A Phase 2, Randomized, Multi-institutional Study of Nivolumab and Ipilimumab versus Nivolumab, Ipilimumab and Stereotactic Body Radiation Therapy for Metastatic Merkel Cell Carcinoma

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Clinical Protocol

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SYNOPSIS

Clinical Protocol

Protocol Title: A Phase 2, Randomized, Multi-institutional Study of Nivolumab and Ipilimumab versus Nivolumab, Ipilimumab and Stereotactic Body Radiation Therapy for Metastatic Merkel Cell Carcinoma.

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

Stereotactic Body Radiation Therapy 24Gy in 3 fractions.

Nivolumab 240 mg/dose IV q2 weeks.

Ipilimumab 1 mg/kg/dose IV q6 weeks.

Treat subjects until disease progression, unacceptable toxicity or subject withdrawal of consent.

Study Phase: 2

Research Hypothesis: Treatment with nivolumab and ipilimumab, or nivolumab and ipilimumab in combination with stereotactic body radiation therapy (SBRT) will improve objective response rate as compared to nivolumab alone historical control in subjects with metastatic Merkel cell carcinoma.

Objectives:

Primary:

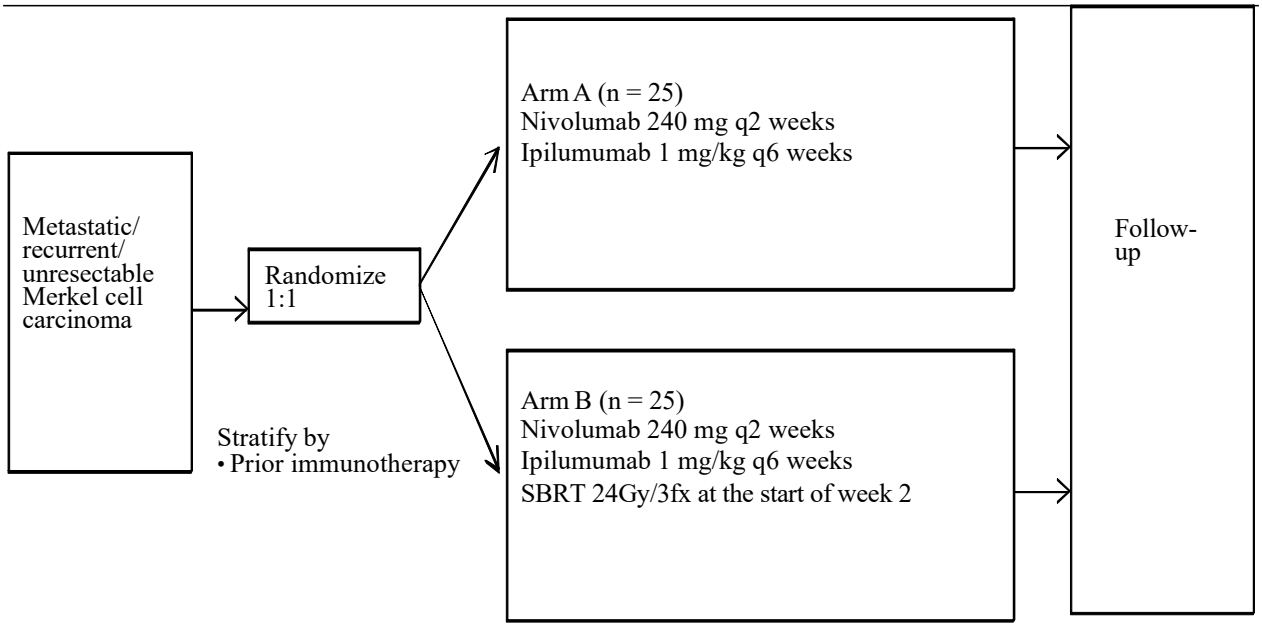
- To compare the efficacy, as measured by objective response rate (ORR), provided by nivolumab plus ipilimumab with or without SBRT in subjects with metastatic Merkel cell carcinoma.

Secondary:

- To compare the progression free survival (PFS) of nivolumab and ipilimumab versus SBRT plus nivolumab and ipilimumab in subjects with metastatic Merkel cell carcinoma.
- To compare the overall survival (OS) of nivolumab and ipilimumab versus SBRT plus nivolumab and ipilimumab in subjects with metastatic Merkel cell carcinoma.
- To evaluate the local control of irradiated tumor provided by SBRT in combination with nivolumab and ipilimumab
- To assess the overall safety and tolerability of of nivolumab and ipilimumab versus SBRT plus nivolumab and ipilimumab in subjects with metastatic Merkel cell carcinoma.
- To evaluate whether PD-L1 expression is a predictive biomarker for ORR.
- To evaluate the Health Related Quality of Life (HRQoL) as assessed by European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30.

Exploratory: See Section 1.3.3 of the protocol.

Study Design:
This is a Phase 2, randomized, multi-institutional study of nivolumab and ipilimumab alone versus in combination with SBRT for subjects (≥18 years) with metastatic Merkel Cell Carcinoma. Approximately 50 subjects will be randomized 1:1 and stratified by prior immunotherapy exposure. Dose reductions will not be allowed.



Treatment Arms:

Randomized 1:1 [Arm A: Arm B]: Treatment until progression on either arm.

Arm A:

Nivolumab 240 mg IV over 30 min q2 weeks and Ipilumumab 1 mg/kg IV over 30 min q6 weeks until progression or unacceptable toxicity

Arm B:

Nivolumab 240 mg IV over 30 min q2 weeks and Ipilumumab 1 mg/kg IV over 30 min q6 weeks until progression or unacceptable toxicity

Radiation to be given at the start of week 2

- 8 Gy x3 doses in over ≤ 2 weeks

SBRT should begin the week following the first dose of nivolumab and ipilimumab. All sites other than skin should receive SBRT in consecutive days. Skin lesions can be treated every other day. The number of lesions receiving SBRT will be at the treating physician's discretion based on anticipated toxicity. Larger or symptomatic lesions are of higher priority for SBRT. At least one target lesion will not receive SBRT, to evaluate ORR. The scatter radiation dose to this target lesion should be monitored if located less than 6cm from the irradiated lesions.

All subjects will be treated until progression of disease, unacceptable toxicity, or subject withdrawal of consent. Palliative radiation therapy will not be permitted while being treated under the protocol. The need for palliative radiation therapy will be considered progressive disease.

Study Population: Metastatic Merkel cell carcinoma subjects

Key Inclusion Criteria:

- At least 18 years of age
- ECOG PS < 2
- Active disease measurable by CT or MRI.
- Prior chemotherapy or immunotherapy will be allowed if new or persistent measurable site(s) of disease are present.
- Prior radiation therapy will be allowed if there is active measurable disease burden.
- All subjects must be either recurrent, unresectable or Stage IV AJCC (7th edition) and have histologically confirmed Merkel cell carcinoma with at least 2 distinct lesions in order to be eligible. Please refer to Appendix 1 for description of AJCC 7th editions of TNM and staging.

- All subjects must have at least 2 distinct lesions as documented by a complete physical examination or imaging studies within 4 weeks prior to randomization. Imaging studies must include a diagnostic CT scan of the involved disease sites and all known sites of resected disease and brain magnetic resonance (MRI) or CT (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions).
- Tumor tissue from the core biopsy or resected site of disease must be provided for biomarker analyses.

Key Exclusion Criteria:

- Subjects with history of Grade 3 toxicity or use of infliximab with prior immunotherapy
- Patients with active brain metastasis.
- Subjects with active, known, or suspected autoimmune disease. Subjects with type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll.
- Subjects with prior history of non-Merkel cell carcinoma malignancies are excluded except adequately treated basal cell, squamous cell skin cancer, chronic lymphocytic leukemia or other indolent diseases not requiring therapy; adequately treated, with curative intent, cancer from which the patient is currently in complete remission per investigator's judgment; or patients with history of breast cancer and no evidence of disease on hormonal therapy to prevent recurrence and patients with prostate cancer on adjuvant hormonal therapy with undetectable PSA are eligible.
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids are permitted in the absence of active autoimmune disease.

Study Drug:

Study Drug		
Medication	**Potency**	**IP/Non-IP**
Nivolumab Solution for Injection	100 mg (10 mg/mL)	IP
Ipilimumab Solution for Injection	50 mg (5 mg/mL)	IP

Study Assessments: Objective response rate is the primary endpoint of the trial. The ORR will be calculated as the percentage of patients who had a complete or partial response that was confirmed by a subsequent radiologic imaging study or clinical exam according to irRECIST criteria among all the patients who received at least one dose of nivolumab and ipilimumab with or without SBRT.

- Screening.
- Treatment Period: Every 12 weeks (± 7 days) from first dose of study drug through 45 weeks (relative to the first dose of study drug)
- Follow-up Period:
  a) Every 12 weeks (± 14 days) through 12 months for subjects who discontinued early from treatment (relative to the first dose of study drug)

b) Every 12 weeks (± 21 days) if > 12 months through 24 months (relative to the first dose of study drug)

c) Every 6 months (± 28 days) if > 24 months through and up to Year 5 (relative to the first dose of study drug).

Statistical Considerations:

Sample Size: From historical data, we will consider 17% response rate as not warranting further study. We will use 40% response rate as a promising result to pursue further study. In other words, we are interested in at least 23% (40% vs. 17%) improvement in treatment efficacy for arms B versus A. For each arm, using a Simon Mini-Max two-stage design with 10% type I error rate and 10% type II error rate, 16 patients will be enrolled in the first stage of the trial. If 2 or fewer patients respond, the treatment will be stopped. If 3 or more patients show a response, 8 additional patients (a total of 24 patients per group) will be enrolled. If the total number responding is 6 or less, we will conclude that the treatment is not effective. If both arms fail at the first or second stage, the trial will stop. No winner will be claimed. The sample size will be 32 if both arms fail at the first stage and 40 if only one arm fails at the first stage. If only one arm pass the second stage, the arm will be the winner. If both arms pass the second stage, we will use the posterior probability, Pr(B>A), (probability of the response rate in arm B higher than in arm A) to select the winner. A non-informative prior of beta distribution, beta(1,1) in both arms will be used to calculate the posterior probability. Arm B will be claimed as the winner if $Pr(B>A)>\delta= 0.8$.

Endpoints:

Primary Endpoint: Objective response rate in all randomized subjects

Secondary Endpoint: Progression free survival and overall survival

Analyses: Patient demographics and toxicity will be summarized using descriptive statistics. Hematologic and non-hematologic toxicity will be analyzed by CTCAE criteria and compared between treatment groups using Pearson′s Chi-square test. All tests will be two-sided with an α (type I) error ≤ 0.05 considered to be statistically significant. Continuous variables will be described by number of patients, mean, standard deviation, median, minimum and maximum. Categorical variables will be tabulated using frequency counts and percentages. The primary analysis of ORR in all randomized subjects will be conducted using a two-sided log-rank test. The hazard ratio and corresponding two-sided 95% confidence interval (CI) will be estimated using a Cox proportional hazards model, with treatment arm as a covariate. PFS medians with 95% CIs and PFS rates at 6, 12, 24, and 36 months with 95% CIs will be estimated using Kaplan-Meier methodology.

Stopping criteria: A Safety Monitoring Committee will be formed to evaluate the toxicity of both arms. Interim analysis will be conducted following accrual of initial cohort of patients in the Simon's two stage design to determine whether SBRT introduces excess unanticipated grade 3 or higher toxicities (i.e. radiation pneumonitis, radiation dermatitis, radiation myelitis) prior to expansion of the cohorts.

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1 INTRODUCTION AND STUDY RATIONALE

1.1 Research Hypothesis

Treatment with nivolumab and ipilimumab with or without SBRT will improve objective response rate when compared to nivolumab alone in subjects with metastatic Merkel cell carcinoma.

1.2 Study Rationale

The proposed trial is a Phase 2 randomized, multi-institutional study of nivolumab and ipilimumab with or without SBRT in subjects with metastatic Merkel cell carcinoma. Merkel cell carcinoma (MCC) is a rare and aggressive cutaneous neuroendocrine malignancy with a propensity for distant metastasis with a 5 year survival rate of 25% in metastatic patients[1]. Currently, there is no standard of care or no available treatment for this patient population. Mono- or polychemotherapy can be used in metastatic MCC, but responses are generally short-lived with poor outcome[2]. Therefore, there is a significant need for improved therapeutic approach for metastatic MCC patients. Unfortunately, studies to define standard care have been limited by the rarity of this cancer.

1.2.1 Rationale for Nivolumab

Epidemiology suggests that MCC may be benefit from immunotherapeutic approach. MCC occurs more frequently in immunocompromised patients suggesting pathogenesis of MCC involves evasion of immune surveillance[3]. Furthermore, approximately 80% of MCC are associated with Merkel cell polyomavirus[4,5], and cancers associated with viral oncogenesis may be more immunogenic. Studies on MCC have been limited by the rarity of this cancer, but immunotherapy appears a promising therapeutic modality[6,7]

There are a series of on-going studies to define the role of immune checkpoint inhibitors in subjects with metastatic MCC. Of particular note, PD1 blockade has emerged as a promising therapeutic modality for metastatic MCC[6,7].

PD-L1 status			
PD-L1 status		PD-L1 by Stage	Percent Positive
Positive	49	Stage I	41.7%
Negative	42	Stage II	50%
Percent Positive	53.8%	Stage III	55%
Percent Negative	46.2%	Stage IV	75%

Table 1. PD-L1 expression in Merkel cell carcinoma. 91 patient samples with Merkel cell carcinoma of all stages were analyzed for PD-L1 expression by immunohistochemistry. Positive PD-L1 status was defined as IHC score > 2+ in more than 5% of tumor cells.

Nivolumab has been chosen as the standard immunotherapeutic agent. This is based on prior studies correlating PD-L1 expression to therapeutic responses to Nivolumab in melanoma[8] and because in our retrospective study of cohort of 91 patients with Merkel cell carcinoma, 53.8% of patients demonstrated PD-L1 expression, and higher stage correlated with higher percentage of patients with PD-L1 expression **(Table 1).** Similar results have been observed by other groups[9]. Indeed, a recent interim report of phase I/II trial of metastatic treatment-naive MCC patients on Pembrilozumab reported 14% complete response rate[10]. Therefore, we anticipate a significant therapeutic efficacy of Nivolumab in MCC, which is being evaluated in an on-going multi-institutional clinical trial on Nivolumab alone for virus-associated cancers including MCC conducted by BMS.

1.2.2 Rationale for Combining SBRT with Nivolumab

More recently, the capacity of radiation therapy to induce systemic responses via immune-activation, termed abscopal effect, has been an area of active research[11-15]. Preclinical studies from our laboratory and others have demonstrated a strong synergy between radiation therapy and immunotherapy **(Fig 1)**[11,16,17]. , which has now been demonstrated in a melanoma clinical trial[18].

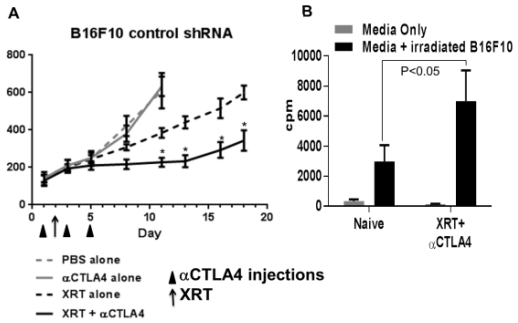


Figure 1. Synergistic antitumor effects of combined radiation therapy and CTLA4 immunotherapy. (A) B16F10 tumor bearing mice were treated with CTLA4 mAb and/or 15Gy local radiation therapy, and tumor growth was assessed at indicated time points. * indicates p<0.05 at indicated time points. **(B)** CD3 T cells purified from spleens from mice in A were sorted, and re-stimulated ex vivo with irradiated B16F10 cells, and proliferation was measured by ^{3}[H]-thymidine uptake.

