit for safety within approximately 100 days from the last dose of Nivolumab.
- Subjects who discontinue treatment for reasons other than tumor progression will continue to have tumor assessments per prior schedule (e.g. every 8 weeks for the first 48 weeks and then every 12 weeks until week 96).
- Follow-up (phone or visit) will continue to occur every 3 months for survival information.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Nivolumab (BMS-936558)

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

Nivolumab has a concentration of 10mg/mL and is provided in a 10mL vial. Nivolumab infusion concentration must be at or above the minimum allowable concentration of 0.35 mg/mL.

Nivolumab will be provided by BMS (Bristol-Myers Squibb) and shipped directly to the site where it is to be administered.

Nivolumab (OPDIVO) is approved for the treatment of unresectable or metastatic melanoma in multiple countries including Japan, the US, and EU. It is also approved for the treatment of metastatic squamous cell NSCLC in the US.

5.1.1 Storage Conditions and Handling

Nivolumab should be stored at between 2-8 degrees Celsius (36-46 degrees Fahrenheit), and protected from light, freezing, and shaken. If any temperature excursions are encountered during storage, they should be reported to BMS. As with all injectable drugs, care should be taken when handling and preparing Nivolumab. Whenever possible, Nivolumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique. Partially used vials should be disposed at the time following procedures for the disposal of anticancer drugs.

5.1.2 Use Time/Stability

Once transferred to IV bags, the solution may be stored for up to 20 hrs in a refrigerator at 2-8 degrees Celsius and used within 4 hours at room temperature and under room light inclusive of administration time. The maximum 4-hour period under room temperature and room light conditions for undiluted and diluted solutions of Nivolumab injection in the IV bag should be inclusive of the product administration period. Please refer to the current Investigator Brochure for further details (Section 3).

5.2 Image-Guided, High Dose Stereotactic Body Radiotherapy

Image-guided, stereotactic body radiotherapy allows for the deivery of high-dose-per-fraction radiotherapy with exquisite precision whie excluding to a large degree normal tissue from being exposed to high-dose regions of irradiation. Stereotactic radiotherapy is defined as the directing of therapy using beams of radiation along any trajectory in 3D space toward a target of known 3D coordinates. The coordinate system is defined by reliable fiducial markers. For the purposes of this study, the tumor itself will serve as the fiducial. Low-dose CT scans will be obtained at the time of treatment delivery, and intensity modulated radiotherapy planning (IMRT) will be utilized.

IMRT is a sophisticated radiation planning and delivery technique that uses a computer controlled multi-leaf collimator to shape the intensity of each radiation treatment beam to optimally deliver the dose to the tumor and protect normal tissue. The radiotherapy delivery systems that will be used in this trial are standard and FDA approved. The dose fractionation scheme (9 Gy x 3) has been used routinely at MSKCC and other tertiary care centers.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

In order for a patient to be enrolled on trial, the following criteria need to be met:

6.2 Subject Inclusion Criteria

1) Signed Written Informed Consent
   - Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines.
   - Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other study obligations.

2) Target Population
   - Males and females ≥ 18 years of age.
   - Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
   - Histologically confirmed metastatic HNSCC, including nasopharynx WHO Type I-III histologies; patients can have simultaneous loco-regional disease. Central biopsy review at MSKCC is not required.
   - Subjects must have at least two lesions:
     - At least one lesion must be safely amenable to irradiation and likely to meet criteria delineated in Section 9.2.1 in the judgment of the treating radiation oncologist. This can be a lesion that was previously irradiated as long as prior radiation was at least 6 months prior to projected first fraction of SBRT and as long as reirradiation dose constraints as outlined in appendix are being met.
     - A separate, not-to-be-irradiated lesion measurable by CT or MRI per RECIST 1.1 criteria.
   - A formalin fixed, paraffin-embedded (FFPE) tumor tissue block or a minimum of 3 unstained slides of tumor sample obtained via excisional, incisional, or core needle biopsy from a metastatic or loco-regionally recurrent lesion. A new baseline biopsy does not need to be obtained for study purposes. If 3 unstained are unavailable from

a metastatic or loco-regionally recurrent lesion, with permission of the PI, FFPE tumor tissue from the primary disease site at the time of original diagnosis is acceptable.

- For oropharynx or nasopharynx primary lesions, documentation of viral status is required (e.g. high risk HPV sub-type PCR, p16 IHC, HPV ISH, EBER, etc). Tests done on primary tumor specimens from date of initial diagnosis at outside institutions are sufficient to meet this criterion.
- Prior palliative or curative radiotherapy must be completed at least 14 days prior to randomization.
- Immunosuppressive doses of systemic medication, such as steroids or absorbed topical steroids (doses >10mg/day prednisone or equivalent) must be discontinued at least 14 days prior to first Nivolumab administration.
- Screening laboratory values must meet the following criteria (using CTCAE v4.0) and should be obtained within 28 days prior to randomization:
    - WBC >= 2 K/microliter
    - Neutrophils >= 1.5 K/microliter
    - Platelets >= 100 K/microliter
    - Hemoglobin >= 9.0 g/deciliter
    - Serum Creatinine <= 1.5 x ULN or creatinine clearance > 40ml/min using the Cockcroft-Gault formula.

        - *Female* CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$

        - *Male* CrCl = $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$

    - AST/ALT <= 3 x ULN (for subjects with liver metastases AST/ALT may be <=5 x ULN).
    - Total bilirubin <1.5 x ULN (except subjects with Gilbert Syndrome who can have total bilirubin <3.0 mg/deciliter)
    - Calcium levels must be normalized and maintained within normal limits for study entry and while on treatment.
    - Subjects with an initial magnesium <0.5 mmol/liter (1.2 mg/deciliter) may receive corrective magnesium supplementation but should continue to receive either prophylactic weekly infusion of magnesium and/or oral magnesium supplementation.
    - Subjects must have a resting baseline O2 saturation by pulse oximetry of >=92% at rest.

3) Reproductive Status
    - Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 28 days prior to randomization.
    - Women must not be breastfeeding

- Women of childbearing potential must agree to follow instructions for method(s) of contraception from time of enrollment for the duration of treatment with Nivolumab plus 5 half- lives plus 30 days for a total of 23 weeks post treatment completion.
- Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving Nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product.
- Women who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile as well as azoospermic men do not require contraception.
- Azoospermic males and women of childbearing potential who are continuously not heterosexually active are exempt from contraceptive requirements. However, they still must have a pregnancy test.

4) Insurance Approval
   - Insurance approval for SBRT should be obtained prior to randomization

6.2 Subject Exclusion Criteria

Target Disease Exceptions

- Active brain metastases (untreated brain metastases or growth on imaging as defined below) or leptomeningeal disease are not allowed. Subjects with brain metastases are eligible if these have been treated and there is no MRI (or CT if MRI contraindicated) evidence of progression for at least 8 weeks after treatment for these metastases is complete and within 28 days prior to first study treatment.
- Histologically confirmed non-squamous histologies are not allowed; an exception is made for WHO Type I-III nasopharynx histologies.

Medical History and Concurrent Diseases:

- Any medical disorder that, in the opinion of the investigator, might increase the risk associated with study participation or interferes with the interpretation of study results.
- Prior active malignancy within the previous 3 years except for locally curable cancers such as basal or squamous skin cancer, superficial bladder, low risk prostate cancer, breast, or cervix cancer. If other prior malignancy was active within prior 3 years, enrollment requires approval of a principal investigator.
- Patients should be excluded if they have an active, known or suspected autoimmune disease. Subjects are permitted to enroll if they have 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
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration should be excluded. Inhaled or topical steroids and adrenal replacement doses >10mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

- As there is potential for hepatic toxicity with Nivolumab, drugs with a predisposition to hepatoxicity should be used with caution in patients treated with Nivolumab-containing regimen.
- Prior treatment with an anti-PD-1, anti-PD-L1, or anti-PD-L2 antibody.
    - NB-patients who have received prior anti-CTLA-4 antibody therapy are eligible assuming such therapy was discontinued within 28 days of enrollment.
- Treatment with any chemotherapy, radiation therapy, biologics for cancer, or investigational therapy within 14 days of randomization.

Physical and Laboratory Test Findings

- Positive test for hepatitis B virus surface antigen or hepatitis C virus ribonucleic acid indicating acute or chronic infection.
- Known history of testing positive for HIV or known AIDS.
- Any grade 4 laboratory abnormalities.

Allergies and Adverse Drug Reaction

- History of allergy to Nivolumab components
- History of severe hypersensitivity reaction to any monoclonal antibody.

Prohibited or Restricted Treatments

The following medications are prohibited during the study:

- Immunosuppressive agents (except to treat a drug-related adverse event).
- Systemic corticosteroids > 10 mg daily prednisone equivalent save for exclusion outlined in the below paragraphs.
- Any concurrent chemotherapy, hormonal therapy, immunotherapy, or investigational agents for treatment of cancer.

Supportive care for disease-related symptoms may be offered to all subjects on the trial.

Permitted Therapies During Study

In either arm, if the investigator deems it medically necessary, non-target lesions can receive conventionally dosed, palliative radiation therapy. Palliative radiotherapy is not permitted within 24 weeks of first study treatment. Subjects receiving palliative radiation therapy will be considered to have had unequivocal progression of disease. Administration of Nivolumab to subjects who received palliative radiation should follow guidelines specified for treatment beyond disease progression. Any subsequent responses to therapy after the receipt of palliative radiation will not be counted towards the calculation of the primary endpoint, but patients who receive palliative radiation who remain on Nivolumab will have continued study-mandated scans until a 2nd progression event or 96 weeks, whichever occurs earlier.

Other permitted therapies include topical, ocular, intra-articular intranasal and inhalational corticosteroids. Adrenal replacement steroid doses including doses > 10 mg daily prednisone are also permitted.

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's head and neck treatment team, the site protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The site principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

This limited waiver will apply only to MSK.

8.0 PRETREATMENT EVALUATION

Screening Procedure Outline:

Subjects will have a screening visit with the investigator and team. The following will be assessed:

8.1.1 Eligibility Assessments

- Informed consent signed
- Assurance that inclusion and exclusion criteria are met
- Medical History within 28 days prior to randomization
- Sufficient tumor tissue for required biomarker analysis obtained before start of study from a metastatic lesion or loco-regionally recurrent site of disease.
    - Block or minimum of 3 slides obtained from core, punch, excisional biopsy; FNA insufficient.
    - Archival material is sufficient.
    - Material from bone is not sufficient as PD-L1 IHC cannot be done on bone.

- If no material is available from a metastatic or recurrent site, with permission of the principal investigator, material from the primary site of disease at the time of original diagnosis is acceptable.

- HPV ISH, HPV PCR, p-16 expression testing, or EBER where for oropharynx and nasopharynx primary lesions, respectively. If not done by an outside facility, this should be repeated at the trial site. This testing could have been performed on primary lesion at time of initial diagnosis.

8.1.2 Safety Assessments

- Assessment of Signs and Symptoms within 28 days prior to randomization
- Physical Examination within 28 days prior to randomization
- Physical Measurements: weight within 28 days prior to randomization
- Vital Signs and Oxygen saturation: blood pressure, heart rate, temperature, O2 saturation via pulse oximetry within 28 days prior to randomization
- Performance status within 28 days prior to randomization
- Prior medication collection: data on all prior systemic therapy received to treat HNSCC within 28 days prior to randomization
- Concomitant Medication Collection: obtained within 28 days prior to randomization
- Laboratory Tests (obtained within 28 days prior to randomization)
  - Complete Blood Count
  - Comprehensive Metabolic Panel (AST, ALT, TBili, BUN, Creatinine, Ca, Mg, Na, K, Cl, Glucose, Amylase, Lipase)
  - TSH, Free T4, T3
  - Hepatitis B surface antigen, hepatitis C antibody
- Pregnancy Test within 28 days prior to randomization.

8.1.3 Efficacy Assessment

- Screening/Baseline Tumor Assessment: CT or MRI of brain, neck, chest, abdomen, pelvis, and all other known sites of disease within 28 days prior to randomization.

8.1.4 Patient Reported Outcome Assessment

- EORTC QLQ-C-30 must be completed before administration of first dose of Nivolumab.

9.1 TREATMENT/INTERVENTION PLAN

Nivolumab should begin within 14 days (+/-4 days) of randomization. The first day of Nivolumab is designated as study Day 1.

Arm 1: On Day 1, patients will receive a one hour infusion of Nivolumab 3mg/kg and then every 14 days (+/-2 days) until treatment progression per RECIST 1.1 criteria, unacceptable toxicity, or withdrawal of consent.

Arm 2: After randomization, patients will complete CT simulation. On Day 1 they will receive their first dose of Nivolumab (3mg/mg); they will receive their first radiation treatment (9 Gy) by study day 14. The additional 2 fractions of radiation (9 Gy per fraction) will be delivered within 10 business days, no more frequently than every other day. Nivolumab 3mg/kg will be administered

every 14 days (+/-2 days) until treatment progression per RECIST 1.1 criteria, unacceptable toxicity, or withdrawal of consent.

9.2 Intervention: Nivolumab

9.2.1 Preparation and Administration:

- Nivolumab injection is to be administered using a volumetric pump with a 0.2/1.2 micron pore size, low protein binding polyethersulfone membrane in-line filter at the protocol-specific doses.
- The line should be flushed at the end of the infusion with sufficient quantity of normal saline per institution SOC.
- Nivolumab is not to be administered as an IV push or bolus injection.
- At the dose of 3mg/kg, the total dose needed will be diluted to a minimum total volume of 60 ml in 0.9% Sodium Chloride or 5% dextrose injection solution.
- Care must be taken to assure sterility of the prepared solution as the produce not contain any anti-microbial preservative or bacteriostatic agent.
- Nivolumab should be administered over a 1-hour period; infusions will be controlled by a volumetric pump.
- Please refer to the current Investigator Brochure for further details.
- Allow the appropriate number of vials of Nivolumab to stand at room temperature for approximately 5 minutes before preparation.
- Ensure that Nivolumab solution is clear, colorless, and essentially free from particulate matter.
- Aseptically withdraw the require volume of Nivolumab into a syringe and dispense into an IV bag.
    a. Add the appropriate volume of 0.9% Sodium Chloride injection solution.
    b. Mix by gently inverting several times. DO NOT shake.
    c. Record the Nivolumab expiration time and date on the IV bag label.
    d. Attach the IV bag containing the Nivolumab solution to the infusion set, in-line filter, and infusion pump.
    e. The infusion rate of the infusion pump should be adjusted to allow for a total infusion time of approximately 60 minutes.
    f. At the end of the infusion period, flush the line with a sufficient quantity of 0.9% Sodium Chloride injection solution or 5% dextrose injection.
- Pharmacy supplies required:
    a. Empty IV bags-50mg, 100mL, 200 mL
    b. 0.9% NaCl bags
    c. 0.2 or 0.22 micron in line filter and infusion tubing
    d. Volumetric infusion pumps.

9.2.2 Selection and Timing of Dose for Each Subject

Subjects randomized to Arm 1 or Arm 2 will receive Nivolumab as a 60 minute IV infusion on Day 1 of the study. Subjects randomized to Arm 2 will receive their first radiation fraction by study day 14. Dose of Nivolumab is 3mg/kg and should be done based on the

body weight of the subject at the start of each cycle. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the original dose, the dose must be recalculated. All doses should be rounded to the nearest milligram or as per institutional guidelines. There are no pre-medications recommended for Nivolumab.

9.2 Intervention: SBRT

9.2.1 Target Selection

- A single target lesion will be selected.
- The lesion must be safely amenable to irradiation in the judgment of the treating radiation oncologist; approval of PI is not required.
- Lesions must be located in one of the following eight locations:
  - Central Lung Tumors: GTVs within 2cm of the proximal bronchial tree (carina, right and left main bronchia, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus right and left lower lobe bronchi.
  - Lung Peripheral: metastases within the lung parenchyma with GTV outside of the proximal bronchial tree as described above.
  - Mediastinal Lymph Nodes: GTV arising within the anatomic space between the lungs, above the diaphragm, and below the thoracic inlet at the level of the top of the sterna notch.
  - Head and Neck: GTV occurring within cervical lymph node levels I-VI and/or retropharyngeal spaces, oral cavity, oropharynx, nasopharynx, hypopharynx, para-nasal sinuses, nasal cavity, and parotid gland/space.
  - Liver: GTV arising within the liver.
  - Spine: metastases will be assigned to the spinal/paraspinal site if the GTV arises within the vertebral bodies expanded by 1cm.
  - Osseous: GTV arising within an osseous structure, part of the axial skeleton, not included in the spinal definition.
  - Abdominal-Pelvic: GTV arising within the anatomic space defined by the diaphragm superiorly, the genitourinary diaphragm inferiorly include the peritoneal and retroperitoneal spaces, not including liver, osseous, or spinal metastases.

- While no specific size constraint exists, the treating radiation oncologist must have a reasonable expectation that the dose constraints outlined in the appendix will be met; if, during planning, dose constraints to outlined normal tissue structures are exceeded, the treating radiation oncologist must receive permission of the study PI (Sean McBride) prior to proceeding with treatment. If permission is not obtained, the patient will be withdrawn from the study.
- In instances where there is a metastatic or recurrent lesion that is either causing symptoms or on the precipice of doing so, the treating radiation oncologist should select this lesion for irradiation.
- Every effort should be made to choose a target lesion outside of a previously irradiated site. However, the treated lesion can be a lesion that was previously

irradiated as long as prior radiation was at least 6 months before the projected first fraction of SBRT and as long as re-irradiation dose constraints as outlined in appendix are met. In cases of re-irradiation, if the re-irradiation dose constraints outlined in the appendix are exceeded, the patient will be withdrawn from the study.

9.2.2 Radiotherapy Simulation and Contouring Guidelines

- All patients will undergo standard IMRT-based treatment planning (VMAT allowed) prior to the first treatment using an appropriate immobilization device.
    - Begins with immobilization of the patient in a reproducible position in a custom-mold followed by acquisition of a CT scan in the treatment planning position. Prior placement of fiducial markers and the use of 4D-CT acquisition is at the discretion of the treating radiation oncologist.
    - The use of intravenous, oral, or rectal contrast is at the discretion of the treating radiation oncologist.
    - The physician segments the tumor and critical normal tissues on the scan and also specifies the dosimetric goals.
    - For spinal cord lesions, MR fusion or CT myelogram prior to CT simulation will be required in order to ensure that the spinal cord is adequately segmented.
- The definition of volumes will be in accordance with ICRU Report #50: Prescribing, Recording, and Reporting Photon Beam Therapy.
    - A gross tumor volume will be entered for the lesion (GTV), based on available imaging data.
    - The clinical target volume (CTV) should be the same as the GTV. No margin is required for microscopic extension.
    - An internal target volume (ITV) can be used at the discretion of the treating radiation oncologist.
    - The planning target volume (PTV) should be the GTV (or ITV) plus 3 mm.
    - Each PTV will be treated to the prescribed dose of 9 Gy x 3.
    - Normal tissues contoured to determine dose volume histogram will incldue lungs, spinal cord, liver, kidney, heart, trachea, esophagus, rectum, bladder, and bowel, if applicable.

9.2.3 Radiotherapy Planning and Treatment Delivery

- Planning:
    - For IMRT-planning, a physicist chooses the most favorable beam directions and inputs the treatment goals into a computer algorithm that designs the intensity patterns to best fulfill the goals of delivering the assigned dose to the target while keeping all relevant normal tissue structures to the limits set out in Appendix Normal Tissue Constraints. The intensity patterns are then downloaded to the treatment machine to drive the multi-leaf collimator during treatment.
- On Line Image-Guided Localization and Treatment Delivery

- The patient immobilization device is itself fixed to the couch of the treatment machine.
- Prior to each treatment, the position of the patient's tumor is verified using 3 dimensional kilovoltage cone beam CT imaging. This is a high resolution CT scan taken of the patient and target structure of interest while the patient is immobilized on the treatment table.
- The cone beam CT image is obtained and image registration between the cone beam CT and the planning CT is performed based on the location of the visible tumor abnormality noted in the CT. The image registration uses vendor-supplied software available at the treatment unit. Thereafter, follow departmental filming policy.
- The patient position is then adjusted to move the patient into the exact position corresponding to the designed IMRT treatment plan so that the prescription dose completely encompasses the target and the critical normal tissues are not within the high dose region.