While the abscopal effect in MCC is only anecdotal[19], our preliminary data suggests its presence in MCC. We conducted a retrospective study of 300 stage I – II MCC patients treated with surgical resection alone vs. surgery and adjuvant radiation therapy at Moffitt Cancer Center. Adjuvant radiation therapy improved LRC (71.5% vs. 37.8% at 3 years, respectively; p<0.001), DFS (57.0% vs. 30.2% at 3 years, respectively; p<0.001) and OS (73% vs. 66%, respectively; p=0.02), on both univariate and multivariate analysis **(Fig 2)**[20]**.** More interestingly, there were trends for improved distant metastasis free survival (DMFS) with adjuvant radiation therapy (67% vs. 59%, respectively; p = 0.07) **(Fig 2).** The overall survival and DMFS benefit from radiation therapy in a disease model prone for distant metastasis suggests the abscopal effect as an underlying mechanism.

Among various immune checkpoint inhibitors, the abscopal effect of SBRT is likely to be most strongly synergistic with nivolumab. There is pre-clinical evidence that radiation therapy up-regulates PD-L1 in tumor cells **(Fig 3)** highlighting the role for PD1 axis in tolerogenic tumor microenvironment antagonizing systemic immune responses during radiation therapy. Consistently, murine studies have demonstrated that targeting PD-L1/PD1 axis results in significantly enhanced anti-tumoral immune responses induced by ionizing radiation[16]. Furthermore, PD-L1 expression was associated with the mechanism of resistance to combined radiation therapy and ipilimumab in melanoma[21].

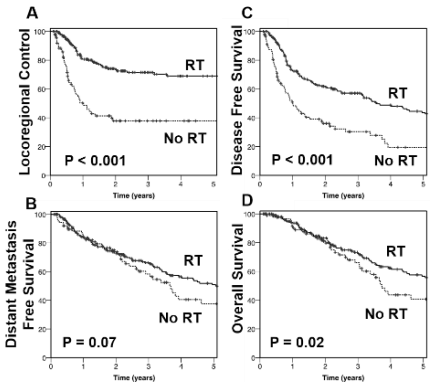


Figure 2. Adjuvant radiation therapy impacts survival in Merkel cell carcinoma. Adjuvant radiation therapy improved (A) 3-year LRC, (C) DFS, (D) OS, which was statistically significant on both univariate and multivariate analysis. There was also a trend toward improved distant metastasis free survival (DMFS) (B) with adjuvant XRT.

The rationale for SBRT to a total dose of 24Gy in 3 fractions as opposed to conventional radiation therapy is several fold. Preclinical studies have demonstrated that high dose per fraction appears to be most immunogenic[22,23] leading to immune activation. At this higher dose per fraction, a more conformal treatment delivered through SBRT is necessary for safety. Moreover, by completing radiation therapy in fewer fractions, we can avoid repeated irradiation to the tumor infiltrating lymphocytes, which will render them ineffective. Also, conformal radiation therapy offered by SBRT will spare lymphoid tissues where the immune synapse occurs during priming. While definitive and adjuvant radiation therapy for MCC has traditionally involved a prolonged course of radiation therapy with wider radiation field, a recent study demonstrates that a single fraction of 8Gy radiation therapy offers durable palliation in MCC[24]. Therefore, a more conformal treatment

delivered through SBRT is more appropriate in the metastatic setting as a modality for systemic immune activation while providing local control benefit with minimal acute and long-term toxicities.

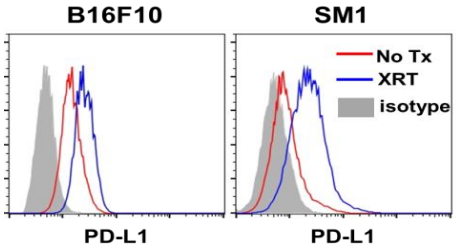


Figure 3. Ionizing radiation upregulates PD-L1 in melanoma. B16F10 and SM1 murine melanoma cells were irradiated to 15Gy and surface expression of PD-L1 was analyzed by flow cytometry.

1.2.3 Rationale for Combining Ipilimumab with Nivolumab and SBRT

Although ipilimumab has not been tested directly in MCC following withdrawal of the clinical trial prior to accrual (NCT01913691), ipilimumab has shown efficacy in melanoma, lung cancer, prostate cancer and multiple other immunogenic cancers. Therefore, a strong clinical activity in MCC is anticipated. Furthermore, the rationale for combining ipilimumab with nivolumab has been well demonstrated by a series of Checkmate studies in different disease sites including melanoma[25-27] and NSCLC[28]. These studies demonstrated significant improvement in objective response rate and progression free survival with the addition of ipilimumab. Notably, the abscopal effect of radiation therapy has been most extensively studied in combination with ipilimumab. Both radiation therapy and ipilimumab are thought to induce priming event for eliciting anti-tumor immune responses. Synergy of these two modalities has been demonstrated in multiple preclinical models[15,17] as well as in the prospective clinical trial[29]. For instance, 14% CR rate with XRT + Ipilimumab in a phase II metastatic melanoma trial is contrasted with 1.5% CR rate in the phase III trial on the Ipilimumab alone arm[29,30]. Interestingly, PD-L1 expression has been proposed as the major mechanism of resistance to the combination of radiation therapy and ipilimumab. Therefore, there is a strong rationale to test whether ipilimumab will further potentiate the efficacy of SBRT and Nivolumab in MCC[21].

1.2.4 Summary

We have a compelling rationale for combining Ipilimumab and SBRT with Nivolumab for metastatic MCC with our preliminary data suggesting a potential abscopal effect of radiation therapy in MCC potentiated by Ipilimumab, and expression of PD-L1 in the majority of MCC patients. Poor prognosis associated with metastatic MCC requires development of a new and effective therapeutic modality.

Therefore, we propose to further augment the therapeutic efficacy of PD1 blockade in patients with metastatic Merkel cell carcinoma by the abscopal effect of stereotactic body radiation therapy (SBRT) and another immune checkpoint inhibitor, ipilimumab to boost immune priming. The optimal sequences of immunotherapy to partner with SBRT to maximize the efficacy of combined treatment remain elusive, and this study will allow for direct comparison of the clinical benefit, as measured by objective response rate, provided by the addition of SBRT to nivolumab and ipilimumab in MCC.

Finally, the proposed clinical trial is strategically designed to define the standard treatment regimens for metastatic Merkel cell carcinoma with acceptable toxicity. The insights on the synergy of SBRT, Nivolumab and Ipilimumab drawn from Merkel cell carcinoma will be applicable to other solid cancers.

1.3 Objectives(s)

1.3.1 Primary Objectives

- To compare the efficacy, as measured by ORR, provided by nivolumab and ipilimumab versus

SBRT plus nivolumab and ipilimumab in subjects with metastatic Merkel cell carcinoma.

1.3.2 Secondary Objectives

- To compare the progression free survival (PFS) of nivolumab and ipilimumab versus SBRT plus nivolumab and ipilimumab in subjects with metastatic Merkel cell carcinoma.
- To compare the overall survival (OS) of nivolumab and ipilimumab versus SBRT plus nivolumab and ipilimumab in subjects with metastatic Merkel cell carcinoma.
- To evaluate the local control of irradiated tumor provided by SBRT in combination with nivolumab and ipilimumab
- To assess the overall safety and tolerability of nivolumab and ipilimumab versus SBRT plus nivolumab and ipilimumab in subjects with metastatic Merkel cell carcinoma.
- To evaluate whether PD-L1 expression is a predictive biomarker for ORR;
- To evaluate the Health Related Quality of Life (HRQoL) as assessed by European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30.

1.3.3 Exploratory Objectives

- To evaluate associations between Merkel polyomavirus expression status and clinical efficacy (ORR, PFS and overall survival (OS))
- To explore potential biomarkers associated with clinical efficacy (ORR, PFS, and OS) and/or incidence of adverse events by analyzing biomarker measures within the tumor microenvironment and periphery (eg, blood, serum, plasma and PBMCs) in comparison to clinical outcomes
- To assess changes in health status and work and activity impairment in treatment groups using the EuroQol EQ-5D and the Work Productivity and Activity Impairment questionnaire (WPAI:GH), respectively.

1.4 Rationale for Study Design

1.4.1 Rationale for Studying Merkel Cell Carcinoma

Merkel cell carcinoma is a rare cutaneous malignancy of neuroendocrine origin, which typically occurs in elderly patients in areas of the body with frequent sun exposure including the head and neck.[1, 2] Merkel cell carcinoma also has a higher incidence in the severely immunosuppressed population, and has recently been found to be associated with infection by the Merkel cell polyomavirus.[3, 4] The incidence of MCC is estimated to be approximately 0.3–0.6/100,000 in the US, and it appears to have been increasing over the last few decades[31].

Merkel cell carcinoma is perhaps the most aggressive and lethal primary skin cancer, with a high rate of locoregional recurrence and the majority of patients die from distant metastasis. Survival rates at 5 years range from 23-80%.[5-9] Despite the poor prognosis, the rarity of this cancer has limited conducting prospective, randomized data guiding to guide treatment. Combined with aggressive behavior of this cancer refractory to most systemic agents, it has been difficult to define the standard of care in MCC.

Treatment of non-metastatic Merkel cell carcinoma typically includes wide excision with 1-2 cm

margins with a sentinel lymph node biopsy[10-14]. Given the high risk of locoregional recurrence following surgery alone, adjuvant radiation therapy (RT) is typically recommended.

Treatment of metastatic MCC has been a clinical challenge and limited options, such that until recently, palliative approach to the management of these patients was acceptable. First-line treatment typically involved platinum based chemotherapy etoposide, and the second line chemotherapy included irinotecan, topotecan and weekly paclitaxel. Surgery and radiation therapy are palliative modalities in metastatic MCC. Unfortunately, the response rate to systemic chemotherapy was low with poor durability of responses.

Therefore, alternative approaches for treatment of MCC have been pursued in recent years including targeted biotherapy. A phase II trial of imatinib, based on high expression of KIT in MCC, demonstrated median progression-free survival at 1 month and 1 year overall survival rate at 17%[32]. Another multi-tyrosine kinase inhibitor, cabozantinib targeting c-met is being tested in a phase II trial. However, promising breakthrough for metastatic MCC came through immunotherapy.

1.4.2 Immunotherapy in Merkel Cell Carcinoma

The concept of cancer immunotherapy for MCC is based on several key aspects of this particular cancer. First, MCC is a viral-associated cancer expressing viral antigens. Because viral proteins represent non-self antigens not encountered in thymus, central tolerance mechanisms are not anticipated for these antigens. Furthermore, prior studies have shown that patients indeed generate adaptive immune response against Merkel viral T antigen, which correlate with tumor load[33,34]. Interestingly, high antibody titers for VP1 appear to have prognostic significance with improved progression-free survival[33]. Improved prognosis was also observed with increased CD8 tumor-infiltrating lymphocytes[35].

There are several on-going clinical trials to harness immunogenicity of MCC. One effort is a phase I/II clinical trial utilizing MCPyV-reactive autologous T cell therapy for metastatic MCC (NCT01758458). Other studies also include intratumoral injection of IL-12 (NCT01440816) or TLR-4 agonist targeting antigen presenting cells to boost anti-tumoral immunity. A phase II cell-based immunotherapy utilizing neukoplast (NK-92) (NCT02465957) is also on-going. However, PD-L1/PD1 axis appears to be the most promising target for cancer immunotherapy in MCC with an excellent response rate.

1.4.3 Rationale for ORR as Primary Endpoint with PFS and OS as a Secondary Endpoint

The intention of this trial is to ascertain the clinical responses of MCC to different combinations of SBRT and immune checkpoint inhibitors, nivolumab and ipilimumab, in metastatic patients. The rate of overall response, complete response and partial response of target lesions will be most sensitive in detecting the incremental benefit from the addition of SBRT and/or ipilimumab to PD1 blockade alone. Larger patient cohorts in each arm will be required to achieve statistical power detect the differences in survival outcomes, PFS and OS, which is not feasible in MCC.

1.4.4 Rationale for Two Experimental Arm Design

Merkel cell carcinoma is a rare malignancy with the incidence estimated to be approximately 0.3–0.6/100,000 in the US[31]. Merkel cell carcinoma is associated with a high rate of locoregional recurrence and the majority of patients die from distant metastasis. Survival rates at 5 years range from 23-80%.[5-9] Despite the poor prognosis, the rarity of this cancer has limited conducting prospective,

randomized data guiding to guide treatment. Combined with aggressive behavior of this cancer refractory to most systemic agents, it has been a clinical challenge to define the standard of care in MCC. Most recently, a promising breakthrough for metastatic MCC came through PD1/PDL1 axis blockade[36,37]. Despite excitement elicited by high response rate to PD1 blockade for metastatic MCC, further optimization to maximize the benefit of immunotherapy is of pivotal importance in this perhaps most aggressive and lethal skin cancer.

Therefore, we propose a randomized phase II trial in which both arms of the trial are experimental. By employing carefully designed two arm Simon's two stage design, we will compare both experimental arms with the historical control as well as each other. Preclinical and clinical evidence extrapolated from other solid malignancies including melanoma suggests improved therapeutic efficacy with acceptable additional toxicity in both proposed experimental arms. Such clinical trial design is not unprecedented. Indeed, even in NRG-HN002 trial, a randomized phase II trial for patients with p16 positive, non-smoking associated, locoregionally advanced oropharyngeal cancer (NCT02254278), a two arm experimental design has been used to expedite optimization of clinical decision making for this relatively common disease entity. Given the rarity of this cancer and absence of standard of care with acceptable therapeutic efficacy, a two experimental arm design is justified.

1.4.5 Rationale for the Dose and Schedule for Nivolumab

Nivolumab was chosen as one of the experimental drugs because of a favorable risk-benefit ratio as seen in the large Phase 1 CA209003[38]. Additionally, other Phase 2 and 3 studies in the nivolumab development program use this dose and regimen. The dose and schedule of nivolumab in this study will be 240 mg every two weeks, which is equivalent to 3mg/kg every two weeks, based upon the analyses of safety, efficacy, and exposure-response data from the Phase 1 study CA209003. Anti-tumor activity was observed at dose levels ranging from 1 to 10 mg/kg in melanoma, NSCLC, and RCC, as well as at dose levels of 0.1 and 0.3 mg/kg in melanoma. The anti-tumor activity of nivolumab in RCC was investigated at dose levels 1 and 10 mg/kg, with the higher activity observed at 10 mg/kg. The observed anti-tumor activity in melanoma, and NSCLC was highest at 3 mg/kg, suggesting that anti-tumor activity approaches a plateau at dose levels of 3 mg/kg and above. Consistent with these observations, the results of the exposure-response analyses for these tumor types show that the probability of a tumor response tended to approach a plateau for trough concentrations produced by 3 and 10 mg/kg every 2 week dosing.

Nivolumab was adequately tolerated up to 10 mg/kg, the highest dose level tested, and no MTD was identified. Although the spectrum, frequency, and severity of nivolumab-related AEs were generally similar across the dose levels tested, the 10 mg/kg doses level had numerically higher Grade 3/4 drug-related SAEs and AEs leading to discontinuation. Therefore, most prior clinical trials employed nivolumab dose of 3 mg/kg Q2W. More recently, a flat dose of 240 mg Q2W has been shown to have comparable efficacy and toxicity while simplifying dosing strategy. Therefore, based upon the totality of the safety, efficacy, and exposure-response data, a flat dose of 240 mg Q2W was selected as the dose anticipated to achieve an appropriate balance of efficacy and risk.

1.4.6 Rationale for the Dose and Schedule for SBRT

Studies have demonstrated that SBRT for ablative treatment of non-symptomatic, solitary metastases is technically feasible. A high rates of in-field cancer control is achieved with acceptable toxicity.

The rationale for this dose fractionation opposed to conventional radiation therapy or higher radiation dose is several fold. Preclinical studies have demonstrated that high dose per fraction appears to be

most immunogenic[22,23] leading to immune activation. At this higher dose per fraction, a more conformal treatment delivered through SBRT is necessary for safety. Moreover, by completing radiation therapy in fewer fractions, we can avoid repeated irradiation to the tumor infiltrating lymphocytes, which will render them ineffective. Also, conformal radiation therapy offered by SBRT will spare lymphoid tissues where the immune synapse occurs during priming. While definitive and adjuvant radiation therapy for MCC has traditionally involved a prolonged course of radiation therapy with wider radiation field, a recent study demonstrates that a single fraction of 8Gy radiation therapy offers durable palliation in MCC[24]. Therefore, a more conformal treatment delivered through SBRT is more appropriate in the metastatic setting as a modality for systemic immune activation while providing local control benefit with minimal acute and long-term toxicities.

Also of note, most disease sites can be treated safely to a dose far exceeding the proposed dose in this clinical trial. However, the intent of higher ablative dose of SBRT is maximal local control in placement of surgical approach with acceptable toxicity. Contrarily, the primary goal of SBRT in this clinical trial is to induce immune activation. Therefore, we will limit our dose to 24Gy in 3 fractions. This dose fractionation can be safely delivered in most disease sites with minimal toxicity with anticipated durable local responses in Merkel cell carcinoma[24]. More importantly, preclinical studies have demonstrated superior immunogenicity with this fractionation over a higher ablative dose in a single fraction secondary to regulatory T cell recruitment associated with higher radiation dose[22,23]. In the absence of clinical evidence that an alternative dose fractionation is equivalent or superior, 24Gy delivered in 3 fractions is deemed optimal to exploit the abscopal effect of radiation therapy.

SBRT will be delivered the week following initiation of nivolumab and ipilimumab. Because immune activation by SBRT is by augmenting immune priming by release of tumor antigen and damage-associated molecular pattern[15], SBRT was deliberately scheduled to follow ipilimumab to ensure that CTLA-4 blockade is already present at the time of delivery of SBRT. PD1 blockade has been one of the major pathways for T cell tolerance or exhaustion. PD-1 and PD-L1 have been shown to be up-regulated immediately following ionizing radiation in a preclinical murine model suggesting the potential role of this tolerance axis in suppressing immunogenicity of SBRT[16] (Fig 3). Therefore, nivolumab will also be initiated the week prior to SBRT.

1.4.7 Rationale for the Dose and Schedule for Ipilimumab

In MDX010-20 (metastatic or unresectable setting), the ipilimumab monotherapy arm was administered 3 mg/kg ipilimumab every 3 weeks for four doses with acceptable toxicity. However, in combination with nivolumab, 3 mg/kg of ipilimumab elicited significant toxicity in Checkmate-067 trial for metastatic melanoma despite improved objective response rate with over 50% of patients unable to complete the study drugs in the combined arm[39]. Subsequently, a number of clinical trials testing combination of nivolumab and ipilimumab adopted lower dose of ipilimumab with acceptable toxicity profiles while retaining improved efficacy[28]. Of particular note, Checkmate-012 study has demonstrated ipilimumab at 1mg/kg Q6W in combination with nivolumab 3mg/kg Q2W is safe with significantly improved efficacy in comparison to nivolumab alone[40]. This combination regimen is also being used for Checkmate-358 study, which includes patients with metastatic Merkel cell carcinoma. Therefore, we will utilize ipilimumab at 1 mg/kg Q6W in combination with nivolumab in this trial.

1.4.8 Rationale for Treating until Progression, Unacceptable Toxicity, or Withdrawal of Consent

Throughout the nivolumab and/or ipilimumab development program, most protocols have dosed until progression, unacceptable toxicity, or withdrawal of consent in the metastatic setting. In the absence of

dose-limiting toxicity, the treatment duration for metastatic cancer in many prior trials was usually not restricted. However, these therapeutic agents also come with toxicity. For instance, despite the protocol specified treatment duration of 3 years in EORTC 18071[41] the median number of doses received for subjects in the ipilimumab arm was 7, corresponding to approximately 1 year duration of treatment. Additionally, there was a large decline in subjects still receiving dosing at the end of induction as compared to those still receiving dosing at the end of 1 year[42]. Furthermore 48.8% of subjects in the ipilimumab arm discontinued treatment due to adverse events related to study drug.

It should be also noted that the combination of both nivolumab and ipilimumab is associated with significantly increased toxicity. In the double-blind, multicenter phase 3 trial (CheckMate 067)[25] testing the safety and efficacy of nivolumab plus ipilimumab versus nivolumab and ipilimumab monotherapies, a significant increase in toxicity was seen in the combination group: grades 3–4 adverse events occurred in 55 % of patients, compared to 16.3 % in patients treated with nivolumab alone, and 27.3 % of patients treated with ipilimumab. Treatment-related adverse events leading to therapy discontinuation occurred in 36.4, 7.7, and 14.8 % of patients, respectively (most commonly diarrhea, fatigue, and pruritus).

Therefore, in order to minimize toxicity leading to discontinuation of study drug while maintaining efficacy of either study drug, ipilimumab is limited to 4 doses while nivolumab will continued until progression, unacceptable toxicity or withdrawal of consent.

1.4.9 Rationale for Evaluation of PD-L1 as a Predictive Biomarker of Efficacy

PD-L1 is expressed by many tumor types and its expression has been noted to correlate with decreased immune system function and worse clinical prognosis. It is hypothesized that PD-L1 expression within the tumor microenvironment, either on tumor cells, macrophages or lymphocytes is a means of evading immune system detection and destruction. Still others postulate that PD-L1 expression on tumor cells is a surrogate for interferon-gamma release from neighboring activated T cells and thus portends a good prognosis for immunotherapy agents, and in particular, agents targeting the PD-1/PD-L1 axis. Preliminary data from two small retrospective analyses supports the latter hypothesis in metastatic melanoma. PD-L1 positive status was associated with improved OS, irrespective of treatment, relative to PD-L1 negative status in subjects with metastatic melanoma (n = 56)[43]. Similarly, objective responses to nivolumab were limited to subjects defined as PD-L1 positive in a subset of subjects from study CA209003 (n = 42), which included 18 melanoma subjects[44]. In both of these studies, a prototype IHC assay was used and PD-L1 positive status was defined as 5% tumor cell membrane staining or higher within a tumor tissue sample.

In our retrospective study of cohort of 91 patients with Merkel cell carcinoma, 53.8% of patients demonstrated PD-L1 expression, and higher stage correlated with higher percentage of patients with PD-L1 expression (Table 1). Similar results have been observed by other groups[9]. The clinical significance of PD-L1 expression as a prognostic and predictive marker for immunotherapy in MCC needs to be further defined, but studies from other disease sites, most prominently from melanoma suggests that PD-L1 positivity is associated with clinical response to nivolumab.

Tumor biopsy specimens from melanoma subjects treated with nivolumab or nivolumab in combination with ipilimumab across three Phase 1 metastatic melanoma studies (CA209003, CA209004 and CA209006) and one Phase I study of completely resected Stage III or Stage IV NED melanoma (CA209007) were evaluated for PD-L1 expression. Using a cutoff of 5% tumor cell membrane staining, the PD-L1 positivity rate ranged from 27% to 45%[45-47] consistent with the rate previously reported by Taube et al[43] at 45% (24/56 subjects) in metastatic melanoma. Importantly, in

the setting of resected Stage III or Stage IV NED in CA209007, a nonsignificant trend for improved RFS was observed in PD-L1-positive subjects versus PD-L1-negative subjects at both a 1% and 5% tumor cell expression cut-off[45]. Therefore, PD-L1 expression may be a prognostic marker that may also predict for nivolumab clinical activity.

1.4.10 Rationale for Quality of Life Evaluation

Available chemotherapy to treat patients with metastatic Merkel cell carcinoma has been been associated with substantial toxicities and unclear clinical benefit. Evaluating quality of life (QoL) in oncology clinical studies is becoming increasingly important to understand the impact of benefit/risk from the patient perspective, and for quality of life adjustments for survival data used in economic models supporting access of new drugs. However, QoL data from investigational trials in this population are just emerging.

The EORTC QLQ C-30 will be used to assess changes from baseline of patients' QoL during and after treatment in the different arms of the study. The EQ-5D will be used to assess general health status and the data will be used to calculate utilities for use in economic models. The WPAI:GH questionnaire for measure of work and activity impairment exhibits strong validity and reliability, plus the ability to evaluate the results on impairment in financial terms. Employers are increasingly concerned about the burden of illness in their workforce and the associated financial impact. Additionally, some payers of healthcare and prescription drugs may want assurance that all cost implications have been considered. The costs of lost productivity, in addition to standard direct healthcare costs are increasingly required to meet requirements from health authorities for a broader societal perspective. The cost of lost productivity as measured by the WPAI:GH will as a result be included as a key cost component of the cost-effectiveness model of nivolumab.

With the emergence of patients that experience long-term survival with immunotherapies, payers, physicians and patients are beginning to question not only about the duration of survival (OS) but also the quality of survival after treatment discontinuation. Therefore, the EQ-5D-VAS will be utilized to assess the quality of survival during the follow-up and survival phase of the trial.

1.5 Product Development Background

1.5.1 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. This functions by aborting the emergence of tumors as they arise and/or causing tumor shrinkage where it is present. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immune surveillance and an effective immune response[48]. This evasion may occur by exploiting any of the checkpoints that control the regulatory immune response, including display of antigens and control of co-stimulatory pathways that affect the proliferation of cells involved in immunity. Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system - either directly by stimulation of immune cells by antibodies directed to receptors on T and B cells or indirectly by cytokine manipulation. T-cell stimulation is a complex process involving the integration of numerous positive, as well as negative,

costimulatory signals in addition to antigen recognition by the T-cell receptor (TCR)[49]. Collectively, these signals govern the balance between T-cell activation and tolerance to antigens[48].

Programmed death receptor-1 (PD-1, CD279), a 55 kD type I transmembrane protein, is a member of the CD28 family of T-cell costimulary receptors that also includes CD28, CTLA-4, ICOS, and BTLA.5 PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM). Two ligands specific for PD-1 have been identified: PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems[50,51]. PD-1 delivers a negative signal by the recruitment of a protein tyrosine phosphatase SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region[52,53]. PD-1 is primarily expressed on activated T cells, B cells and myeloid cells[54].

Further evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice. PD-1-deficient mice develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus[55-57]. The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain and many of these phenotypes emerge at different times and show variable penetrance. In addition to the phenotypes of null mutations, PD-1 inhibition by antibody-mediated blockade in several murine models has been found to play a role in the development of autoimmune diseases such as encephalomyelitis, graft-versus-host disease, and type I diabetes[58,59]. Taken together, these results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self antigens.

Preclinical animal models of tumors have shown that blockade by PD-1 by monoclonal antibodies (mAbs) can enhance the anti-tumor immune response and result in tumor rejection. Antitumor activity by PD-1 blockade functions in PD-L1+ tumors as well as in tumors that are negative for the expression of PD-L1[60-65]. This suggests that host mechanisms (ie, expression of PD-L1 in antigen-presenting cells) limit the antitumor response. Consequently, both PD-L1 positive and negative tumors may be targeted using this approach. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on other hematologic cells as well, including activated T cells. However, aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies[66-72]. PD-L1 expressed by tumor cells has been shown to enhance apoptosis of activated tumor-specific T cells in vitro[54]. Moreover, the expression of PD-L1 may protect the tumor cells from the induction of apoptosis by effector T cells[73]. Retrospective analyses of several human tumor types suggest that tumor over-expression (as measured by immunohistochemistry (IHC)) of PD-L1 may permit immune evasion by tumors. In renal cell carcinoma, high surface expression levels of PD-L1 on tumor cells are related to tumor aggressiveness[69,70]. Subjects with high tumor and/or lymphocyte PD-L1 levels are 4.5 times more likely to die from their cancer than subjects exhibiting low levels of PD-L1 expression. In addition, in multivariate analysis, high expression of PD-L1 is correlated to have a worse overall survival rate compared to low expression levels of PD-L1[74].

Nivolumab is a fully human, IgG4 (kappa) isotype, mAb that binds PD-1. Blockade of the PD-1 pathway by nivolumab was studied using the mixed lymphocyte reaction (MLR). PD-1 blockade resulted in a reproducible enhancement of both proliferation and IFN-γ release in the MLR[75]. The effect of nivolumab on antigen-specific recall response was investigated using a cytomegalovirus (CMV) -restimulation assay with human peripheral blood mononuclear cells (PBMCs), and was evaluated by an enzyme-linked immunosorbent assay (ELISA). These data

indicated that nivolumab, versus an isotype-matched control antibody, augmented IFN-g secretion from CMV-specific memory T-cells in a dose-dependent manner. PD-1 blockade by nivolumab is therefore considered a promising immunotherapeutic option.

1.5.2 Ipilimumab Mechanism of Action

Traditional cytotoxic approaches to the treatment of cancer are associated with efficacy and toxicity limitations. Thus, there is a clinical need for the development of new therapies for the treatment of cancer. Blockade of CTLA-4 (CD152) is a novel approach to the treatment of human malignancies that offers an immune-mediated alternative to cancer treatment. CTLA-4 is an activation-induced T-cell surface molecule. CTLA-4-mediated signals are inhibitory and turn off T-cell dependent immune responses. Disrupting CTLA-4 interaction with its ligands B7-1 (CD80) and B7-2 (CD86), which are expressed on APCs, augments immune responses. In vivo blockade of CTLA-4, utilizing anti-CTLA-4 monoclonal antibody (mAb), induced regression of established tumors and enhanced anti-tumor immune responses in several murine tumor models. Blockade of CTLA-4-mediated signals is effective in inducing rejection of immunogenic cancers in mice. Moreover, when anti-CTLA-4 mAb is used in conjunction with granulocyte macrophage colony stimulating factor-secreting tumor vaccines, poorly immunogenic cancers in mice are rejected. These findings suggest that CTLA-4 blockade, alone or in combination with vaccines, can induce a potent anti-tumor response.

Advances in understanding the mechanisms regulating T-cell activation have allowed the development of better strategies for the immunotherapy of tumors and infectious diseases. Full activation of naïve T cells requires not only stimulation of the antigen receptor by peptide/major histocompatability complexes, but also co-stimulatory signals mediated by engagement of CD28 by B7 molecules[76]. T cells constitutively express CD28 and expression of B7 molecules is limited to APCs, such as dendritic cells, activated macrophages, and activated B cells[76]. CD28-B7 co-stimulatory signals are critical for the induction of T-cell proliferation, cytokine secretion, and effector functions.

Mechanisms have evolved that regulate and restrict T-cell activation. CTLA-4 (CD152) is an activation-induced T-cell surface molecule that also binds CD80 and CD86, but with greater avidity than CD28. CTLA-4 ligation down-regulates T-cell responses. Several studies have demonstrated that, in vitro, soluble anti-CTLA-4 mAb enhanced T-cell responses, whereas directly crosslinking CTLA-4 results in blockade of cell cycle progression, diminished cytokine expression, and decreased proliferation[77-80]. Blockade of CTLA-4/B7 interactions prevents induction of peripheral T-cell tolerance upon vaccination with peptides under tolerogenic conditions, suggesting that CTLA-4 is involved in the induction of anergy[81].

In addition to being expressed on activated effector T cells, CTLA-4 is constitutively expressed on the surface of T-regulatory cells. T-regulatory cells suppress immune responses, but the role of CTLA-4 in this process is controversial[82]. The observation that CTLA-4 knockout mice suffer a fatal lymphoproliferative disorder supports the idea that CTLA-4 functions as a key negative regulator of T-cell responses[83-85]. However, blockade of CTLA-4 function by the antibody does not lead to any detectable non-specific T-cell activation or proliferation, although the antibody can augment autoimmune responses in mice prone to specific autoimmune disease[86]. Using anti-CTLA-4 mAbs, CTLA-4 blockade enhanced rejection of B7 transfected tumors and induced rejection of unmodified tumor cells and immunity to rechallenge in a T-cell-dependent mechanism[87]. Blockade of CTLA-4 interaction with its ligands also enhances host responses against bacteria[88] and parasites[89] and limits viral spread in human immunodeficiency virus-infected T cells in vitro[90].