- Once the patient's correct position is confirmed, the treatment will be delivered. During treatment the patient is monitored carefully to assure that there is no motion; if motion is noted, further imaging may be warranted.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 ASSESSMENTS DURING TREATMENT

10.1.1 Safety Assessments

- Targeted Physical Examination: Focused exam and history on AEs stemming from immune MOA. This will occur on Day 1 of treatment and within 72 hours prior to Nivolumab administration at the following time points;
  - Every 2 weeks for the first month of treatment
  - Every 4 weeks for months 2-6 of treatment
  - Every 6 weeks until week 96 or progression
- Vital Signs: must include, at minimum, blood pressure on Day 1 of treatment and within 72 hours prior to Nivolumab administration at the following time points;
  - Every 2 weeks for the first month of treatment
  - Every 4 weeks for months 2-6 of treatment
  - Every 6 weeks until week 96 or progression
- Concurrent medication review on Day 1 of treatment and within 72 hours prior to Nivolumab administration at the following time points;
  - Every 2 weeks for the first month of treatment
  - Every 4 weeks for months 2-6 of treatment
  - Every 6 weeks until week 96 or progression
- Physical Measurements: to include weight and performance status. This will occur on Day 1 of treatment and within 72 hours prior to Nivolumab administration at the following time points;
  - Every 2 weeks for the first month of treatment
  - Every 4 weeks for months 2-6 of treatment
  - Every 6 weeks until week 96 or progression

- Adverse Event Assessment and attribution: This will occur on Day 1 of treatment and within 72 hours prior to Nivolumab administration at the following time points;
  - Every 2 weeks for the first month of treatment
  - Every 4 weeks for months 2-6 of treatment
  - Every 6 weeks until week 96 or progression
- Laboratory Tests: CBC w/ differential, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Glucose, amylase, lipase, TSH (with reflexive Free T4 and T3) will occur within 48 hours of 1st Nivolumab dose and within 72 hours prior to each subsequent dose of Nivolumab.

10.1.2 Efficacy Assessments

- Tumor Assessment: tumor assessments of non-irradiated lesions via CT or MRI of all known sites of disease should occur 8 weeks after treatment initiation (day 1) (+/-2 weeks) and then every 8 weeks (+/- 2 weeks) for the first 48 weeks and every 12 weeks (+/- 2 weeks) until progression or week 96 (whichever occurs first). At each time-point, subjects should have CT/MR of neck, chest, abdomen, and pelvis with contrast. Subjects with a history of brain metastasis should have surveillance MRI per the above schedule or sooner if clinically indicated. If additional sites of disease not encompassed by the above imaging are noted, imaging of these lesions should also occur at the study mandated time points.

Both MRI and contrast enhanced CTs are adequate imaging modalities for this study. CT with contrast or MR of the neck, chest, abdomen, pelvis, and all other known sites of disease are to be performed for tumor assessments per the timing above.

CT scans should be acquired with 5mm slices with no intervening gap. A non-contrast CT of the chest and a contrast enhanced MRI of the abdomen are acceptable if the patient has a contraindication to CT with contrast.

PET/CT is acceptable so long as the CT component is of diagnostic quality.

MRI brain scans during on-study treatment are required if there is a prior history of lesions present at screening, or as clinically indicated.

10.1.3 Outcomes Research Assessment

- EORTC QLQ-C-30: will be completed on or before Day 1 of treatment, and then, starting at week 8 (+/- 2 weeks), every 8 weeks (+/-2 weeks) for the first 48 weeks and every 12 weeks (+/- 2 weeks) until either week 96 or disease progression (whichever occurs first).

10.1.4 Exploratory Biomarker Testing

- PBMC composition: should be evaluated on blood drawn up to 7 days prior to treatment and then Days 14 (+/- 3 days) and 28 (+/-3 days) and then upon progression (within 1 week).
- Soluble Biomarkers: can include PD-L1, and PD-1. should be evaluated on blood drawn up to 7 days prior to treatment and then Days 14 (+/- 3 days) and 28 (+/- 3 days)and then upon progression (within 1 week).

10.2 Assessments During Follow-Up

There will be a single mandated follow-up visit:

- Follow-Up Visit: occurs within 100 days from the last dose of Nivolumab (FU1)

10.2.1 Safety Assessments at follow-up visit:

- Targeted Physical Examination
- Vital Signs: at a minimum, must include blood pressure.
- Adverse events assessment
- Review of concomitant medication

10.2.2 Subject Status

- Survival: at follow-up and then every 12 weeks thereafter (phone or visit acceptable).

	Screening	Treatment				FU
	Baseline	Day 1[A]	Q2 weeks (+/- 2 Days)	Q2 weeks (+/- 2 Days) for 1st month, every 4 weeks for months 2-6, every 6 weeks until week 96 or progression	Start at week 8 (+/- 2 weeks) and then q8 weeks (+/- 2 weeks) for first 48 weeks and then q12 (+/- 2 weeks)	Follow Up Visit
Consent	X					
Biopsy	X					
HPV/EBER Testing[B]	X					
Vital Signs	X	X		X		X
Targeted Physical Exam	X	X		X		X
Physical Measurements	X	X		X		
Performance Status	X	X		X		X
Adverse Event Assessments	X	X		X		X
Concomitant Medication	X	X		X		X
Laboratory Test	X	X	X			
Pregnancy Test	X					
Nivolumab			X			
Radiation		X[C]				
CT/MR for RECIST	X				X	
EORTC QLQ-C30	X				X	
Blood Draw for PMBCs/Soluble Biomarkers[D]		X		X		X

A: Laboratory tests can occur within 48 hours prior to 1st Nivolumab Dose
B: HPV/EBER testing required only for oropharynx and nasopharynx primary lesions, respectively
C: The first radiation fraction will begin no later than day 14 and the remaining two fractions will be delivered over 10 business days
D: Blood draws for PMBCs/soluble biomarkers will be collected up to 7 days prior to D1 treatment, D14(+/- 3d), D28(+/- 3d), and progression of disease only

Note: baseline biopsy does not need to be obtained if sufficient biopsy material for required PD-L1 testing from a metastatic or loco-regionally recurrent lesion already exists. If sufficient biopsy material is not available, efforts should be made to biopsy a recurrent/metastatic site. If that is not feasible then, with the permission of the PI, material from the primary tumor specimen at initial diagnosis may be used. Blood draw for PMBCs/soluble biomarkers are study mandated.

11.0 TOXICITIES/SIDE EFFECTS

An adverse event is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign, symptom, or disease temporally associated with the use of study drug/radiation or not considered related to the study drug/radiation. All AEs should be defined using the CTCAE v 4.0. All grade 1-5 adverse events should be reported and attributed.

The causal relationship to study drug is determined by the investigators and should be used to assess all AEs. The causal relationships are defined as follows:

- Related: there is a reasonable causal relationship between study drug/radiation administration and the AE.
- Not related: there is not a reasonable causal relationship between study drug/radiation administration and the AE.

The common understood meaning of "reasonable causal relationship" is that there is evidence to suggest a causal relationship.

11.1 Nivolumab Toxicity Management

For Nivolumab monotherapy, the safety profile is similar across various tumor types. There is no pattern in the incidence, severity, or causality of AEs to Nivolumab dose level. In phase 3 controlled studies, the safety profile of Nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using the below mentioned safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping Nivolumab treatment and timely immunosuppressive therapy or other supportive care. For complete details please to the Investigator Brochure v.14 that accompanies this protocol.

11.1.1 Dose Delay Criteria

Because of the potential for clinically meaningful Nivolumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected AEs of selected categories. [See current Investigator Brochure]

Dose delay criteria apply for all drug-related adverse events. All study drugs must be delayed until treatment can resume.

Dose delay criteria apply for all drug-related AEs. Nivolumab must be delayed until treatment can resume.

Nivolumab administration should be delayed for the following:

Any Grade ≥ 2 non-skin, drug-related AE, with the following exceptions:

- Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related AE

Any Grade ≥3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, total bilirubin, or asymptomatic amylase or lipase:

- Grade 3 lymphopenia or leukopenia does not require dose delay.
- If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
- If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.

Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

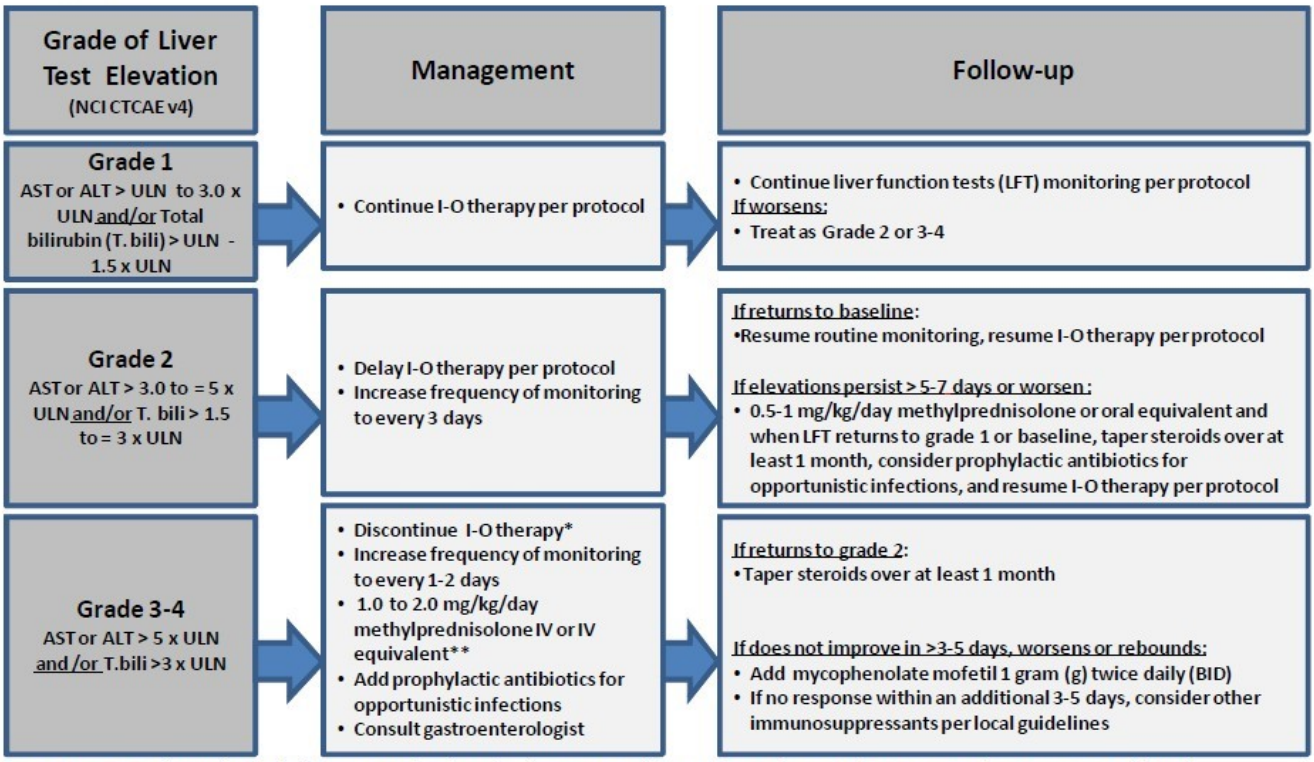
11.1.2 Management Algorithms for Immuno-Oncology Agents

Immuno-Oncology (I-0) agents are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Nivolumab is considered an immune-oncology agent in this protocol. Early recognition and management of adverse events associated with immune-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies
- Skin
- Neurological

Hepatic Adverse Event Management Algorithm

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



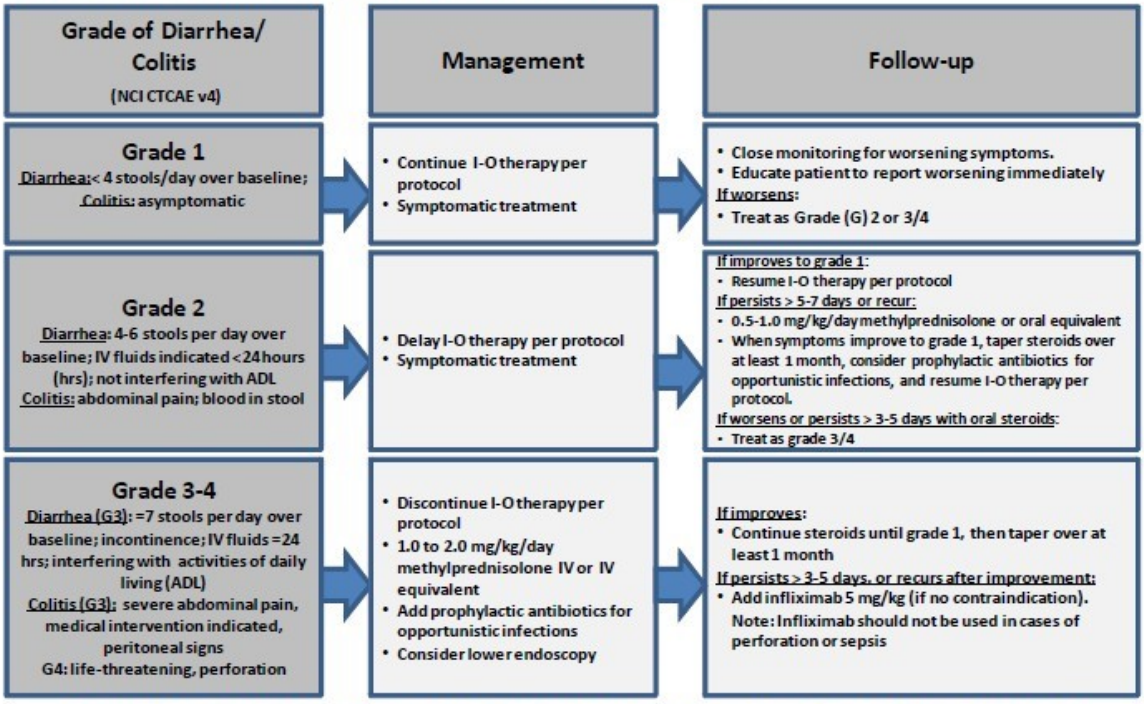
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

GI Adverse Event Management Algorithm

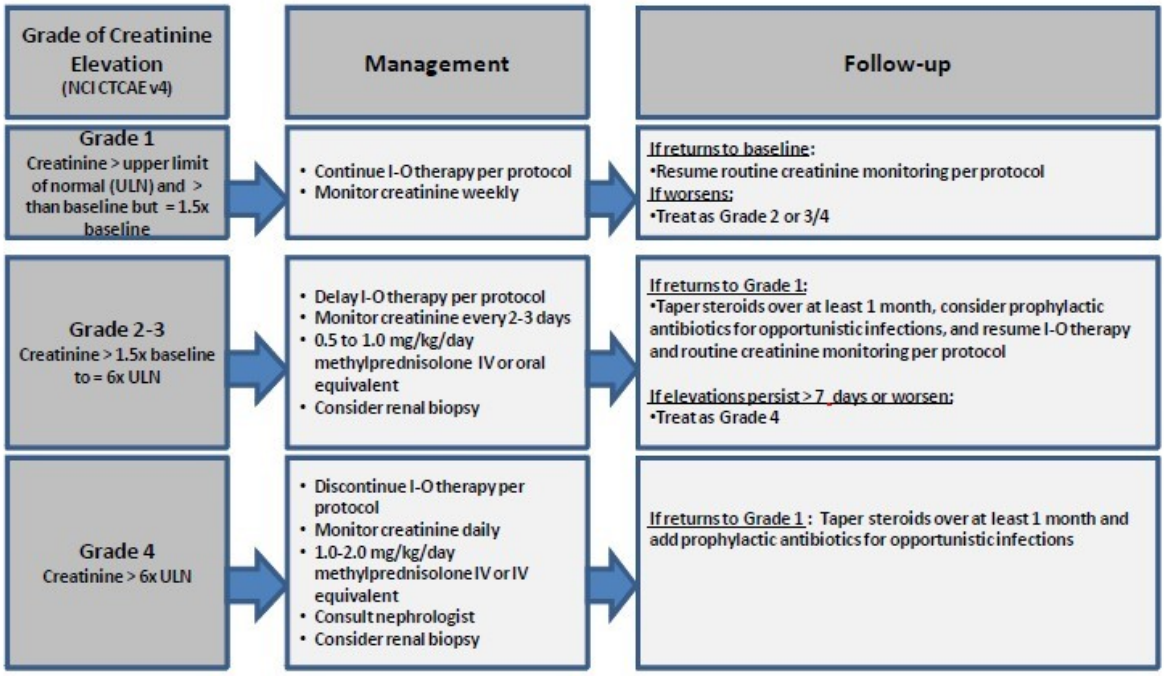
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

Renal Adverse Event Management Algorithm

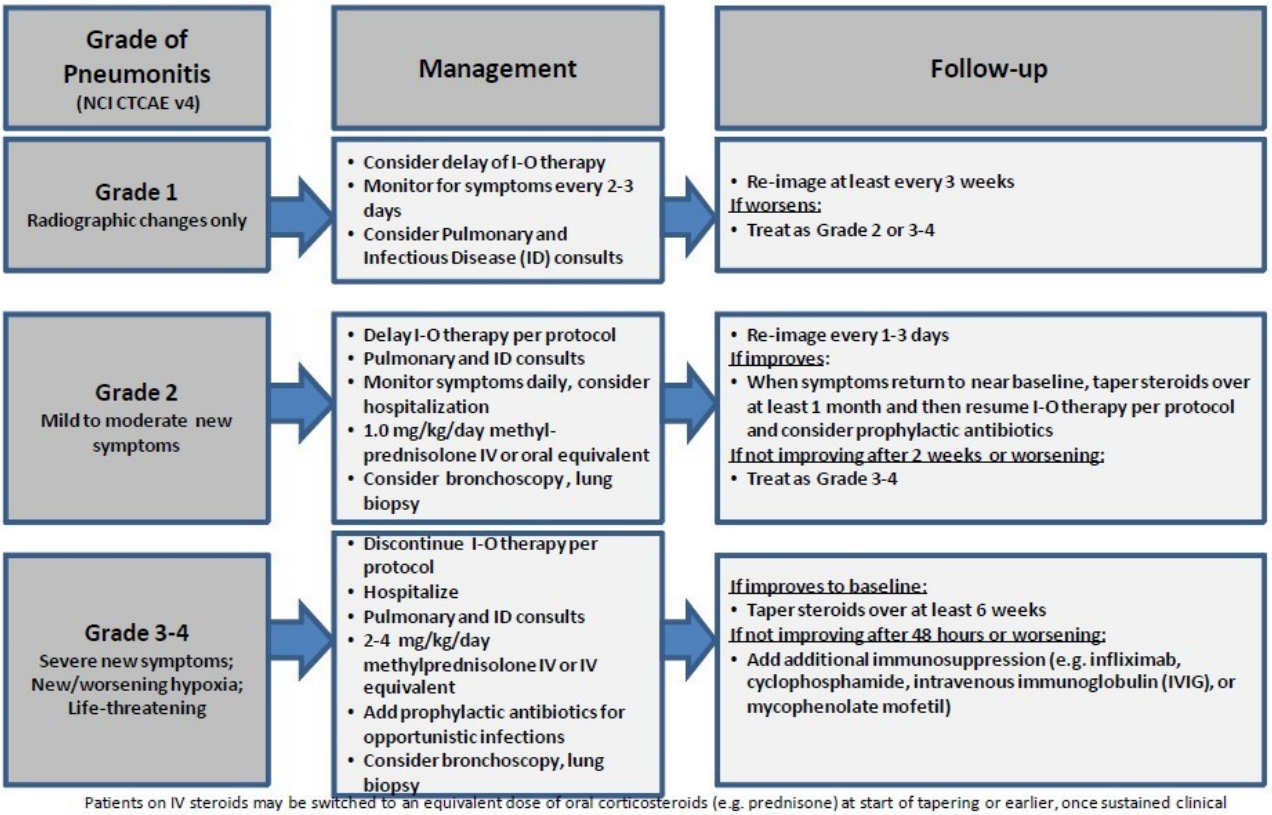
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