1.5.3 SBRT Background

Stereotactic Body Radiotherapy (SBRT) reduces the overall time of radiation treatment and offers a greater potential for cell kill compared to standard fractionation schemas of 1.8-3.0 Gy/Day. This technique allows for rapid delivery of tumorcidal doses of radiotherapy and provides ablative treatment to metastases. The significance of this approach is several fold. First, a highly conformal radiation therapy targeting the metastatic tumor burden can be delivered in high dose per fraction safely with minimal normal tissue toxicity. Second, by avoiding normal tissue irradiation, we may maximize immunogenic cell death from tumor cells while minimizing immune tolerance mechanisms evoked by irradiation of normal tissue. Third, SBRT is rapidly deployable and can be delivered to metastatic lesions with little or no interruption of systemic therapy allowing a tightly coordinated schedule in combination with nivolumab and/or ipilimumab.

Studies have demonstrated that SBRT for ablative treatment of non-symptomatic, solitary metastases is technically feasible, with acceptable toxicity and high rates of in-field cancer control[91,92]. SBRT or ablative RT approaches have been studied in many clinical trials in different disease sites including 4 Radiation Therapy Oncology Group (RTOG) clinical trials: RTOG 0236, 0813/0915, 0438 and 0613 for solitary lesions in lung, liver and spinal metastases respectively in a cooperative group trial setting. These trials have provided a framework for successful delivery and quality assurance of complex radiotherapy in the cooperative group setting. These trials have demonstrated that ablative doses with the Biologically Effective Dose (BED) >100 are needed to achieve high control rates in several disease sites for definitive management.

1.5.4 Summary of Safety

Nivolumab Monotherapy

One Phase 1 study (CA209003) has contributed much to the clinical experience with nivolumab monotherapy in subjects with melanoma and other solid malignancies[38]. CA209003 is a Phase 1 open label, multiple dose escalation study in 304 subjects with select previously treated advanced solid tumors, including melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), colorectal cancer, and hormone-refractory prostate cancer. Subjects received nivolumab at doses of 0.1, 0.3, 1, 3 or 10 mg/kg intravenously every 2 weeks, up to a maximum of 2 years of total therapy. As of 03-Jul-2012, a total of 107 melanoma subjects were treated with nivolumab in the dose range of 0.1 - 10 mg/kg.

No maximal tolerated dose was identified in CA209003. The incidence, severity and relationship of AEs were generally similar across dose levels and tumor types. Nivolumab related AEs of any grade occurred in 72.4% of subjects. The most frequent nivolumab related AEs occurring in over 5% of subjects included: fatigue (25.7%), rash (13.5%), diarrhea (11.8%), pruritis (10.2%), nausea (7.9%), decreased appetite (7.9%), hemoglobin decreased (5.9%) and pyrexia (5.3%). The majority of events were low grade, with Grade 3 - 4 drug related AEs observed in 14.8% of subjects. The most common Grade 3 - 4 drug-related AEs occurring in over 1% of subjects were: fatigue (1.6%), lymphopenia (1.3%), abdominal pain (1%), diarrhea (1%), hypophosphatemia (1%) and pneumonitis (1%). At least one SAE was reported for 150 (49.3%) of the 304 subjects at all dose levels. Grade 3 - 4 SAEs were reported for 23 subjects (7.6%). Drug-related SAEs occurred in 11.5% of subjects. Grade 3 - 4 drug-related SAEs reported in at least 2 subjects included: diarrhea (3 subjects, 1.0%), pneumonitis (3 subjects, 1.0%), pneumonia (2 subjects, 0.7%) and lipase increased (2 subjects, 0.7%). Additional select treatment-related AEs have occurred with low frequency (< 5%) but are considered clinically meaningful, as they require greater vigilance for early recognition and prompt intervention. These AEs

include: ALT increased (4.3%), AST increased (3.6%), pneumonitis (3.3%), hypothyroidism (3.0%), hyperthyroidism (1.3%), renal failure (1.0%), adrenal insufficiency (0.7%) and colitis (0.7%). Grade 3 - 4 events of pneumonitis were reported in 3 subjects (1.0%) as described above (1 event was Grade 4). Grade 3 events of colitis, ALT increased, and AST increased were reported in 2 subjects (0.7%) each. Grade 3 events of adrenal insufficiency, hyperthyroidism, and hypothyroidism were reported in 1 subject (0.3%) each. Treatment-related AEs leading to discontinuation were reported in 18 (5.9%) of the 304 treated subjects on CA209003. Of the treatment-related AEs leading to discontinuation, the only events reported in more than 1 subject were pneumonitis (4 subjects; 1.3%) and hepatitis (2 subjects; 0.7%). There were 3 (1%) drug related deaths; each occurred after development of pneumonitis. Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB.

Ipilimumab Monotherapy

In MDX010-20 (metastatic or unresectable setting), the ipilimumab monotherapy arm was administered 3 mg/kg ipilimumab every 3 weeks for four doses. In this arm, there were 79% drug related adverse events, with 21% being Grade 3/4 and 3/131 (2%) being Grade 5[93]. The most frequent adverse events of interest were pruritis (33%), diarrhea (33%), rash (30%), colitis (8%), endocrine disorders (9%), (aspartate aminotransferase) AST/ (alanine aminotransferase) ALT increased (2%), and hepatitis (1%). Any grade immune related adverse events were 60% and the Grade 3/4 immune related adverse events for the same cohort was 13% with the most frequent adverse events being diarrhea (5%), colitis (5%), rash (2%), and endocrine disorders (3%)[30]. Additional details on the safety profile of ipilimumab, including results from other clinical studies, are also available in the ipilimumab IB.

Nivolumab and Ipilimumab dual therapy

The safety profile of delivering nivolumab and ipilimumab concurrently was evaluated in a phase I trial in melanoma[27]. Among the 53 patients, grade 3 or 4 adverse events, regardless of attribution, were observed in 72% of patients, and grade 3 or 4 treatment-related events were noted in 53%, with the most common events being elevated levels of lipase (in 13% of patients), aspartate aminotransferase (in 13%), and alanine aminotransferase (in 11%). A total of 6 of 28 patients (21%) had grade 3 or 4 treatment-related events that were dose-limiting. Nivolumab at a dose of 3 mg per kilogram and ipilimumab at a dose of 3 mg per kilogram exceeded the maximum doses that were associated with an acceptable level of adverse events (three of six patients had asymptomatic grade 3 or 4 elevated lipase levels that persisted for ≥3 weeks). The doses in of nivolumab at 1 mg per kilogram and ipilimumab at 3 mg per kilogram were identified as the maximum doses that were associated with an acceptable level of adverse events (grade 3 uveitis in one patient and grade 3 elevated levels of aspartate aminotransferase and alanine aminotransferase in one). Given significant toxicity associated with full doses of nivolumab and ipilimumab, dose reduction in ipilimumab was further evaluated in NSCLC (Checkmate-032)[94]. In this study, grade 3 or 4 treatment-related adverse events occurred in ten (19%) of 54 patients in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg cohort. The most commonly reported grade 3 or 4 treatment-related adverse events were increased lipase and diarrhea. Eight patients (15%) in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg cohort had dose delays due to treatment-related adverse events. The most frequent serious adverse events were dyspnea experienced by nivolumab 3 mg/kg plus ipilimumab 1 mg/kg cohort, and diarrhoea, experienced by two (4%) patients in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg cohort. 4 (7%) patients discontinued treatment because of treatment-related adverse events: one patient each with colitis, pneumonitis, and peripheral neuropathy; one patient with dyspnea and pneumonitis. Combination of full dose PD1 blockade (pembrilozumab) with low dose ipilimumab was further studied in Keynote-029 study[95].

This phase I/II study of pembrolizumab 2 mg/kg plus low-dose IPI 1 mg/kg every 3 weeks (Q3W) for 4 doses, followed by pembrolizumab 2 mg/kg Q3W for up to 2 years, demonstrated grade 3 toxicities in 6 of 19 evaluable pts (2 of 9 renal cell carcinoma patients, 4 of 10 melanoma patients). Two patients experienced 2 grade 3 toxicities each: elevation of pancreatic enzymes and hyperthyroidism in 1 patient and lipase elevation and pneumonitis in another patient. The remaining grade 3 toxicities were ALT/AST elevation (n = 2), colitis (n = 1), and uveitis (n = 1).

SBRT

The safety of SBRT technique in various disease sites has been extensively studied. RTOG 0236[96] was a multicenter phase II trial for peripheral T1-T2 N0M0 non-small cell lung cancer. A total of 59 patients were accrued for the study, and 55 were evaluable. Patients each received three fractions of 18 Gy (54 Gy total) of SBRT, and treatment lasted between one-and-a-half to two weeks. Treatment-related grade three and grade four side effects were reported in 15 patients and in two patients, respectively. No grade five adverse events were reported. Another phase II clinical trial evaluated the role of SBRT in colorectal liver metastases[97]. Forty-two patients with inoperable colorectal liver metastases not amenable to radiofrequency ablation (RFA) were treated with SBRT for a total number of 52 lesions. All patients received a total dose of 75 Gy in 3 consecutive fractions. No patients experienced radiation-induced liver disease or grade ≥3 toxicity. RTOG 0631 was a multicenter phase II/III trial to assess the feasibility and safety of spine radiosurgery (SRS) for localized spine metastases in a cooperative group setting. Patients with 1-3 spine metastasis received 16 Gy single fraction SRS. Forty-six patients were accrued, and 44 were eligible. There were 4 cervical, 21 thoracic and 19 lumbar sites. There were no cases of grade 4-5 acute treatment-related toxicity[98]. A phase II prospective trial also evaluated SBRT for unresectable locally recurrent head and neck squamous cell carcinoma[99]. 50 patients with recurrent head and neck cancer within a previously irradiated field that received ≥60 Gy were enrolled. Patients received concurrent cetuximab plus SBRT (40-44 Gy in 5 fractions on alternating days over 1-2 weeks). Acute and late grade 3 toxicity was observed in only 6% of patients despite SBRT was given in re-irradiation setting. SBRT was also evaluated for patients with locally advanced pancreatic cancer and borderline resectable pancreatic cancer treated at the Moffitt Cancer Center. A retrospective review of 72 pancreatic patients treated with a median dose of 35Gy in 5 fractions demonstrated no acute grade 3 toxicity, and late grade 3 toxicity was minimal 5.3%[100].

This clinical trial was designed to deliver radiation therapy with minimal additional toxicity to nivolumab and ipilimumab. First, this clinical trial utilizes SBRT, which allows conformal radiation delivery with minimal radiation spillover to the surrounding normal tissue to prevent toxicity. We will only be treating the gross tumor with tight margin with a rapid dose fall off allowing minimal normal tissue irradiation. Second, the dose of SBRT in this trial is far lower than the regular SBRT doses in various sites. For instance, the typical SBRT dose for a lung lesion or a liver lesion is 20Gy x 3 fractions. In this trial we are only prescribing to 8Gy x 3 fractions with minimal toxicity anticipated. Third, we are also allowing simultaneous integrated boost, or dose-painting. This technique will allow 8Gy x 3 fractions to the center of the tumor, but at the periphery of the tumor adjacent to the normal tissue, we can lower the dose to 5Gy x 3 fractions, further ensuring safety profile.

1.5.5 Summary of Clinical Activity

Nivolumab Monotherapy

Several immune checkpoint inhibitors targeting PD1 or PD-L1 are being tested currently. A recent interim report of phase I/II trial of metastatic treatment-naive MCC patients on pembrilozumab reported 14% complete response rate[10]. Therefore, we anticipate a significant therapeutic efficacy of

nivolumab in MCC, which is being evaluated in an on-going multi-institutional clinical trial on Nivolumab alone for virus-associated cancers including MCC conducted by BMS.

Otherwise, the clinical activity of nivolumab was demonstrated in multiple tumor types. In CA209003[38] the clinical activity of nivolumab was demonstrated in melanoma, RCC, and NSCLC. Clinical activity was noted across a range of doses (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg). In CA209003, as of the clinical cut-off date of 03-Jul-2012, a total of 304 subjects with melanoma, RCC, and NSCLC have been evaluated for clinical activity. A response of either CR or PR, as determined by investigator assessed tumor evaluations based on modified RECIST 1.1, has been reported at all dose levels. No responses (CR or PR) have been reported in subjects with colorectal carcinoma or castrate-resistant prostate cancer.

Among 106 subjects with advanced melanoma who received nivolumab and were evaluable for response, the preliminary objective response rates were 6/17 (35%), 5/18 (28%), 11/34 (32%), 7/17 (41%), and 4/20 (20%) for melanoma subjects treated at 0.1, 0.3, 1, 3, and 10 mg/kg, respectively. Duration of response range from 3.6 to 11.2, 1.8 to 9.2, 1.9 to 24.9, 9.2 to 22.4, and 17.0 to 25.7 months in the melanoma subjects treated at 0.1, 0.3, 1, 3, and 10 mg/kg, respectively. Stable disease over 24 weeks occurred in an additional 1/18 (6%), 4/34 (12%), 1/17(6%) melanoma subjects at 0.3, 1, and 3 mg/kg, respectively. Finally, the PFS-24 week was 41%, 33%, 48%, 55%, and 30% in melanoma subjects treated at 0.1, 0.3, 1, 3, and 10 mg/kg, respectively.

SBRT Monotherapy

The local control rate of irradiated tumors following SBRT is excellent. For instance, five-year local control rate stage I non-small cell lung cancer patients treated with 54 Gy in 3 fractions is in excess of 80%[96]. On a particular note, MCC metastases treated with SBRT to 8Gy in a single fraction achieved complete responses in 45% of tumors with durable local control in 77% of treated tumors with a median follow up of 277 days[24].

The abscopal effect or the capacity of radiation therapy to impact tumors outside the radiation field has been recognized for several decades in case reports[14]. However, its clinical relevance had not been fully recognized until recent years. With the advent of immune checkpoint inhibitors, the abscopal effect has been more formally tested in clinical trials[101]. Most recent evidence for the abscopal effect of radiation therapy is found with metastatic melanoma. A phase II clinical trial of 20 patients with metastatic melanoma treated with combination of radiation therapy and systemic ipilimumab (3 mg/kg) every three weeks for a total of four treatment cycles demonstrated 55% objective response rate including a 9.1% complete response, far exceeding the historical control for ipilimumab alone[29]. Multiple other clinical trials are on-going to evaluate the efficacy of radiation therapy in combination with systemic immunotherapy[101].

Ipilimumab Monotherapy

Ipilimumab has not been directly tested in Merkel cell carcinoma. The anticipated clinical activity in MCC is inferred from its efficacy in other solid cancers, most prominently another skin cancer, melanoma. In melanoma, a completed Phase 3 study (MDX010-20)[93] has demonstrated a clinically meaningful and statistically significant survival benefit in pre-treated advanced melanoma. The study compared the OS of ipilimumab plus a melanoma-specific vaccine (gp100) to that of gp100 alone. A second comparison defined the OS of ipilimumab alone vs gp100 alone. Both comparisons demonstrated statistically significant improvements in OS (P = 0.0004 and 0.0026, respectively). The 1-year survival for the two ipilimumab-containing groups, respectively, was 44% and 46% respectively, compared to 25% for the gp100 control group. The 2-year survival was 22%, 24% and

14% respectively. The median survival was 10, 10.1, and 6.4 months, for ipilimumab plus gp100, ipilimumab monotherapy, and gp100 monotherapy, respectively.