Pulmonary Adverse Event Management Algorithm

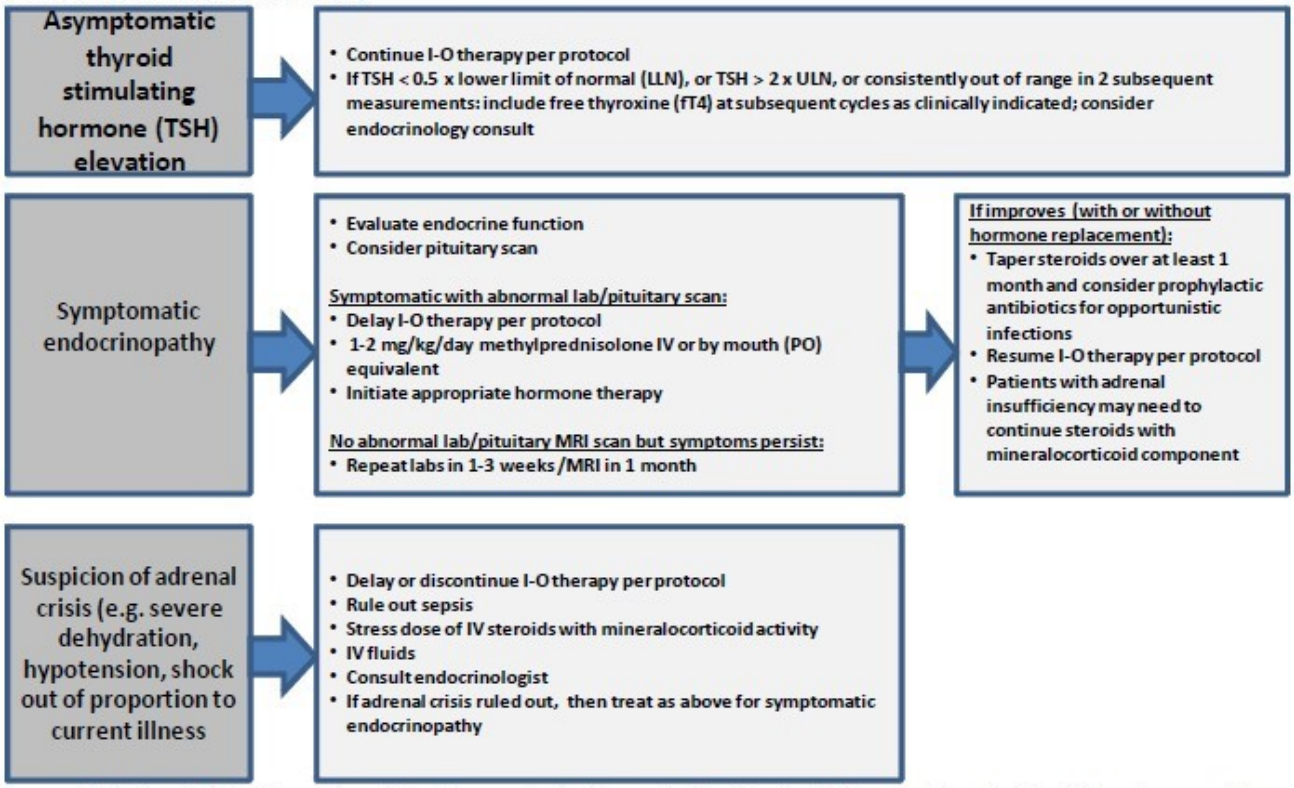
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

Endocrinopathy Management Algorithm

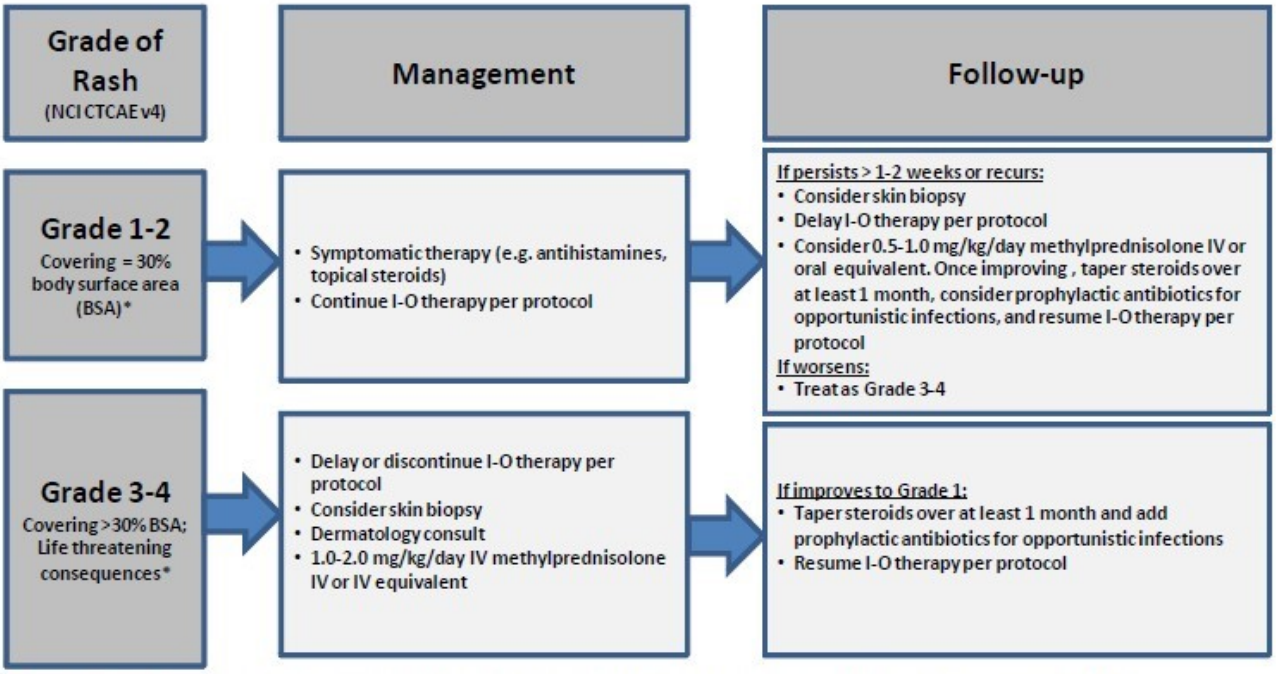
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

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



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

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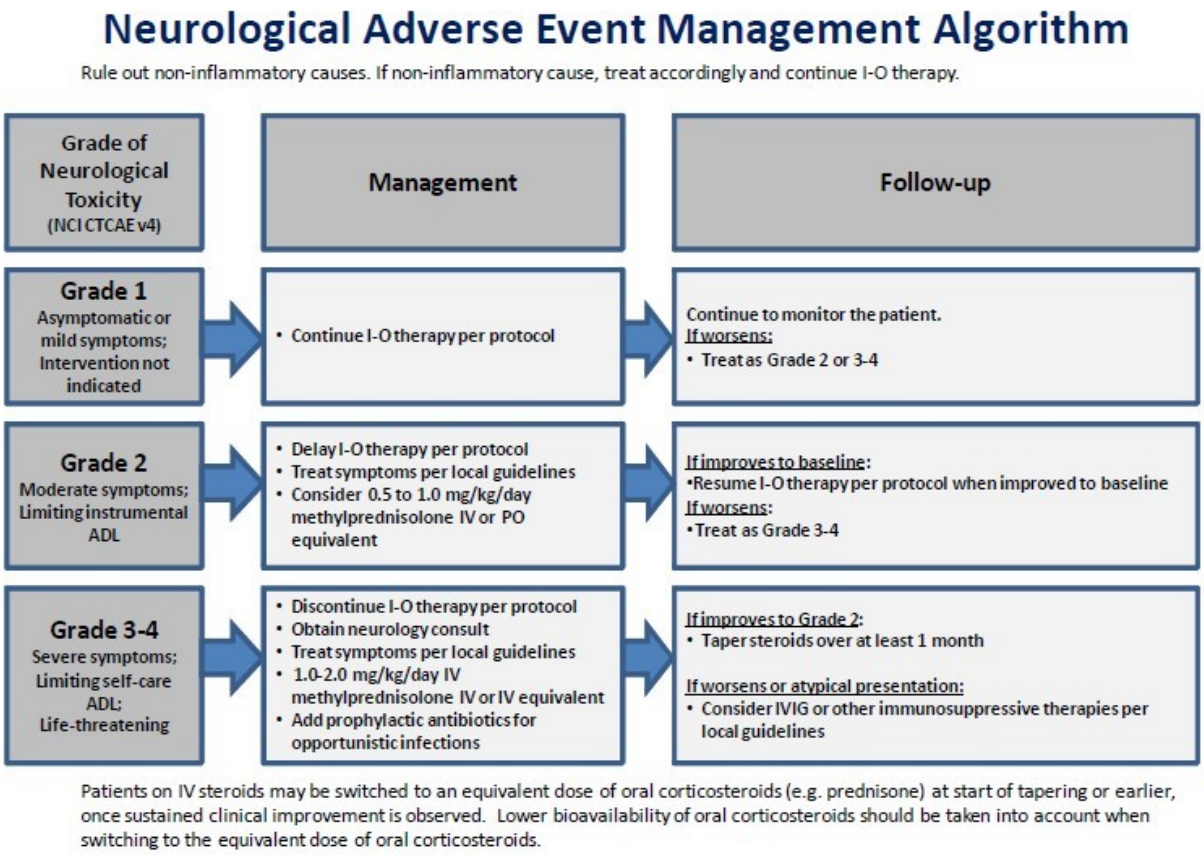

11.1.3 Dose Modifications

Dose reductions or dose escalations are not permitted.

11.1.4 Criteria to Resume Treatment

Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade <= 1 or baseline value, with the following exceptions:

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

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time-point per protocol. However, if the treatment is delayed past the next scheduled time-point per protocol, then next scheduled time-point will be delayed until dosing resumes.

Treatment may be delayed for up to a maximum of 6 weeks from the last dose; if treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified.

11.1.5 Treatment of Infusion Reaction

Since Nivolumab contains only human IgG protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reacitons. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash pruritus, athralgias, blood pressure shifts, bronchospasms, or other symptoms. All Grade 3 or 5 infusion reacitons should be reported within 24 hours to the primary investigator and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE v 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 [e.g., 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 electronic case report form (eCRF). 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 [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; pressor or ventilatory 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 (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

11.2 Management of Toxicities Related to Radiotherapy

Supportive Care During Radiotherapy

- Antiemetics can be ordered at the discretion of the treating radiation oncologist.
- Mucositis/esophagitis may be ameliorated with sucralfate or gastrointestinal cocktail (e.g. Tyleon #3 suspension, benadryl elixir, Maalox, viscous lidocaine).
- Intravenous hydration is recommended in patients with inadequate oral intake.
- Treatment-related diarrhea can be managed with loperamide.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Primary Endpoint:

To compare overall response rate (ORR) in non irradiated lesions during the first 96 weeks after treatment initiation as determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria between patients receiving Nivolumab and SBRT to those receiving Nivolumab alone. ORR rate is defined as the number of patients randomized to a given arm with a best overall response (BOR) of complete response (CR) or partial response (PR) divided by the total number of patients randomized to the given arm.