1.5.6 Clinical Pharmacology Summary

Ipilimumab Monotherapy

Ipilimumab has a terminal half-life of approximately 15.4 days. The expected in vivo degradation of monoclonal antibodies is to small peptides and amino acids via biochemical pathways that are independent of cytochrome P450 enzymes.

The PPK of ipilimumab was studied with 785 subjects (3200 serum concentrations) with advanced melanoma in 4 Phase 2 studies (CA184004, CA184007, CA184008, and CA184022)[102], one Phase 3 study (CA184024) and one Phase 1 study (CA184078). The PPK analysis demonstrated the PK of ipilimumab is linear and exposures are dose proportional across the tested dose range of 0.3 mg/kg to 10 mg/kg, and the model parameters are time-invariant, similar to that determined by noncompartmental analyses.

Upon repeated dosing of ipilimumab, administered q3w, minimal systemic accumulation was observed by an accumulation index of 1.5-fold or less and ipilimumab steady-state concentrations were achieved by the third dose. The ipilimumab CL of 16.8 mL/h from PPK analysis is consistent with that determined by noncompartmental PK analysis. The terminal T-HALF and Vss of ipilimumab calculated from the model were 15.4 days and 7.47 L, respectively, which are consistent with that determined by noncompartmental analysis. Volume of central compartment (Vc) and peripheral compartment were found to be 4.35 L and 3.28 L, respectively, suggesting that ipilimumab first distributes into plasma volume and, subsequently, into extracellular fluid space. CL of ipilimumab and Vc were found to increase with increase in BW. However, there was no significant increase in exposure with increase in BW when dosed on a mg/kg basis, supporting dosing of ipilimumab based on a weight normalized regimen. The PK of ipilimumab is not affected by age, gender, race, immunogenicity (anti-drug antibody status), concomitant use of chemotherapy, prior therapy, BW, performance status, or tumor type. Other covariates had effects that were either not statistically significant or were of minimal clinical relevance. Additional details are provided in investigator brochure.

Nivolumab Monotherapy

Single-dose PK of nivolumab was evaluated in subjects with multiple tumor types in MD1106-01 whereas multiple dose PK is evaluated in subjects in CA209003. In addition, a population pharmacokinetic (PPK) model has been developed with data from ± 909 subjects from MDX1106-01[103], ONO-4538-01[104], ONO-4538-02[105], CA209003[38], and CA209010[106] in subjects with progressive advanced/metastatic clear-cell renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy, CA209063[107] and CA209037[108]. The body weight normalized dosing produces approximately constant trough concentrations over a wide range of body weight, and hence is appropriate for future clinical trials of nivolumab. Clearance of nivolumab is similar in all tumor types studied and is independent of dose range studied (0.1 to 10 mg/kg).

Single-dose PK of nivolumab was evaluated in 39 subjects with multiple tumor types in study MDX1106-01 in the dose range of 0.3 to 10 mg/kg. The median Tmax across single doses ranged from 1.6 to 3 hours with individual values ranging from 0.9 to 7 hours. The PK of nivolumab is linear in the range of 0.3 to 10 mg/kg with dose proportional increase in Cmax and AUC(INF) with low to moderate inter-subject variability observed at each dose level (ie,

coefficient of variation (CV) ranging from 7 to 45%). Geometric mean clearance (CL) after a single intravenous (IV) dose ranged from 0.13 to 0.19 mL/h/kg, while mean volume of distribution (Vz) varied between 83 to 113 mL/kg across doses. The mean terminal T-HALF of nivolumab is 17 to 25 days, which is consistent with half-life of endogenous IgG4, indicating that the elimination mechanism of nivolumab may be similar to IgG4. Both elimination and distribution of nivolumab appear to be independent of dose in the dose range studied. Additional details are provided in the Investigator Brochure.

1.6 Overall Risk/Benefit Assessment

There continues to be a significant unmet need for patients with metastatic Merkel cell carcinoma. This is illustrated by poor survival outcome in patients with metastatic MCC and that there is no standard of care treatment in metastatic MCC.

Nivolumab monotherapy has demonstrated clinical activity across several tumor types, including advanced prior-treated melanoma, with objective response rates of 20 - 41% in 106 melanoma subjects treated at various dose levels in CA209003. The most common AEs of nivolumab monotherapy included fatigue, rash, pruritis, diarrhea, and nausea. MCC appears to be also strongly responsive to PD1 blockade and there is an on-going study of nivolumab alone in metastatic MCC.

Ipilimumab has shown to enhance the therapeutic efficacy of nivolumab in several tumor types including melanoma and NSCLC. The most common AEs of ipilimumab include rash, pruritis, diarrhea, colitis, and endocrine disorders.

Given the high discontinuation rate due to toxicity with ipilimumab 3 mg/kg in combination with nivolumab, a data safety monitoring committee will be involved to periodically evaluate the emerging data and trends.

It is the hypothesis of the trial that there will be improvements in ORR by the addition of SBRT and/or ipilimumab to nivolumab in metastatic MCC. The robust clinical activity demonstrated by PD1 blockade in metastatic MCC, the proven benefit of SBRT and ipilimumab in subjects with various solid cancers, the manageable safety profile, and the lack of standard of care for subjects with metastatic MCC with poor prognosis supports further development of optimal therapy to define standard of care in this population of subjects.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

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

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

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

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

2.3 Informed Consent

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

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

Informed consent form will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1. Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.

2. Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.

3. Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.

4. Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

5. If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.

6. Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

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

8. The consent form must also include a statement that regulatory authorities have direct access to subject records.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 STUDY POPULATION

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

3.1 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. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care
- Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, tumor biopsies, and other requirements of the study.

2. Signed Written Informed Consent

- All subjects must be either recurrent, unresectable or Stage IV AJCC (7th edition) and have histologically confirmed Merkel cell carcinoma with confirmed pathology in order to be eligible. Please refer to Appendix 1 or description of AJCC 7th editions of TNM and staging.
- At least 18 years of age
- ECOG PS < 2
- Active disease measurable by CT, MRI, or clinical exam
- Prior chemotherapy or immunotherapy will be allowed if new or persistent measurable site(s) of disease are present.
- Prior radiation therapy will be allowed if there is active measurable disease burden.
- All subjects must have at least 2 distinct lesions as documented by a complete physical examination or imaging studies within 4 weeks prior to randomization. Imaging studies must include a CT scan of the involved disease sites and all known sites of resected disease and brain magnetic resonance (MRI) or CT (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions).
- Tumor tissue from the core biopsy or resected site of disease must be provided for biomarker analyses. Prior surgery that required general anesthesia must be completed at least 4 weeks before study drug administration. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before study drug administration.
- All baseline laboratory requirements will be assessed and should be obtained within 14 days of randomization. Screening laboratory values must meet the following criteria.

  i) WBCs ≥ 2000/μL
  ii) Neutrophils ≥ 1500/μL
  iii) Platelets ≥ 100 x 10^3/μL
  iv) Hemoglobin ≥ 9.0 g/dL
  v) Creatinine Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or creatinine clearance > 40 mL/minute (using Cockcroft/Gault formula)
  vi) AST ≤ 3 x ULN
  vii) ALT ≤ 3 x ULN

viii) Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who must have total bilirubin < 3.0 mg/dL)

- Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a screen failure (ie, subject has not been randomized / has not been treated). If re-enrolled, the subject must be re-consented.

3. Age and Reproductive Status

- Men and women, at least 18 years of age
- Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.
- Women must not be breastfeeding
- WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) plus 5 half-lives of study drug plus 30 days (duration of ovulatory cycle). The half-life of nivolumab and ipilimumab is up to 25 days and 18 days, respectively. WOCBP should therefore use an adequate method to avoid pregnancy for a total of 23 weeks post-treatment completion (Appendix 3).
- Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) plus 5 half-lives of the study drug (s) plus 90 days (duration of sperm turnover). The half-life of nivolumab and ipilimumab is up to 25 days and 18 days, respectively. Men should therefore use an adequate method of contraception for a total of 31 weeks post-treatment completion (Appendix 3).
- Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, they must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. (Refer to Appendix 3.)

3.2 Exclusion Criteria

1. Target Disease Exceptions

- Subjects with active brain metastasis

2. Medical History and Concurrent Diseases

- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids are permitted in the absence of active autoimmune disease.
- Subjects requiring palliative radiation therapy at presentation.

- Subjects with history of Grade 3 toxicity or use of infliximab with prior immunotherapy.
- Subjects with active, known, or suspected autoimmune disease. Subjects with type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll. For any cases of uncertainty, it is recommended that the Medical Monitor be consulted prior to signing informed consent.
- Subjects with prior history of non-Merkel cell carcinoma malignancies are excluded except adequately treated basal cell, squamous cell skin cancer, chronic lymphocytic leukemia or other indolent diseases not requiring therapy; adequately treated, with curative intent, cancer from which the patient is currently in complete remission per investigator's judgment; or patients with history of breast cancer and no evidence of disease on hormonal therapy to prevent recurrence and patients with prostate cancer on adjuvant hormonal therapy with undetectable PSA are eligible.
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids are permitted in the absence of active autoimmune disease.
- Any serious or uncontrolled medical disorder or active infection that, in the opinion of the investigator, may increase the risk associated with study participation, study drug administration, or would impair the ability of the subject to receive protocol therapy.

3. Physical and Laboratory Test Findings

- Positive test for hepatitis B virus surface antigen (HBVsAg) or hepatitis C virus ribonucleic acid (HCV RNA) indicating acute or chronic infection.
- Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

4. Allergies and Adverse Drug Reaction

- History of Grade 3 or higher allergy to humanized monoclonal antibodies

5. Other Exclusion Criteria

- Prisoners or subjects who are involuntarily incarcerated
- Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Pregnant or nursing women
- Psychological, familial, sociological, or geographical conditions that potentially hamper compliance with the study protocol and follow-up schedule; those conditions should be discussed with the subject before registration in the trial

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3 Women of Childbearing Potential

A Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels. If the serum FSH level is >40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

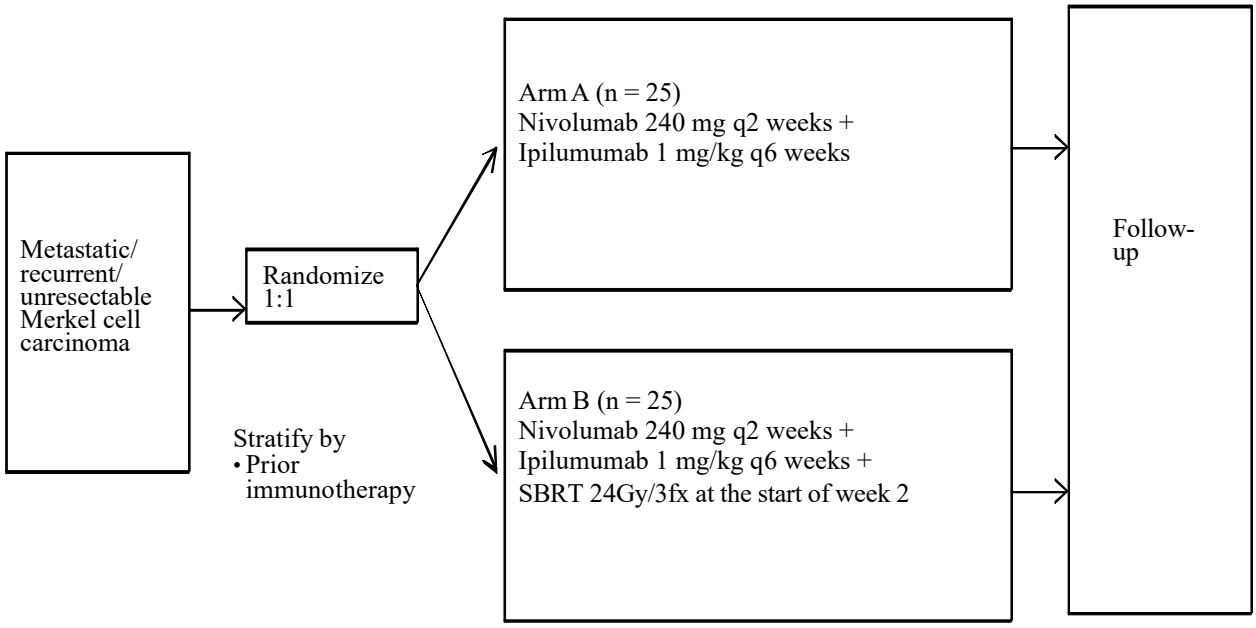
Other parenteral products may require washout periods as long as 6 months.

4 INVESTIGATIONAL PLAN

4.1 Study Design and Duration

The study design schematic is presented in Figure 3.1-1.

Figure 4.1-1: Study Design Schematic



The subjects will be treated in both arms until disease progression, unacceptable toxicity, or subject withdrawal of consent.

This study will consist of three phases: screening, treatment, and follow-up. For a complete list of study required procedures, please refer to Section 5.

Screening Phase:

- Begins by establishing the subject's initial eligibility and signing of the informed consent form (ICF).
- Subject is assessed for complete study eligibility within the required timeframe found in Table 7.1-1.
- A pregnancy test for WOCBP should be documented within 24 hours prior to the start of the first dose of study medication.
- All subjects must have at least 2 distinct lesions as documented by a complete physical examination or imaging studies within 4 weeks prior to randomization. Imaging studies must include a CT scan of the involved disease sites and all known sites of resected disease and brain magnetic resonance (MRI) or CT (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions).

Treatment Phase:

- Following confirmation of the subject's eligibility, the randomization call to the Moffitt Cancer Center Biostatistics Core can be made. The subject is randomly assigned to the Arm A (nivolumab + ipilimumab) or Arm B (nivolumab + ipilimumab + SBRT).
- Within 2 weeks from randomization the subject must receive the first dose of study medication (Day 1 of Week 1)
- On-study laboratory assessments should be drawn within 72 hours prior to dosing
- Adverse event assessments for grade ≥ 2 toxicities should be documented at each clinic visit and WOCBP must have a pregnancy test every four weeks +/- 1 week.
- Treated subjects will be evaluated for recurrence every 12 weeks +/- 7 days
- Patient Reported Outcome (PRO) instruments must be completed after randomization, prior to the dose of study therapy.

Follow- up Phase:

- Begins after 1 year of treatment or when the decision is made to discontinue a subject from study therapy.
- Patient may continue on the study drug under the treatment protocol indefinitely during the follow-up phase.
- After completion of the first two follow -up visits, subjects will be followed every 3 months for survival.
- Subjects who discontinue treatment for reasons other than disease progression will continue to have surveillance assessments (until progression) every 12 weeks ± 14 days during the first year after randomization, every 12 weeks ± 21 days during the second year, every 6 months ± 4 weeks between Year 3 and Year 5 with the last assessment at Year 5.
- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All toxicities (≥ grade 2) will be documented for a minimum of 100 days after the last dose of study medication.

The total duration of the study from start of randomization to final analysis of OS is expected to be 84 months (36 months of accrual + 48 months of follow-up), assuming an accrual rate of 17 subjects/year during years 1 – 3.

Stopping criteria: A Safety Monitoring Committee will be formed to evaluate the toxicity of both arms. Interim analysis will be conducted following accrual of initial cohort of patients in the Simon's two stage design to determine whether SBRT introduces excess unanticipated grade 3 or higher toxicities (i.e. radiation pneumonitis, radiation dermatitis, radiation myelitis) prior to expansion of the cohorts.

4.2 Concomitant Treatments

4.2.1 Prohibited and/or Restricted Treatments

- The following medications are prohibited during the treatment and follow-up phases (before recurrence) of the study (unless utilized to treat a drug-related adverse event):
- Immunosuppressive agents

- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 4.4.2)
- Any concurrent anti-neoplastic therapy (including, but not limited to chemotherapy, hormonal therapy, immunotherapy, radiation therapy, or standard or investigational agents for treatment of Merkel cell carcinoma other than specified per protocol).

4.2.2 Permitted Therapy

Subjects are permitted the use of topical, ocular, intra-articular, intranasal and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted even if > 10 mg daily prednisone (or equivalent). A brief course of corticosteroids for prophylaxis (eg, for contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Intravitreal injections of vascular endothelial growth (VEGF) inhibitors are permitted if used according to the approved ocular indication, such as macular degeneration.

4.3 Discontinuation of Subjects following any Treatment with Study Drug

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

- Subject's request to stop study treatment
- Progression of the target lesion
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Additional protocol specified reasons for discontinuation (see Section 4.5.7).

In the case of pregnancy, the study drug will be permanently discontinued in an appropriate manner unless the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug.

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 7. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

4.4 Post Study Drug Study Follow up

In this study, ORR, PFS, OS and toxicity are key endpoints. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who

discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 7 until death or the conclusion of the study.

4.4.1 Withdrawal of Consent

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

4.4.2 Lost to Follow-Up

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

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor- retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

5 STUDY DRUG

This is a non-blinded study which includes investigational products:

Product	Potency	Appearance	Packaging	Storage Conditions
Nivolumab (Solution for Injection)	10 mg/mL	Clear to pale yellow liquid; may contain particles	10 mL/vial	Store at 2-8'C; protect from light or freezing
Ipilimumab (Solution for Injection)	5 mg/mL	Clear to pale yellow liquid; may contain particles	10 mL/vial	Store at 2-8'C; protect from light or freezing

Premedications or medications used to treat infusion-related reactions should be sourced by the local site. Solutions used as diluents (0.9% Sodium Chloride or 5% Dextrose) should also be sourced by the local site.

5.1 Investigational Product

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

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

In this protocol, investigational products are: nivolumab and ipilimumab.

5.2 Non-investigational Product

Not applicable.

5.3 Storage and Dispensing

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

Study drug not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Infusion-related supplies (eg, IV bags, in-line filters, 0.9% sodium chloride injection, 5% dextrose

injection) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

Please refer to the current version of the Investigator Brochure (IB) and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for nivolumab and ipilimumab.

The infusion duration of nivolumab is 30 minutes and for ipilimumab 30 minutes.

5.4 Method of Assigning Subject Identification

After a subject's initial eligibility is established and informed consent obtained, subjects will be assigned a study number/ID. Once enrolled and study number assigned, patients will be randomized in a 1:1 ratio. The following information is required for subject randomization:

- Subject number
- Date of birth
- AJCC M classification

Subjects meeting all eligibility criteria will be randomized in a 1:1 ratio to Arm A (Nivo + Ipi) or Arm B (Nivo + Ipi + XRT) stratified by the following factors:

- Prior immunotherapy

5.5 SBRT and Drug Dosing Schedule

5.5.1 Dosing Schedule

First dose must be administered within 2 weeks following randomization. Subjects may be dosed up to ± 2 days before or after the scheduled date if necessary.

The Dosing schedule is described in Table 5.5-1 and Table 5.5-2.

Table 5.5-1: Dosing Schedule Arm A

	Week 1	Week 2	Week 3	Week 5
Arm A: Nivolumab+ Ipilimumab	240 mg Nivolumab + 1 mg/kg Ipilumumab		240 mg Nivolumab	240 mg Nivolumab
	Week 7			
	240 mg Nivolumab Every 2 weeks + 1 mg/kg Ipilumumab Every 6 weeks until progression or unacceptable toxicity			

Table 5.5-2: Dosing Schedule Arm B

	Week 1	Week 2	Week 3	Week 5
Arm A: Nivolumab+ Ipilimumab+ SBRT	240 mg Nivolumab + 1 mg/kg Ipilumumab	24Gy/3fx SBRT (may be completed by Week 3)	240 mg Nivolumab	240 mg Nivolumab
	Week 7			
	240 mg Nivolumab Every 2 weeks + 1 mg/kg Ipilumumab Every 6 weeks until progression or unacceptable toxicity			

If a subject cannot receive a dose within 2 days of its scheduled administration date, the dose should be completely omitted. When the subject is able to re-initiate treatment, dosing should resume at the time of the next scheduled dose. Missed doses will not be replaced.

5.5.2 Antiemetic Premedications

Antiemetic premedications should not be routinely administered prior to dosing of drugs. See Section 5.5.8 for premedication recommendations following a nivolumab or ipilimumab related infusion reaction.

5.5.3 Dose Modifications

There will be no dose modifications permitted. Dose reductions or dose escalations are not permitted.

5.5.4 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agents in this protocol. Management algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events: Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathies, Skin, and Neurological. (Appendix 4)

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

The recommendations are to follow the algorithms in the nivolumab investigator brochure for immune related events; while the ipilimumab investigator brochure contains similar algorithms, the algorithms in the nivolumab brochure have been aligned to accommodate combinations as well as nivolumab monotherapy.

Therefore, the algorithms recommended for utilization are attached for reference.

For subjects expected who require more than 4 weeks of corticosteroids or other immunosuppressants to manage an adverse event, consider the following recommendations

- Antimicrobial/antifungal prophylaxis per institutional guidelines to prevent opportunistic infections such as Pneumocystis jiroveci and fungal infections.
- Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate.
- In patients who develop recurrent adverse events in the setting of ongoing or prior immunosuppressant use, an opportunistic infection should be considered in the differential diagnosis.

Additional details on the safety of nivolumab and ipilimumab , including results from clinical studies, are available in the IB.

5.5.5 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.

Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab, ipilimumab or both). All study drugs must be delayed until treatment can resume.

Nivolumab and ipilimumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
    - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for asymptomatic amylase or lipase, AST, ALT, or total bilirubin:
    - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay. It is recommended to consult with the principle investigator for Grade 3 amylase or lipase abnormalities.
    - 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 adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

5.5.6 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 a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin 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 (Section XX) should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled timepoint per protocol. However, if the treatment is delayed past the next scheduled timepoint per protocol, the next scheduled timepoint will be delayed until dosing resumes. If the design of the study defines that doses may not be omitted [skipped], strongly recommend adding "Doses may not be skipped"

If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in discontinuation section.

5.5.7 Discontinuation Criteria

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 the 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, diarrhea, colitis, neurologic adverse event, hypersensitivity reactions, and infusion reactions
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic adverse event, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except those noted below
        - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
        - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
            - AST or ALT > 8 x ULN
            - Total bilirubin > 5 x ULN
            - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Any dosing interruption lasting > 6 weeks with the following exceptions:

- Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted
- Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted

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

5.5.8 Treatment of Nivolumab or Ipilimumab Related Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (Insert version e.g.: 4.0) guidelines.

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

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations.

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

Stop the nivolumab or ipilimumab 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 or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor

the subject until resolution of symptoms. The amount of study drug infused must be recorded on the 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 or ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

5.5.9 Treatment Beyond Progression

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

Subjects will be permitted to continue treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria:

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

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

Subjects should discontinue study therapy upon further evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions). New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm).

However, given the uncertainties around defining progression versus pseudoprogression during immunotherapy, treatment will be allowed to be continued beyond protocol-defined progression if, in the judgment of the treating physician, further benefit to the patient is possible with continuation of

therapy. For statistical analyses, this will need to be described in patient population information. E.g. 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.

5.6 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the subject's medical record and eCRF.

5.7 Destruction of Study Drug

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

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

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

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

6 RADIATION THERAPY

Metastatic lesions with the following distribution are eligible to be treated with SBRT on this protocol:

1 – 4 metastases distinct from the measurable target lesion that will not be irradiated to evaluate responses to the abscopal effect and immunotherapy. Larger lesions are given preference for SBRT to maximize tumor antigen release. The irradiated lesion will not be included the calculations for measurable disease.

SBRT will be given Week 2 - 3, please see Section 5.5 and 6. SBRT should begin Week 2, and therefore, the radiation planning process should begin as the patient is registered for the study prior to randomization. SBRT for all metastases should be completed within 2 weeks of the first dose of SBRT. Not all metastases need to receive radiation therapy on the same day.

Most commercially available photon producing treatment units are allowed. As such, conventional linear accelerators, specialized linear accelerators with image guidance (e.g., Novalis, Trilogy, Synergy, Artiste, TrueBeam) are allowed. These units can be used with conformal dose delivery or IMRT. Specialized dose painting accelerators (e.g., Cyberknife, Gammaknife or Tomotherapy) are allowed provided they meet the technical specifications of the protocol and are used in a fashion that passes the credentialing required by the protocol. Conventional linear accelerators without add- on IGRT must have some other IGRT capability like CT-on-rails in the treatment room.

IGRT is required for this study. Either 3DCRT or IMRT (including VMAT) are all acceptable planning techniques. Planning techniques may differ for each lesion to be treated provided that the tumor motion is properly accounted for with each technique when the target or targets are in or near the thorax region.

6.1 Dose Specification

6.1.1 Dose Fractionation

Patients will receive 24Gy in 3 fractions of radiation in 3 consecutive days for non-skin lesions. Skin lesions are allowed to be treated every other day. Simultaneous integrated boost or dose-painting will be allowed to meet normal tissue dose constraints. If dose-painting is utilized, we recommend V21Gy > 90% of GTV and V24Gy > 1cc. This dose is well below the standard dose fractionation employed by SBRT in various disease locations ranging from 30Gy to 45Gy in 3 fractions, which have been deemed safe on available evidence and/or expert consensus in each disease site. Therefore we do not anticipate treatment related toxicity.

6.1.2 Technical Factors

6.1.2.1 Physical Factors

Only photon (x-ray) beams with photon energies $\geq$ 6MV will be allowed with the exception of radiation therapy to the skin for which electron beams will be allowed. For metastases located within 3 cm of the lungs, photon energies of 6-10MV are required. For lung central and lung peripheral metastases, photon beam energies > 10 MV are allowed only for a limited number ($\leq$50% of all beams or all beam angles) of beams that must travel more than a cumulative distance of 10 cm through soft tissue (not lung) to reach the isocenter OR a shorter distance if the tumor abuts the chest or abdominal wall (i.e., to spare skin dose).

FFF photon beams are allowed if the institution has performed SBRT credentialing with FFF beams.

Minimum Field Aperture (Field Size) Dimension

Because of uncertainties in beam commissioning resulting from electronic disequilibrium within small beam apertures, in general an equivalent square field dimension of 3 cm is recommended for fields used for treatment delivery for sites using standard 3-D conformal techniques where nearly all of the PTV is encompassed for each beam. It is understood that this may exceed the technical requirements for small lesions. In such cases, the prescription dose is still prescribed to the edge of the defined planning treatment volume (PTV). For sites using dose painting including IMRT techniques, where by design the entire PTV is not encompassed for each beam, smaller beam apertures are allowed.

All institutions must use heterogeneity correction algorithms approved by IROC Houston independent of the treatment planning technique. All doses should be reported in terms of dose-to-water and not in terms of dose-to-medium.

Stereotactic Targeting

For the purposes of this protocol, the term 'stereotactic' implies the targeting, planning, and directing of radiation beams along any trajectory in 3-D space toward a target of known 3-D coordinates. The coordinate system is defined by reliable 'fiducials.' A fiducial may be external or internal to the patient's body. External fiducials may relate to a frame or treatment device.

Internal fiducials may be implanted markers OR reliably identifiable anatomy that is clearly visible on orthogonal kV imaging including the tumor itself. In all cases, the relationship between the fiducial and the actual tumor position in real time should be reliably understood for both planning and treatment.

Isocenter Placement

When using a gantry mounted linear accelerator for this protocol, the isocenter is defined as the common point of gantry, collimator, and couch rotation for the treatment unit. For other types of treatment units (e.g., Tomotherapy or CyberKnife), a reference point in space that is typically positioned at the center of the target is used instead of a mechanical isocenter.

When treating multiple lesions, it is best to use multiple isocenters, each centered on a separate lesion. Treating different targets on different days is allowed in order to decrease treatment time for a single day. For widely spaced lesions (over 10 cm apart), localization is improved when the isocenter is placed in the center of each target and image guidance is performed individually for each target. This is due to the limitation of most IGRT systems which ignore necessary rotational corrections when table shift coordinates are derived. Some platforms, including Cyberknife and Tomotherapy, are inherently non-isocentric. These platforms take special account in the setup and treatment process to rigorously detect and account for rotations to avoid errors making them exempt from the separate isocenter for each lesion requirement. For other platforms, the use of a single isocenter to treat multiple lesions in proximity to each other may be allowed if the institution has credentialed successfully for SBRT treatment of 2 lesions with a single isocenter setup.

Composite Dose Calculations

Composite plans should be generated to incorporate the dose to surrounding normal tissues from each metastasis treated. The composite doses to critical normal tissues will be used to evaluate plan compliance. Composite planning refers to dose summation from multiple treatment sites on a single CT scan that encompasses the relevant anatomy. Composite treatment planning is best accomplished by obtaining a planning CT dataset that incorporate all targets and relevant critical structures in the imaging study. If this is not possible due to restrictions on the size of the imaging study that can be

managed by the treatment planning system, CT datasets should be divided into two parts and treatment fields should be adjusted so that dose spillage from the treatment of targets in one dataset to the next is minimal such that the dose contributions do not require summation. The two datasets should be obtained so that they have some amount of overlap that can be used to fuse the information using a rigid registration technique. The use of deformable registration to sum dose is not allowed. In general, it is best to perform CT scanning with the patient in the same position. This implies that, for example, all lesions planned on a gated CT scan must be treated with gating. If technical limitations are encountered in summing dose, contact the PI with questions regarding composite planning.

Localization, Simulation, and Immobilization

Patient Positioning (Immobilization)

Patients will be positioned in a stable position capable of allowing accurate reproducibility of the target position throughout treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. Patient immobilization must be reliable enough to ensure that the gross tumor volume (GTV) does not deviate beyond the confines of the planning treatment volume (PTV). Positioning patients on flat couches and relying solely on image-guidance for reproducible set-up is strongly discouraged.

Simulation

All patients will undergo CT-based treatment planning in custom made immobilization devices. CT scan range must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting (if used) and be adequate to ensure contouring of all targeted metastases, as well as necessary organs at risk (OAR), defined below. High-resolution CT scans should be obtained with uniform slice thickness of ≤ 3mm (ideally 1 – 2 mm) throughout. If a single CT scan cannot be obtained due to a large spatial separation between metastases (i.e., cervical and femoral metastases), or planning system slice number limitation, multiple CT scans are allowed provided that OAR are entirely encompassed in a single CT scan. CT imaging should be performed so that a composite dose distribution including all treated metastases can be created. Ideally all metastases will be treated in one treatment position. When treating multiple metastases such as a lung and extremity, varying the treatment position may be necessary (i.e. simulation with arms up and arm to the side). Thus, more treatment positions can be used at the discretion of the treating oncologist, but every effort should be made to obtain a composite distributions.

The use of IV contrast is required for liver metastases. For other metastases (central & peripheral lung, cervical/mediastinal, abdominal-pelvic, and spinal/paraspinal), the use of IV contrast is encouraged but will be left to the discretion of the treating physician. The use of other contrast agents is left to the discretion of the treating oncologist. Planning datasets without intravenous contrast may be used for dose calculation.

The use of bolus is required for skin primary disease or metastases. The thickness of bolus should ensure adequate coverage of the involved skin.

Respiratory Motion Assessment and Management

All metastases with potential for respiratory motion should be evaluated by appropriate means including 4D CT scan, implanted fiducial marker, or flouroscopy at the time of simulation. Respiratory motion management (RMM) including abdominal compression, active breathing control, breath hold, end expiratory gating, or fiducial marker tracking, is recommended for any metastasis to be treated with motion > 5mm. A recommended approach would be to use an ITV technique for motion < 1cm, but for motion > 1cm (typically too large for a free breathing ITV) motion management including but

not limited to abdominal compression, active-breathing control (ABC), gating, breath hold, etc. should be used.