To serially evaluate tumor response to therapy, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable tumor lesion. At baseline, tumor lesions/lymph nodes will be categorized as measurable or nonmeasurable.

12.1.1 Measurable Lesions

Of note, for purposes of this study, irradiated lesions are not considered measurable.

Measurable lesions must be accurately measured in at least one dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10mm by CT/MRI scan
- 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. At baseline and in follow-up, only the short axis will be measured and followed.

12.1.2 Non-measurable lesions

- All other lesions including small lesions (longest diameter <10mm or pathological lymph nodes with >=10 to <15mm short axis), as well as truly non-measurable lesions.
- Lesions considered to be truly nonmeasurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung.

12.1.3 Special Considerations Regarding Lesion Measurability

- Bone scan, PET scan or plain films are inadequate to measure bone lesions. However, these techniques can be used to confirm the presence of 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/MRI can be considered as measurable lesions if the SOFT TISSUE component meets the definition of measurability.
- Blastic bone lesions are non-measurable.

12.1.4 Cystic Lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions since they are, by definition simple cysts.
- “Cystic lesions” thought to represent cystic metastases can be considered as measurable lesions, if they meet the aforementioned definition of measurability. However, non-cystic lesions are preferred.

12.1.5 Lesions with Prior Local Treatment

- Tumor lesions situated in the previously irradiated area can be included as target lesions as long as there is documented radiographic disease progression in that site after completion of radiotherapy.

12.1.6 Baseline Documentation of “Target” and “Non-Target” Lesions

12.1.6.1 Target Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size, be representative of all involved organs, and should lend themselves to reproducible repeated measurements.

A sum of diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted below, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

12.1.6.2 Non-Target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should be recorded at baseline. Measurements are NOT required and these lesions should be followed as “present”, “absent”, or in rare cases, “unequivocal progression”. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form.

12.1.7 Tumor Response Evaluation

Complete Response (CR): disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10mm.

Partial Response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as a reference the baseline sum of diameters.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as a reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). IN addition the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. Note: the appearance of one or more new lesions is also considered progression.

Stable Disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference the smallest sum diameters while on study.

12.1.8 Evaluation of Non-Target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified.

Complete Response (CR): disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10mm short axis).

Non-CR/Non-PD: persistence of one or more non-target lesions.

Progressive Disease: unequivocal progression of existing non-target lesions (Note: the appearance of one or more new lesions is also considered progression) or the appearance of new malignant lesions. The finding of new lesions should be unequivocal.

- To achieve unequivocal progression on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- If unequivocal progression is seen, the subject should be considered to have had an overall PD at that point.

FDG-PET Evaluation

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of qualitative assessment of FDG-PET scanning to complement CT scanning in assessment of progression, particularly new disease. New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm.

- Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
  - If positive PET at follow-up corresponds to new site of disease, this is PD
  - IF the positive PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site.
  - If the positive PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

12.1.9 Response Criteria

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

The best overall response is determined once all the data for the subjects is known. It is the best response recorded from the start of the study treatment until, in our own trial, 2 years. The subjects best overall response will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Best response is defined as the best response at all time points. When SD is believed to be the best response, it must also meet protocol specified minimum time from baseline (8 weeks). If the minimum time is not met when SD is otherwise the best time point response, the subjects best response depends on the subsequent assessments. For

example, a subject who has SD at first assessment, PD at second and does not meet minimum duration of SD, will have best response of PD. The same subject lost to follow-up after the first SD assessment will be considerd not evaluable.

12.1.10 Verification Scans

- Verification of Response: confirmation of response (CR or PR) is required. Confirmed CR or PR will be claimed only if the criteria for each are met at a subsequent time point (minimum 4 weeks after criteria for an objective response are first met).
- Verification of Progression: progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered not to have progressive disease per RECIST 1.1.

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

12.2 Secondary End Points:

12.2.1 Duration of Response

The duration of objective response is measured from the time measurement criteria are first met for confirmed PR/CR until the first date the progressive disease is objectively documented (taking as a reference for progressive disease the smallest measurements recorded on study). Duration of response will be measured from the time, in months, that the criteria for objective response are first met until the date of a progression event. A subject with objective response who does not have a progression event at 96 weeks will be censored.

12.2.2 Overall Survival

Overall survival is defined as the time from randomization to the date of death from any cause. For subjects that are alive, their survival time will be censored at the date of last contact. Overall survival will be censored for subjects at the date of randomization if they were randomized but had no follow-up.

12.2.3 Progression Free Survival (PFS)

PFS is defined as the time from randomization to the date of RECIST-defined progressive disease (PD) or death from any cause. For subjects that are alive with CR, PR, or SD, they will be censored at the end of the two year, study mandated tumor assessments. PFS will be censored for subject at the date of randomization if they were randomized but had no follow-up.

12.2.5 Treatment Related Adverse Events

These will be defined for each arm using CTCAE v 4.0 criteria.

12.2.6 Health-Related Quality of Life

The EORTC-QLQ-C-30 is one of the most commonly used QoL instruments in oncology studies and has been assessed in previous studies evaluating health related quality of life in patients with head and neck cancer. It is a 30 item instrument compromising six functional scales (physical functioning, cognitive functioning, emotional functioning, social functioning, role functioning, and global quality-of-life) as well as nine symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Except for overall health status and global quality of life items, responses for all items are 4-point categorical scales ranging from 1 (not at all) to 4 (very much). The overall health/quality of life responses are 7 point Likert scales.

The questions on the EORTC-QLQ-C30 will be scaled and scored using the recommended EORTC Quality of Life Group procedures. Raw scores will be transformed using a linear scale ranging from 0 to 100, with a higher score representing a higher level of functioning or a higher level of symptoms. Clinical significance will be defined as differences of at least 10 points (on a 0-100 scale). For example, a mean increase of >= 10 points on a functional scale would indicated a moderate improvement, whereas a mean decrease of >= 10 points would be interpreted as moderate worsening.

12.3 EXPLORATORY END POINTS:

12.3.1 Baseline PD-L1 Expression on Tumor Cells

Fresh biopsies will be provided for biomarker analysis if accessible and deemed safe and clinically necessary by the investigator. An archived biopsy of metastatic or loco-regionally recurrent disease obtained prior to therapy is acceptable if the fresh biopsy is not clinically indicated. If neither fresh nor archived material are available from recurrent/metastatic site, archived material from the primary disease at diagnosis is allowable with permission of PI. On-treatment biopsies are not required.

Expression of PD-L1 expression on tumor cells will be assessed using an automated immunohistochemical assay developed by BMS and Dako. PD-L1 positivity will be defined as at least 5% of tumor cells showing cell surface PD-L1 staining of any intensity in a section containing at least 100 tumor cells that could be evaluated. Expression of PD-L2 expression on tumor infiltrating lymphocytes (TILs) may also be assessed. Additional IHC studies may be conducted evaluating CD4, CD8, FOXP3, HLA Class I,

Antigen Presenting Machinery (APM), and HPV oncoproteins expression. PD-L1 IHC will be conducted by BMS (see appendix for additional information)

12.3.2 Peripheral Blood Mononuclear Cells Composition (PBMCs)

Peripheral blood samples will be taken prior to initiation of study therapy and at designated time points. Ideally, peripheral blood samples should be used for immunophenotyping or characterization of the immune cell subsets in the periphery, including, but not limited to, T cells, B cells, NK cells, or subpopulations of the aforementioned immune cell types. These samples may also be used to assess immune cell function or antigen specific T cell proliferation.

12.3.3 Serum Biomarkers

Blood samples for exploratory serum biomarker analysis will be drawn at the time points indicated. Blood samples will be processed to collect serum and then put in frozen storage. Samples may be assessed by ELISA, seromics and/or other relevant multiplex based protein assay methods for immune or HNSCC-related factors that will predict for Nivolumab and/or Nivolumab+SBRT benefit. Although numerous potential serum-based biomarkers are under investigation, we will look at soluble PD-1 and PD-L1. However, other biomarkers may be of interest and future analyses may include them.

12.3.4 Neo Antigen Expression (optional)

Neo-epitope analysis using whole exome sequencing may also be conducted on baseline biopsy specimen and evaluated as a predictor of response to therapy.

13.1 CRITERIA FOR REMOVAL FROM STUDY

Treatment with Nivolumab will continue until RECIST 1.1-defined progression, unacceptable toxicity, failure to obtain PI approval for radiation plans that exceed normal tissue dose constraints as outlined in the appendix, or withdrawal of consent.

13.2 Discontinuation Criteria for Nivolumab

Treatment should be permanently discontinued for the following:

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

  - Any drug related LFT abnormaltiy that meets the following criteria require discontinuation;
    - AST or ALT > 8x ULN
    - Total bilirubin > 5x ULN
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN.
- Any grade 4 drug-related adverse event or laboratory abnormaltiy, except for the following events which do NOT require discontinuation:
  - Isolated grade 4 electrolyte imbalances that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
  - Isolated grade 4 electrolyte imbalances that are not associated with clinical sequelae and are corrected with supplementation within 72 hours of their onset.
- Any dosing delays lasting > 6 weeks with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to reinitiating treatment in a subject with a dosing delay lasting > 6 weeks, the primary investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
  - Dosing delays > 6 weeks that occur for non-drug related reaosns may be allowed if approved by the primary investigator. Prior to reinitiating treatment in a subject with a dosing delay lasting > 6 weeks, the primary investigator must be consulted. Tumor assessments should continue as perp protocol even if dosing is delayed.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgement of the investigator, presents a substantial clinical risk to the subject with continued Nivolumab dosing.

13.3 Treatment Beyond Disease Progression with Nivolumab

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease (PD). Subjects will be permitted to continue on treatment with Nivolumab beyond initial RECIST 1.1 PD as long as they are meeting the following criteria:

- Investigator-assessed clinical benefit without rapid disease progression.
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g. CNS metastases)
- Subject provides written informed consent prior to receiving any additional nivolumab treatment, using an ICF describing any reasonably forseeable risks or discomforts, or other alterative treatment options.

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

All decisions to continue treatment beyond initial progression must be discussed with the primary investigator and documented in the study records. Subjects will be reconsented with an ICF describing any reasonable foreseeable risks or discomforts.

Subjects should discontinue study therapy upon further evidence of progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10mm (except for pathological lymph nodes, which must have a short axis of at least 15mm). 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 15mm).

For statistical analyses that include investigator assessed progression date, subjects who continue treatment beyond initial investigator-assessed RECIST 1.1 defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event. Responses beyond this 1st progression event will not be counted towards the primary endpoint of overall response rate.

Patients who have initial progression who are deemed eligible and decide to continue Nivolumab therapy will continue to have study mandated scans per Section 10.1 until further progression or 96 weeks, whichever occurs first.

14.0 BIOSTATISTICS

11.1 Primary Objective

The primary objective of this study is to compare best overall response (BOR) rate by 96 weeks as determined by the investigator using RECIST 1.1 criteria between patients receiving Nivolumab and SBRT and those receiving Nivolumab alone. BOR rate is defined as the number of patients randomized to a given arm with a best overall response of complete response (CR) or partial response (PR) of non-irradiated lesions divided by the total number of patients randomized to the given arm. In order to ascertain this endpoint, efforts will be made so that patients will be followed for 96 weeks or until progression of disease (and treatment cessation), whichever comes first.

Based upon an estimated ORR of 15% in a PD-L1 unselected population in the Nivolumab alone arm (based on data from Siewert, et al; see background) and an ORR of 45% in the Nivolumab and SBRT arm, the enrollment of 54 patients with a two-sample proportion test will provide a one-sided alpha of 0.10 and a power of 0.80. Assuming a 10% drop-out rate, we will enroll a total of 60 patients. Patients will be randomized to the two treatment arms in a 1:1 ratio. Patients will be stratified based upon viral status (virus negative versus virus positive; virus status is defined by EBV (EBER testing) or HPV (p16, HPV ISH, HPV PCR) testing). Assuming a constant enrollment of 3 subjects per month, it would take approximately 20 months to randomize 60 patients. Calculations were completed using software R 3.1.1 and EAST 6.

To ensure eligible endpoints are well defined, a minimum of 6 months of follow up after treatment initiation is required. Patients lost to follow-up prior to 6 months (24 week scan) will be replaced, regardless of response. Patients lost to follow-up between 6 months and 24 months will be included in the ORR calculation.

Secondary objectives:

OS and PFS will be evaluated by the regular survival analysis tools such as Kaplan-Meier and competing risks methods. Comparisons will be conducted between the two arms by the stratified log-rank test and Gray's test.

The DOR will be calculated from the time of response to progression or last follow up and analyzed using the Kaplan-Meier method among patients who showed response.

All tr-AEs will be tabulated and summarized. The cumulative incidence of all tr-AEs and Grade 3+ tr-AEs, etc., will be compared between the two arms by using Gray's test. For this analysis all randomized subjects who received at least one dose of study drug will be included.

The questions on the HRQOL will be scaled and scored using the recommended EORTC Quality of Life Group procedures. Raw scores will be transformed using a linear scale ranging from 0 to 100, with a higher score representing a higher level of functioning or a higher level of symptoms. Wilcoxon rank sum tests will be conducted to compare the scores across the two arms and longitudinal plots will be made to visually examine the pattern of change of scores at each specified time point. If appropriate, an exploratory linear mixed model will also be used to incorporate correlations among various time points, and include additional variables such as interaction between treatment and number of assessments, site of the primary tumor, baseline score, and performance status.

Because the toxicity of Nivolumab combined with SBRT is unclear, we will utilize an interim stopping rule for Arm 2 based on the first 20 randomized to this arm to protect later patients from unacceptably high toxicity rate. Using data from recently reported early phase trials of Nivolumab in NSCLC, we view 14% as an acceptable rate of acute (within 3 months of study initiation) >= Grade 3 treatment-related adverse events; an unacceptable rate of acute >= Grade 3 treatment-related adverse events is 30%. If more than 5 (e.g. 6 or more) of the first 20 patients experience an acute >= Grade 3 treatment-related adverse event, the trial will be stopped early. If the true toxicity rate is 30%, the above boundary assures a 58% probability of stopping the trial at interim analysis; if the true toxicity rate is 40%, there is an 87% chance of stopping the trial early. If the true toxicity rate is 14%, the above boundary has only a 5% probability of stopping the trial early. Of note, for radiation dermatitis, only Grade 4 treatment-related adverse events will be included in the interim analysis.

For the exploratory objectives, all lab measurements will be summarized and descriptive statistics will be provided. When correlation between lab measurements and treatment outcomes are of interest, Wilcoxon rank sum tests will be conducted to examine the difference between responders and non-responders within each arm. An exploratory multivariate logistic regression analysis to determine whether, once adjusted for relevant clinical covariates and treatment arm, tumor PD-L1 or serum immunophenotypic changes predict for response to Nivolumab.

To clarify we define population for the above analyses

- Randomized subjects for ORR analysis: all enrolled subjects who were randomized and provided at least 6 months of follow-up after treatment initiation. This is the dataset for the primary objective and irORR.
- All randomized subjects: all enrolled subjects who were randomized. This is the dataset for baseline demographics and time-to-event endpoints (PFS, OS).
- Treated subjects: all randomized subjects who received at least one dose of study drug. This is the dataset for safety evaluation. For instance, if a subject receives a single dose of Nivolumab but withdraws from study prior to the first dose of radiation, that subject will be considered treated.
- Biomarker Subjects: all randomized subjects with available biomarker data.
- PRO subjects: all subjects with available Patient Reported Outcomes (PRO) data.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.3 Randomization

Patients will be randomized to the Nivolumab and SBRT arm or Nivolumab only arm. For patients enrolled, immediately after consent is obtained, the RSA at MSKCC will register participants in the Protocol Participant Registration (PPR) system. Once the participant's eligibility is established the registration will be finalized and the participants will be randomized using the Clinical Research Database (CRDB). Randomization will be accomplished by the method of random permuted block, and will be stratified by viral status (positive or negative). After treatment arm is determined by randomization, RSAs will notify the physicians at MSKCC of the treatment arm and participant ID via email within 24 hours of randomization. All Data will be collected and analyzed at MSKCC. Compiled data will be submitted to the biostatistician on study (Dr. Zhigang Zhang) for analysis.

16.1 DATA MANAGEMENT ISSUES

Data will be managed by a designated RSA from the Department of Radiation Oncology at MSKCC. All data will be managed in compliance with institutional policy and kept in iMedidata.

List of variables and population characteristics

- Patient demographic data (date of birth, height, weight)
- Medical history
- Concomitant medication
- Adverse events
- Laboratory Values
- Tumor Assessment Data
- Quality of Life Assessment Data
- Tumor PD-L1 status
- MDSC results

16.2 Quality Assurance

Routine data-quality reports will be generated to assess missing data and inconsistencies. Accrual rates, and extent and accuracy of evaluations and follow-up, will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.
Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of once per year, more frequently if indicated.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at MSKCC were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at http://deainfo.nci.nih.gov/grantspolicies/datasafety.htm. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at *http://mskweb2.mskcc.org/irb/index.htm.*

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research quality assurance) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees, *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center’s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., National Institutes of Health sponsored, in-house sponsored, industrial sponsored, National Cancer Institute cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

Prior to enrollment of each patient, the risks, benefits, and objectives of the study will be reviewed with the participant, including a discussion of the possible toxicities and side effects. Alternative, non-protocol, treatment options will be discussed with the patient. It will be reviewed that participation in this clinical trial is voluntary and that the patient may withdraw consent at any time. The study is designed with careful safety monitoring for toxicity including physician visits and lab work. Specific guidelines for symptom management are in place to protect the study participant.

Human Subjects Involvement and Characteristics: all patients at MSKCC who meet the inclusion criteria will be eligible. Both men and women and members of all ethnic groups are eligible for this trial.

Consent Process: all patients who meet the inclusion criteria will be eligible. Participation is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines. The informed consent procedure is described in Section 18.0.

Possible Toxicities/Side Effects: there are risks associated with treatment as described in Section 11.0; however, patients screened for enrollment will be deemed appropriate for treatment independent on this study.

Benefits: Image-Guided, high dose radiotherapy has the potential to augment tumor response to Nivolumab.

Costs: patients will be charged for physician visits, routine laboratory tests, radiologic studies, and radiation therapy. The patients will not be billed for Nivolumab.

Alternatives: the alternative to this trial would be either standard cytotoxic chemotherapy or enrollment on other, open trials in HNSCC.

Confidentiality: every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patients' names and any other identifying information will not be used in reports or publications resulting from this trial. Other authorized agencies and appropriate internal personnel and external personnel (monitors from BMS), its authorized agents, the FDA, and other governmental agencies may review patient records as required.

Patient Safety: patients are monitoring by physicians and oncology nurses who are very familiar with clinical trials. In the case of an adverse reaction, immediate medical attention is available. In the evenings and weekends, we have 24-hour urgent care facility for outpatients. The PI and co-PIs will be available at all times to organize any necessary intervention.

Monitoring of Data to Ensure Safety: this study will be monitoring by the institutional IRB. This incorporates an independent data and safety monitoring committee established by arrangement with the National Cancer Institute. The analysis of safety will include all

patients' adverse events, including all toxic effects of treatment, will be tabulated individually, and summarized by severity and causality.

17.2 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

Suspected transmission of an infectious agent via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury are not always serious by regulatory definition, these events must always be handled as an SAE.

Any component of a study endpoint that is considered related to the study therapy (radiation or Nivolumab) should be reported as an SAE.

SAE reporting is required as soon as the participant signs consent ***and*** is registered. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

An SAE must be reported to the IRB/PB within 5 calendar days of the event. The IRB/PB requires a Clinical Research Database (CRDB) SAE report should be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

The report should contain the following information:

Fields populated from Medidata:

- Subject's name (generate the report with only initials if it will be sent outside of MSK)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB AE report should be completed as above. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.2.1

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on BMS or an approved form; pregnancies on a Pregnancy Surveillance Form.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

For studies conducted under an Investigator IND in the US include the following:

For studies conducted under an Investigator IND in the US, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information. BMS will be provided with a simultaneous copy of all adverse events filed with the FDA.

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

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

All SAEs should simultaneously be faxed or e-mailed to BMS at:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

- An SAE report should be completed for any event where doubt exists regarding its seriousness.
- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection in the protocol.
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
- If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
- If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 48 hours to BMS using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization. All SAEs should be followed to resolution or stabilization.

17.2.2 Non Serious Adverse Events

The collection of non-serious adverse events should begin at initiation of treatment. Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they have become serious. Follow-up is also required for non-serious SAEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF.

All non-serious adverse events should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of Nivolumab.

Laboratory Test Result Abnormalities

The following laboratory test results abnormalities should be captured as non-serious or serious AEs.