If a treatment for multiple metastases (i.e., lung and spine) is designed on a CT scan employing motion management (i.e., abdominal compression), all metastases should be treated with the chosen motion management technique in order to generate an accurate composite dose calculation.

Localization Using Daily IGRT

As an SBRT protocol, this study requires the use of IGRT. NRG Oncology defines IGRT as a computer assisted process that uses imaging devices that generate a series of coordinates for shifting the patient support system in three orthogonal directions (sometimes including rotational changes) to position the treatment beams relative to target regions. The allowed technologies are as follows: cone-beam CT (CBCT) using either a specially mounted kV imaging head or the MV treatment beam with an opposed electronic imaging panel, dual fixed-position in-room kV imaging systems that are orthogonal or near orthogonal, an in-room standard diagnostic CT scanner that is geometrically linked to the treatment unit, and the Tomotherapy approach.

Although all of these units are allowed, some might not be appropriate for some disease sites. For example, orthogonal imaging techniques result in overlapping structures that are not as easily visualized compared to 3D cone-beam approaches. Simple portal imaging approaches that do not use computer assistance are not considered to be suitable for this study.

When the treatment equipment is not equipped with any device that allows direct visualization of anatomical structures using the treatment beam, the recommendations of AAPM Task Group Report 142 for testing the coincidence of the imaging and treatment reference points must be implemented. For example, verification of treatment and imaging isocenter coincidence must be performed routinely for the CyberKnife, Tomotherapy units as well as any BrainLab equipment that does not include an electronic portal imaging device (EPID) that intercepts the treatment beam.

The minimum IGRT requirement for each metastatic location is listed in Table 6-2. Volumetric imaging refers to 3D modalities (e.g., kV cone-beam, MV cone-beam, CT on rails) while orthogonal imaging refers to 2D modalities (e.g., kV OBI, ExacTrac). For volumetric imaging, appropriate CT window/level thresholds must be employed for registration at each metastatic location as outlined in Table 6-3. Additional IGRT may be employed at the discretion of the treating physician (i.e., orthogonal kV imaging prior to required volumetric imaging or volumetric imaging even if only orthogonal kV imaging is required). Note that when orthogonal kV imaging is employed for sites where respiratory motion is expected and not controlled via motion management techniques, care must be taken to ensure accurate targeting of the ITV within the treatment. For example, static kV imaging at an undetermined breath hold position would not be adequate IGRT for treating a free-breathing lung tumor.

Use of a shortened CT planning scan for registration may be important for IGRT systems that cannot handle a large number of CT slices. A subset of the planning CT scan can be uploaded to the IGRT system for localization of each metastasis. The CT data should include the metastasis of interest plus at least 5cm superiorly and inferiorly. Please note that composite dose must be calculated on a single CT scan encompassing all pertinent OAR.

Table 6.1-1

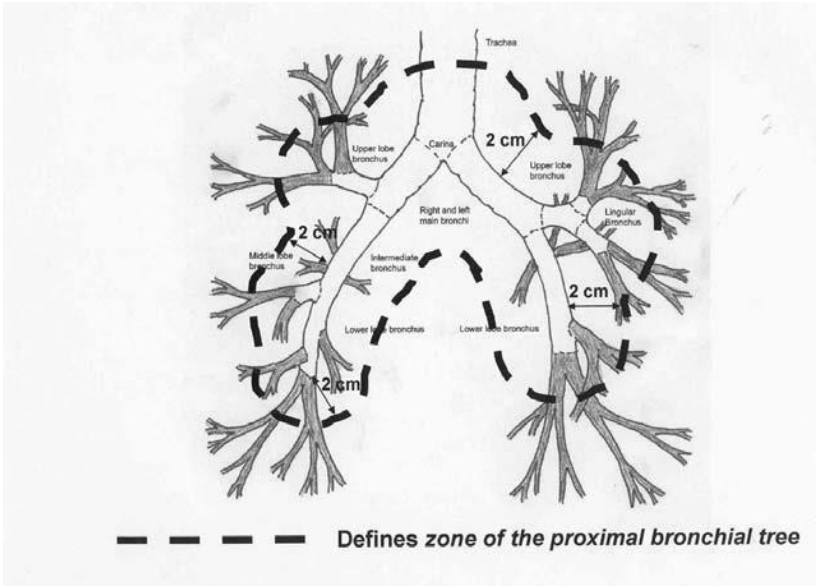
Metastatic Location	Minimum IGRT Requirement	
	No Fiducials	**With Fiducials****
Lung--Peripheral+	Volumetric (3D)	Orthogonal kV (2D)
Lung—Central+	Volumetric (3D)	Orthogonal kV (2D)
Mediastinal/Cervical LN	Volumetric (3D)	N/A
Liver+	Volumetric (3D)	Orthogonal kV (2D)
Spinal	Orthogonal kV (2D)	Orthogonal kV (2D)
Osseous*	Orthogonal kV (2D)	N/A
Abdominal-pelvic+	Volumetric (3D)	Orthogonal kV (2D)

*NOTE: When osseous/rib metastases are classified into another metastatic location, follow the IGRT guidelines for that site.

**NOTE: When a metastasis contains an implanted fiducial that is clearly visible on kV orthogonal or volumetric imaging, either method can be used

+NOTE: Registration using a soft tissue surrogate for the tumor is recommended for lung, liver, and abdominal-pelvic metastases for both 3D and 2D IGRT datasets.

Fig 6.2.1-1. Central lung definition.



6.2 Treatment Targeting Volume

6.2.1 Metastasis location

Because of the potentially increased risk of pneumonitis from combining SBRT with nivolumab, conservative SBRT planning is recommended for lung lesions. A tight dose constraint for lung (V20 < 4% with mean lung dose < 4Gy) is required to minimize the risk of radiation pneumonitis[109] (Table 6.5.5-1).

Lung Central: Central lung tumor is defined as GTV within 2 cm of proximal bronchial tree as described in RTOG 0813/0915: Tumor within or touching the zone of the proximal bronchial tree, defined as a volume 2 cm in all directions around the proximal bronchial tree (carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus right and left lower lobe bronchi). [See Figure 6.2.1-1] Tumors that are immediately adjacent to

mediastinal or pericardial pleura (PTV touching the pleura) also are considered central lung tumors. A visual representation is shown below in Figure 6-1.

Lung Peripheral: Metastases within the lung parenchyma with GTV outside of the proximal bronchial tree as described above.

Mediastinal: 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 sternal notch. Sternal metastases will be assigned to the mediastinal location based on potential for normal tissue toxicity.

Head and Neck: GTV occurring within head and neck parenchyma or cervical lymph node Levels I-VI and/or retropharyngeal spaces.

Liver: GTV arising within the liver. Rib or skin lesions immediately adjacent to the liver will be assigned to the liver metastasis location.

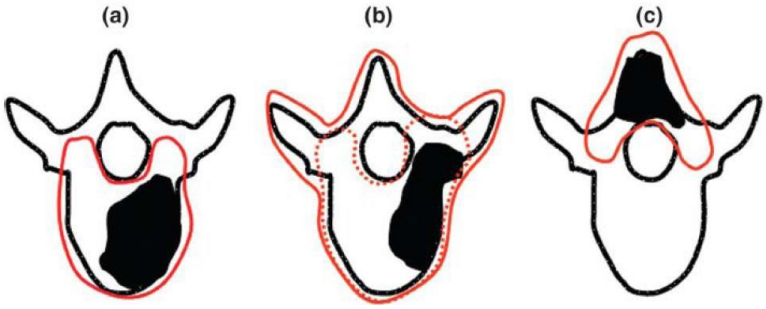


Fig 6.2.1-2. Diagram of Spine Metastasis and Target Volume

Spinal: Metastases will be assigned to the spinal/paraspinal site if the GTV arises within the vertebral bodies expanded by 1 cm. Spinal metastases, shown in Figure 6-2 in black, can involve:

- The vertebral body only OR
- The vertebral body and pedicle OR
- Posterior elements only

For each of these metastases, the PTV delineation will include:

- the involved vertebral body and both pedicles (solid red line in Figure 6.2.1-2a) OR
- a more generous delineation of the involved vertebral body and both pedicles (dashed red line in Figure 6.2.1-2b) OR
- the involved vertebral body, both pedicles, and the anterior and posterior elements of the spine (solid red line in Figure 6.2.1-2b) OR
- the spinous process and laminae (solid red line in Figure 6.2.1-2c)

The target volume may be chosen at the discretion of the treating Radiation Oncologist based on the extent of tumor involvement.

Metastases arising in the ribs within 1 cm of the edge of the vertebral body should be included in the spinal metastasis location but osseous metastases planning guidelines are to be used.

Osseous: GTV arising within an ossesous structure, part of the axial skeleton, not included in the

spinal definition.

- Rib metastases that are within 1 cm of the vertebral bodies will be classified into the spinal metastasis location given the similar normal tissues at risk.
- Rib/scapular metastases within the thorax adjacent to lung parenchyma will be classified into the lung metastasis location given the similar normal tissues at risk.
- Rib/osseous metastases adjacent to mediastinal or cervical structures will be classified into the mediastinal/cervical lymph node location given the similar normal tissues at risk.
- Rib metastases adjacent to the liver will be classified into the liver location given the similar normal tissues at risk
- Rib metastases adjacent to the stomach/abdominal wall will be classified into the intra-abdominal location given the similar normal tissues at risk
- Sternal metastases will be considered part of the mediastinal/cervical lymph nodes location given the similar normal tissues at risk.

Abdominal-pelvic: GTV arising within the anatomic space defined by the diaphragm superiorly, the genitourinary diaphragm inferiorly including the peritoneal and retroperitoneal spaces, not including liver, osseous, or spinal metastases.

Skin: GTV arising within the skin or the underlying subcutaneous tissue. If the volume of GTV mandates photon beams for treatment, the lesion will be considered part of the neighboring anatomic location.

Extremities: GTV arising within the upper and lower extremities.

6.3 Dosimetry

6.3.1 Target Volume Definition Based on Metastatic Location

Specific SBRT planning parameters depend on the location of the treated metastasis as well as mechanism used for motion management/evaluation. In general the GTV is defined as the entirety of the primary or metastatic lesions as seen on planning CT scan aided by additional diagnostic imaging studies (i.e., PET/CT or MRI). Use of additional diagnostic studies is left to the discretion of the treating physician. The CTV=GTV; there is no margin added for microscopic extension. In general, either a helical CT or 4DCT will be used for defining the GTV/ITV depending upon the tumor motion encountered, although both scans may be acquired at the time of simulation. Typically, the ITV is generated using either expiratory/inspiratory phase scans or from reconstructed maximum intensity projection (MIP) scans. Maximum/minimum intensity projections (MIP/MinIP) should be used with caution because the MIP reconstruction for lung or MinIP reconstruction for liver may erroneously define an ITV in cases of significant irregular breathing or when tumors abut soft tissue structures (e.g., the diaphragm for MIP) or fat (for the MinIP).

- A GTV to ITV expansion of greater than 1cm in any one direction is strongly discouraged and alternative respiratory management technique is suggested.
- When osseous/rib or skin metastases are classified into other specific metastatic locations, the planning guidelines for that metastatic location should be used. If rib metastases are grouped into the spinal metastasis location, then the metastasis should be contoured as defined for osseous metastases, but the prescription doses for the spinal region should be used.

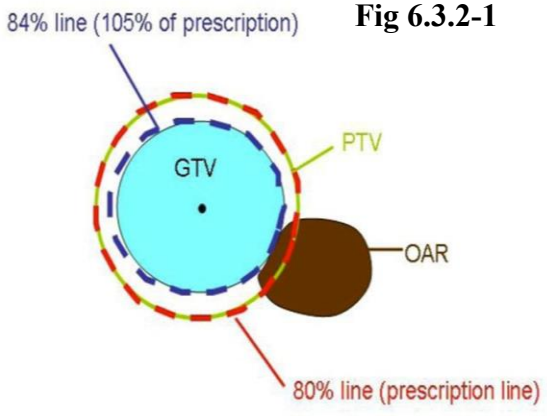
- Mediastinal lymph nodes should undergo motion assessment and an ITV should be generated to account for motion.
- In general CTV/ITV to PTV expansion will include 5mm circumferential margin and 7mm craniocaudal margin, but may be modified at the treating physician's discretion.

6.3.2 Planning Techniques

General Considerations: A variety of planning techniques can be used to deliver SBRT for each metastasis. General guidelines include the following:

- Multiple coplanar or non-coplanar beam arrangements are acceptable.
- Typically 7-13 static radiation beams with equal weighting are used. It is recommended that at least 10 beams be used when possible.
- A minimum field dimension of 3 cm should be observed treating small metastases.
- Dynamic conformal arcs are acceptable. It is recommended that arcs span at least 340 degrees.
- For non-IMRT or dose painting techniques, the conformal field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e., no additional "margin" for dose buildup at the edges of the blocks or MLC jaws beyond the PTV). The only exception will be when observing the minimum field dimension of 3 cm when treating small lesions.
- The prescription isodose line covering 95% the PTV will generally be 80-90% but may range from 60-90% where the maximum dose is 100%. As a result, a "hotspot" will exist within the PTV that is equal to the prescription dose divided by the prescription isodose line (i.e., 24Gy/0.6 = 40Gy when 24Gy is prescribed to the 60% isodose).
- Doses higher than the prescription isodose (i.e., hotspots) should be manipulated to occur within the target.

Fig 6.3.2-1



Dose calculations: All dose distributions shall include corrections for

tissue heterogeneities. IROC Houston approved algorithms must be used. All doses should be reported in terms of dose-to-water and not in terms of dose-to-medium.

Successful treatment planning will require accomplishment of all of the following criteria: These criteria will be assessed on dose calculated independently for each metastasis (i.e., not from composite dose calculations)

- Normalization: The treatment plan should be initially normalized such that 100% corresponds to the maximum dose within the PTV (MAXPTV). While this point will typically correspond to the PTV center of mass, it can be located elsewhere within the PTV.
- Prescription Isodose Surface Coverage: The prescription isodose surface will be chosen such

that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface. Doses less than 95% of the prescription dose are restricted to the outside edges of the PTV as shown in Figure 6-3. The prescription isodose surface selected MUST be ≥ 60% and ≤90% of the dose maximum within the PTV (MAXPTV). The MAXPTV corresponds to the normalization point (100%) of the plan as noted in number 1 above.

- Target Dose Heterogeneity: Rather than prioritizing target dose homogeneity, SBRT treatment planning prioritizes adequate minimum target coverage and rapid dose fall-off gradients outside of the target. Hot spots within targets are generally accepted without consequence since targets are mostly tumor. The only exception is when the hotspot within the PTV also intersects an OAR (see Figure 6.3.2-1).
- Critical Organ Doses: Respect all critical organ dose-volume limits listed in Section 6.5) below
- High-Dose Spillage:
  - Location: Any dose > 105% of the prescription dose should occur within the PTV and not within the normal tissues outside the PTV. See Figure 6.2.3-1.
  - Volume: Acceptable isodose distributions should be as conformal as possible. To this end the ratio of prescription isodose volume to PTV should be as small as possible.
    - The ratio of the prescription isodose volume to the PTV volume should be < 1.2. Acceptable variations include a ratio of 1.2-1.5. Ratios above 1.5 will be considered unacceptable variations. The prescription line for each lesion will be contoured for calculation of this ratio. The prescription line will be labelled as V_24. Contours with identical doses should be distinguished according to the convention described in section 6.5.
    - Guidelines for the ratio of the 50% prescription isodose volume to the PTV volume (R50%) and for the maximum dose at 2cm (D2cm) from the PTV are given in Table 6-4. Because it may become more difficult to restrict the 50% isodose volume when dose is summed from treatment of multiple metastases, this ratio should be evaluated for dose calculated for a single metastasis (i.e., not for composite dose). Additionally, the 50% isodose volume may be elongated deliberately in order to avoid OAR thereby making it difficult to meet the guidelines in Table 6-4. This is acceptable as long as normal tissue constraints are met.
    - Given that conformal tumor coverage is often more difficult to achieve in lung than in more homogeneous organs, these ratios should serve as a guide for liver, abdominal-pelvic, mediastinal/cervical metastases as well.
    - Elliptically shaped metastases as well as extremity metastases may not meet these guidelines. This is acceptable as long as normal tissue constraints are respected.
    - These criteria will not be required in treating very small tumors (<2.5 cm axial GTV dimension or < 1.5 cm craniocaudal GTV dimension) in which the required minimum field size of 3 cm (see Section 6.2) results in the inability to meet a conformity ratio of 1.5.