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

17.2.3 Pregnancy

If it is discovered that a study participant is pregnant or may have been pregnant at the time of study exposure, the investigator(s) must immediately notify the primary investigator and the MSKCC IRB.

In most cases, the study drug/radiation will be permanently discontinued in an appropriate manner.

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with the IRB, the pregnant subject may continue the study drug, after a thorough discussion of benefits and risk with the subject.

Protocol required procedures for study discontinuation and follow-up must be performed on the subject unless explicitly contraindicated by pregnancy.

17.2.4 Overdose or Misadministration of Radiation

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

17.2.5 Potential Drug Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIS, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury must meet the following criteria:

- ALT or AST > 3x ULN (or >5x ULN in patients with liver metastases)
- Total Bilirubin > 2x ULN
- No other immediately apparent alternative explanation.

17.4 Safety Reports

MSK must submit external safety reports to the MSK IRB/PB according to institutional guidelines.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

Appendices will be stored in a separate file and will be submitted in electronic and/or paper format. If electronic format, please submit on file per appendix.

TUMOR SAMPLE PD-L1

This information is provided to investigators who will be submitting tumor samples to BMS representatives for analysis. Please do not include otherwise.

Tumor Tissue Specimens

Pre-treatment tumor tissue specimens in the form of a paraffin embedded block or a minimum of 3 unstained slides, with a single section on positively charged slides will be submitted for central PD-L1 immunohistochemistry (IHC) assessment. These biopsy samples should be excisional, incisional, punch or core needle. Fine needle aspirates or other cytology specimens are insufficient for downstream biomarker analyses. PD-L1 stained tissue sections will be assessed by a pathologist and scored as PD-L1 positive if membrane staining is observed.

These tumor samples may also be assessed for the expression of other immune or melanoma related genes, RNAs and/or proteins, as well as, the presence of immune cell populations using a variety of methodologies inclusive of, but not limited to immunohistochemistry (IHC), qRT-PCR, genetic mutation detection and fluorescent in-situ hybridization (FISH). Various molecular markers with potential predictive value for the treatment of melanoma with Nivolumab, and other immunotherapies are currently under investigation and may be assessed in this study. These tumor tissue biomarkers include, but are not limited to PD-1, PD-L2, tumor infiltrating lymphocytes (TILs) or subpopulations of TILs and a Th1 immune mRNA expression signature. In addition, other methods of measuring tumor PD-L1 expression may also be assessed. Tissue from the resected solitary lesions may be assessed for residual tumor cells and for markers expected to accompany tumor shrinkage in this study, including, but not limited to TILs and subsets thereof.

NORMAL TISSUE DOSE CONSTRAINTS

Structures	Todal Dose/fxs or Volume ≤	To:	Limit or Guideline*	Comments
Spinal Cord *(CONFORMAL /IMRT THERAPY ONLY- AP-PA MAX CORD DOSE SHOULD NOT EXCEED Rx= 500cGyx5)*	*26Gy/3fx* *28Gy/4fx* *30 Gy/5fx*	Max Point Dose	LIMIT	**NO PREVIOUS RADIATION** †Guideline becomes LIMIT for circumferential PTVs (PTV encircles the Spinal Cord)
	14.5Gy/3fx *16 Gy/4fx* *18Gy/5fx*	Max Point Dose (Myelo-defined cord)	LIMIT	WITH PREVIOUS RADIATION (ONE COURSE ONLY, *treated >3 MONTHS previously*). Previous prescription ≤30Gy/10fx, 45-50Gy/25fx or other conventional txt given at ≤3Gy per frac. *OR* **14Gy** max cord dose from single frac *OR* **21 Gy** max cord dose from hypo frac IGRT. No chemo during txt and for at least 2 wks prior) †Guideline becomes LIMIT for circumferential PTVs (PTV encircles the Spinal Cord) ***Note that P-32 should be considered as part of the current course if the contoured plaque is 2mm or closer from the cord.***
	24Gy/3fx *27.2Gy/4fx* *30 Gy/5fx*	Max Point Dose†	Guideline†	**NO PREVIOUS RADIATION.** †Max Point Dose Guideline becomes LIMIT for circumferential PTVs (PTV encircles the Spinal Cord)
	18Gy/3fx *21Gy/4fx* *23Gy/5fx*	$D_{0.35cc}$		
	13.9Gy/3fx *15.6Gy/4fx* *17Gy/5fx*	Max Point Dose† (Myelo-defined cord)	Guideline†	WITH PREVIOUS RADIATION as defined above. †Max Point Dose Guideline becomes LIMIT for circumferential PTVs (PTV encircles the Spinal Cord) ***Note that P-32 should be considered as part of the current course if the contoured plaque is 2mm or closer from the cord.***
	10Gy/3fx *12Gy/4fx* *14Gy/5fx*	$D_{0.35cc}$		

Esophagus	**LEVEL I** 27.6Gy/3fx 30.2Gy/4fx 32.2Gy/5fx **LEVEL II** 30Gy/3fx 34Gy/4fx 50Gy/5fx	Max Point Dose	Guideline	***Attempt level I first. If Level I compromises coverage attempt level II. If Level II compromises coverage consult physician.*** **No previous treatment.** *(If previous treatment, use Max Point Dose of 25Gy/5fx)* *These Guidelines (start with LEVEL I. If not possible, use LEVEL II), while desirable, are secondary to target coverage unless they are specifically instructed by the MD.*
	LEVEL I 16.8Gy/3fx 18.1Gy/4fx 19Gy/5fx **LEVEL II** 22Gy/3fx 25Gy/4fx 27.5Gy/5fx	D_{5cc}		
Heart	30Gy/3fx 34Gy/4fx 50Gy/5fx	Max Point Dose	Guideline	Based on RTOG0915 and RTOG0813 - pericarditis endpoints
	24Gy/3fx 28Gy/4fx 32Gy/5fx	D_{15cc}	Guideline	
Brachial Plexus	†27Gy/3fx 32Gy/4fx 35Gy/5fx	Max Point Dose	Guideline	**No previous radiation.** †For Rx of 10Gy x 3fx., 30 Gy can be used as a 3 fx limit.
	17.7Gy/3fx 20Gy/4fx 22Gy/5fx	Max Point Dose		**With previous radiation**
Larynx	Prescription	Max Point Dose	Guideline	No Hot Spots
Liver	V(15Gy) < Volume of (**Liver_not_GTV** - 700cc)** for 3 fx treatments**		**LIMIT**	**At least 700cc of **Liver-not-GTV** must receive less than 15Gy in 3 fx. *At MD discretion for small Liver_not_GTV, spare 1/3, may be less than 700cc.*
	15%	NTCP	Guideline	Use Lyman mean dose model, Liver_Mean_AB3 (n=1, m=0.12, a/b=3). Evaluate Liver_NOT_GTV
Stomach/ Bowel	30Gy	D_{5cc}	Guideline	**No previous radiation.**
	Equivalent of 65Gy in 2Gy frac	Max Point Dose	Guideline	**<u>To be used for cases with previous radiation only</u>.** Total dose (from all treatment), assume a/b=3, at least 3 months since previous rads
	Equivalent of 85Gy in 2Gy frac to prev txt'ed region	D_{5cc}	**LIMIT**	
Kidney	33% of *spared* kidney volume	V_{15Gy} for 3 fx	**LIMIT**	**No previous radiation.** Both "spared kidney" and "total kidney" constraints must be met. If patient has limited kidney function, limits will have to be customized
		V_{18Gy} for 5 fx		
	35% of total kidney volume	V_{15Gy} for 3 fx		
		V_{18Gy} for 5 fx		

Cauda- BOTH GUIDELINE AND LIMIT APPLY	*26Gy/3fx* *30Gy/4fx* *35 Gy/5fx*	Max Point Dose	**LIMIT**	**NO PREVIOUS RADIATION**
	15Gy/3fx *17Gy/4fx* *20Gy/5fx*	Max Point Dose	**LIMIT**	WITH PREVIOUS RADIATION (ONE COURSE ONLY, ***treated >3 MONTHS previously***). Previous prescription ≤30Gy/10fx, 45-50Gy/25fx or other conventional txt given at ≤3Gy per frac. *OR* **18Gy** max cauda dose from single frac *OR* **24 Gy** max cauda dose from hypo frac IGRT. No chemo during txt and for at least 2 wks prior) ***Note that P-32 should be considered as part of the current course if the contoured plaque is 2mm or closer from the cauda.***
	22Gy/3fx *26Gy/4fx* *30Gy/5fx*	D_{5cc}	Guideline	**NO PREVIOUS RADIATION.**
	13Gy/3fx *15Gy/4fx* *17Gy/5fx*	D_{5cc}	Guideline	WITH PREVIOUS RADIATION as defined above.
Rectum	41.8Gy/5fx	Max Point Dose	Guideline	Circumferential Dose on any "slice" - evaluated using 3D dose display. Hypofractionated constraints based on MSK prostate hypofractionation protocol 09-035
	38.5Gy/5fx	D_{1cc}		
Bladder	26Gy/3fx 29Gy/4fx 32Gy/5fx	Mean Dose	Guideline	Whole bladder (BED equivalent of 60Gy in 2 Gy/fx)
Femur	30Gy/5fx	D_{5cc}	Guideline	
Femur	30Gy/5fx	D_{5cc}	Guideline	
Optic Structures	16.2Gy/3fx 19.6Gy/4fx 23Gy/5fx	Max Point Dose	Guideline	Physician approval requiered to exceed guideline.
	20Gy/3fx 22.6Gy/4fx 25Gy/5fx	Max Point Dose	**LIMIT**	Peer review required to exceed limit
Brain Stem	*30Gy/5fx* *31.2Gy/5fx* OR 24Gy/3fx	*$D_{05\%}$ **</i> *Max Point Dose* Max Point Dose	**LIMIT**	**No previous radiation.** **Use D05 limit if no brainstem/PTV overlap. If there is brainstem/PTV overlap, use only max point dose limit.* ***With Previous radiation**, limit cumulative dose to **D05 of 70Gy in 2Gy/fx equivalent**. At least 3 months in between treatments.*
Brain	*see note*	*see note*		***No more than 3 courses of treatment to the same site in the brain- at least 2 of the treatments must be conformal, only 1 may be WBRT***
Skin	33Gy/3fx 36Gy/4fx 39.5Gy/5fx	Max Point Dose	Guideline	Skin = Outermost 5mm of the patient surface
	30Gy/3fx 33.2Gy/4fx 36.5Gy/5fx	D_{10cc}	Guideline	