Table 6.3.2-2

PTV Volume (cc)	Ratio of 50% Prescription Isodose Volume to PTV Volume, R50%	Maximum Dose at 2cm (D2cm) from PTV in any direction as % of Prescribed Dose
1.8	< 7.5	<57.0
3.8	< 6.5	<57.0
7.4	< 6.0	<58.0
13.2	< 5.8	<58.0
22.0	< 5.5	<63.0
34.0	< 5.3	<68.0
50.0	< 5.0	<77.0
70.0	< 4.8	<86.0
95.0	< 4.4	<89.0
126.0	< 4.0	<91.0
163.0	< 3.7	<94.0

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

NOTE: For tumors within 2 cm of the skin, it may be difficult to meet the values for D2cm and R50%. In these cases, these criteria will not be used.

6.4 Planning Priorities

Every attempt should be made to successfully satisfy all of the planning goals and OAR criteria without deviation. In some circumstances, it may not be possible to meet all the ideal criteria leading to plans with an acceptable deviation. Thus, suggested priority of planning goals in order of importance is:

- Respect spinal cord, cauda equina, sacral plexus and brachial plexus dose constraints.
- Meet dose "compactness" constraints including the prescription isodose surface coverage, high dose spillage (location and volume), and intermediate dose spillage (D2cm, and R50%) as these define the "essence" of SBRT. Dose compactness should be assessed for plans based on treatment dose for a single lesion at a time.
- Meet critical structure constraints other than those listed in 1. The OAR constraints are last in priority (except for nervous system tolerance), because they are the least validated. The "essence" of a stereotactic plan is captured mostly in the dose compactness criteria, thereby justifying their higher priority. As an example in a case where not all goals can be met, it would be suggested to meet dose compactness goals without deviation even at the expense of a non-spinal cord normal tissue having acceptable deviation. Unacceptable deviations should be avoided in all cases.
- In cases where PTV coverage cannot be achieved while avoiding unacceptable deviations to OAR, coverage of a section of PTV including or immediately adjacent to the OAR may be as low as 70% of the prescription dose ONLY in this situation (see Section 6.5.4).
-

6.5 Critical Structures

6.5.1 Planning SBRT Near Prior Radiotherapy Volumes

The toxicity of delivering SBRT to multiple metastases in close proximity to prior conventionally fractionated EBRT volumes is not known. Therefore, overlap of protocol treatment SBRT isodoses with prior fractionated external beam volumes must be avoided.

6.5.2 Organs at Risk

For all metastases specific organs at risk (OAR) must be contoured. The specific OAR to be contoured will depend on the location of metastases to be treated. In general, OAR within 3cm any single metastasis should be contoured.

Lung Central/Lung Peripheral/Mediastinal/Head and Neck metastases:

- Proximal tracheobronchial tree (as defined by Timmerman et al 2006)
- Lungs, left/right/combined
- Heart
- Great vessels
- Esophagus (from cricoid to gastro-esophageal junction)
- Spinal cord
- Chest wall
- Brachial plexus
- Skin
- Liver
- Kidney, left/right
- Larynx
- Stomach
- Brain/brainstem
- Orbits
- Optic nerve/chiasm
- Oral cavity
- Cochlea
- Pharyngeal constrictors
- Parotid gland
- Submandibular gland
- Thyroid

Abdominal-pelvic metastases (liver, adrenal, lymph nodes):

- Stomach
- Duodenum
- Spinal cord
- Kidney, left/right
- Bowel,large/small
- Rectum
- Bladder
- Skin
- Lungs, left/right/combined

- Liver
- Chestwall
- Sacral plexus
- Cauda equina

Spinal Metastases:

- For all spinal metastases, the partial spinal cord volume defined as 5-6 mm above and below target should be contoured.
- For thoracic and cervical spinal metastases follow guidelines for pulmonary/ mediastinal/cervical metastases depending upon nearby organs at risk
- For lumbar metastases follow guidelines for Abdominal-pelvic metastases.

Osseous, Skin, Extremity Metastases:

- OAR for osseous, skin and extremity metastases will depend on the location of the osseous metastasis

NOTE: OAR listed above should be contoured if located within 3cm of the osseous metastases.

6.5.3 Contouring of Normal Tissue Structures

In order to verify each of these limits, the organs must be contoured such that appropriate volume histograms can be generated. Instructions for the contouring of these organs are as follows:

Spinal Cord

The spinal cord will be contoured based on the bony limits of the spinal canal ending at L2. The spinal cord should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV. This is best defined with fused MRI if available.

Cauda Equina

Starting at the conus (end of spinal cord, typically around L1 or L2) include the entire spinal canal into the sacrum to the filum. This is best defined with fused MRI if available.

Sacral Plexus

Include the nerve roots from L5 to S3 on each side from the neuroforamina to the coalescing of the nerves at the obturator internus muscle. This is best defined with fused MRI if available.

Esophagus

The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The esophagus should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV.

Brachial Plexus

The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neuroforamine on the involved side from around C5 to T2. However, for the purposes of this protocol, only the major trunks of the brachial plexus will be contoured using the subclavian and axillary vessels as a surrogate

for identifying the location of the brachial plexus. This neurovascular complex will be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the second rib. If PTV of all metastases are more than 10 cm away from the brachial plexus, this structure need not be contoured. This structure is best defined with fused MRI if available.

Heart

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

Trachea and Proximal Bronchial Tree

The trachea and proximal bronchial tree will be contoured as two separate structures using mediastinal windows on CT to correspond to the mucosal, submucosa and cartilage rings and airway channels associated with these structures. For this purpose, the trachea will be divided into two sections: the proximal trachea and the distal 2 cm of trachea. The proximal trachea will be contoured as one structure, and the distal 2 cm of trachea will be included in the structure identified as proximal bronchial tree.

Proximal Trachea

Contouring of the proximal trachea should begin at least 10 cm superior to the extent of the PTV for lung metastases or 5 cm superior to the carina (whichever is more superior) and continue inferiorly to the superior aspect of the proximal bronchial tree.

Proximal Bronchial Tree

The proximal bronchial tree will include the most inferior 2 cm of distal trachea and the proximal airways on both sides as indicated in Figure 6.2.1-1. The following airways will be included according to standard anatomic relationships: the distal 2 cm of trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the lingular bronchus, and the right and left lower lobe bronchi. Contouring of the lobar bronchi will end immediately at the site of a segmental bifurcation. If there are parts of the proximal bronchial tree that are within GTV, they should be contoured separately, as "proximal bronchial tree GTV", not as part of the "proximal bronchial tree".

Whole Lung

Both the right and left lungs should be contoured as one structure. Contouring should be carried out using pulmonary windows. All inflated and collapsed lung should be contoured; however, gross tumor (GTV) and trachea/ipsilateral bronchus as defined above should not be included in this structure.

Proximal Bronchial Tree Plus 2 cm

As part of determining if lung metastases are central or peripheral, adhering to the eligibility the zone of the proximal bronchial tree, the SBRT protocols defined an artificial structure

2 cm larger in all directions from the proximal bronchial tree. If the GTV falls within this structure, the patient is eligible for this protocol. Most treatment planning systems have automatic contouring features that will generate this structure without prohibitive effort at the time of treatment planning. This structure is not required by the protocol, but its construction is suggested to facilitate appropriateness of patient selection. Alternately, participating sites may use ruler tools in the treatment

planning software to ensure protocol compliance.

Skin

The skin will be defined as the outer 0.5 cm of the body surface. As such it is a rind of uniform thickness (0.5 cm) which envelopes the entire body in the axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations (e.g., the scalp on the top of the head).

Great Vessels

The great vessels (aorta and vena cava, not the pulmonary artery or vein) will be contoured using mediastinal windowing on CT to correspond to the vascular wall and all muscular layers out to the fatty adventitia. The great vessel should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV. For right sided tumors, the vena cava will be contoured, and for left sided tumors, the aorta will be contoured.

Stomach

The entire stomach and its contents should be contoured as a single structure as a continuation of the esophagus and ending at the first part of the duodenum.

Duodenum

The wall and contents of the 1st, 2nd, and 3rd parts of the duodenum will be contoured as one structure beginning where the stomach ends and finishing as the superior mesenteric artery crosses over the third part of the duodenum.

Bowel (Large/Small)

From the ileocecal area to include the ascending, transverse, descending and sigmoid colon as one structure.

Rectum

The entire rectum with contents from the peritoneal reflection of the sigmoid to the anus.

Bladder

This organ will be contoured as bladder wall exclusive of urinary contents

Kidney (renal cortex)

Both the right and left kidney, excluding renal pelvis/collecting system, should be contoured in their entirety (the renal cortex)

Liver

The entire liver minus the GTV targets.

Bile ducts

May use the portal vein from its juncture with the splenic vein to its right and left birfurcation in the liver as a surrogate to identify the bile ducts.

Femoral Heads

The ball of the head and socket joint.

PTV + 2 cm

As part of the QA requirements for "low dose spillage" listed above, a maximum dose to any point 2 cm away in any direction is to be determined (D2cm). To facilitate this QA requirement, an artificial structure 2 cm larger in all directions from the PTV is required. Most treatment planning systems have automatic contouring features that will generate this structure without prohibitive effort at the time of treatment planning. If possible this structure should be constructed as a single contour that is 2 cm larger than the PTV.

Other Structures

The constraints tables below contain other structures. These are required if the structure is within 10 cm of the PTV.

6.5.4 Contouring of the Target Lesions

The primary endpoint of this clinical trial is ORR of a non-irradiated lesion to the combination of immunotherapy and radiation therapy outside the field. In order to avoid the direct cytotoxic effect on the target lesion by scatter radiation, GTV of the target lesion will need to be contoured if within 10cm of the radiation field and ensure mean dose < 2Gy to the volume.

6.5.5 Critical Organ Dose-Volume Limits

Composite dose plans including all treated metastases and organs at risk are recommended to minimize toxicity from the field overlap. To facilitate composite planning, dose to all metastases should be calculated on a single CT scan simultaneously with in-plane resolution of at least 3 x 3 x 3mm. If this is not possible, composite plans should be generated incorporating the dose from each metastasis treated. The composite doses to critical normal tissues will be used to evaluate plan compliance.

Tables 6.5.5-1 lists maximum dose limits to a point or volume within several critical organs based on the 3 fraction SBRT.

The spinal cord doses are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation. However, some OAR (ie, the esophagus, trachea, bronchi and heart within the lung) may be situated adjacent to the treated GTV/PTV. As such, there is no specified limit as tumors that are immediately adjacent to that organ will not be able to be treated to any of the prescription doses without irradiating a small volume of that organ to the prescribed dose. In such a case, the planning needs to be done so that there is no hot spot within that organ, even if that organ is part of the GTV, PTV, i.e., that no part of any OAR receives more than 105% of the prescribed dose In addition, the volume of the OAR in question needs to be minimized, both in length and in the width (i.e., circumference), with efforts made to reduce the dose to the contralateral wall of the organ.

For non-spinal cord organs at risk with known sensitivity to high doses of radiation (including the bowel, esophagus, and stomach) included within a PTV or immediately adjacent to PTVs, a prescription dose at the lower end of acceptable variation should be used. Additionally, every effort should be made to cover the GTV with the prescription dose while ensuring rapid falloff to the organ at risk. Coverage of a section of PTV including or immediately adjacent to the OAR may be as low as 70% of the prescription dose ONLY in this situation. Every effort should be made to cover 100% of the GTV by the prescription dose at the lower end of acceptable variation. Since the tumor and normal tissue may not allow strict avoidance, the larger volume limits will not be scored as protocol Deviations Unacceptable if exceeded.

For tumors that are not immediately adjacent to any OAR, centers are encouraged to observe prudent treatment planning principles in avoiding unnecessary radiation exposure to critical normal structures; we expect that the OAR doses will be as low as achievable.

Table 6.5.5-1 OAR Dose Limits for 3 fraction SBRT

Serial Organ	Volume	Volume Dose (Gy)	Avoidance Endpoint (Reference)
Spinal Cord	<0.03 cc	18	Myelitis (Timmerman)
	<1.2 cc	13	Myelitis (Timmerman)
Ipsilateral Brachial Plexus	< 0.03 cc	26	Brachial Plexopathy (Timmerman)
	<3 cc	22	Brachial Plexopathy (Timmerman)
Cauda Equina	<0.03 cc	25.5	Neuritis (Timmerman)
	<5 cc	21.9	Neuritis (AAPM TG-101)
Sacral Plexus	<0.03 cc	24	Neuropathy (AAPM TG-101)
	<5 cc	22.5	Neuropathy (AAPM TG-101)
Trachea and Bronchus*	<0.03 cc	30	Stenosis/Fistula (Z4099)
	<5cc	25.8	Stenosis/Fistula (Timmerman)
Esophagus*	<0.03 cc	27	Stenosis/Fistula (Timmerman/RTOG0618)
	<5cc	17.7	Stenosis/Fistula (Z4099)
Heart/Pericardium	<0.03cc	30	Pericarditis (Z4099)
	<15 cc	24	Pericarditis (Z4099)
Great vessels*	<0.03cc	45	Aneurysm (Z4099)
	<10 cc	39	Aneurysm (Z4099)
Skin	<0.03cc	33	Ulceration (Z4099)
	<10cc	31	Ulceration (Timmerman)
Stomach	<0.03cc	30	Ulceration/Fistula (Timmerman)
	<10cc	22.5	Ulceration/Fistula (Timmerman)
Duodenum*	<0.03cc	24	Ulceration (Timmerman 2006)
	<10cc	15	Ulceration (Timmerman 2006)
Bowel*	<0.03 cc	34.5	Ulceration
	<20cc	24	Colitis/Fistula (Z4099)

Rectum*	<0.03 cc	49.5	Ulceration (Timmerman)
	<3.5 cc	45	Proctitis/Fistula (Timmerman)
	< 20 cc	27.5	Proctitis/Fistula (Timmerman)
Bladder	0.03cc	33	Cystitis/Fistula (Timmerman)
	<15 cc	16.8	Cystitis/Fistula (AAPM TG-101)
Penile bulb	< 3cc	25	Impotence (Timmerman)
Femoral heads	<10 cc	24	Necrosis (Timmerman)
Bile duct	< 0.03 cc	36	Stenosis (Timmerman)
Renal hilum/vascular trunk	<15 cc	19.5	Malignant Hypertension (Timmerman)
Parallel Organ	**Volume**	**Volume Dose (Gy)**	**Avoidance Endpoint (Reference)**
Lung (total)	< 4% lung volume	20	Pneumonitis/Lung Function
	Mean lung dose	<4 Gy	Pneumonitis (Timmerman)
	1500 cc	10.5	Basic Lung Function (Z4099)
	1000 cc	11.4	Pneumonitis (Z4099)
Ipsilateral kidney	<130 cc	12.3	Nephritis (Timmerman 2006)
Total Kidney	<200cc	15	Basic Renal Function
Liver	<700 cc	17.1	Liver function

*NOTE: Avoid circumferential irradiation.

6.6 Documentation Requirements

Treatment Interruptions

In general, treatment interruptions should be avoided by preventative medical measures and nutritional, psychological, and emotional counseling. Treatment breaks, including indications, must be clearly documented on the treatment record.

6.7 Compliance Criteria

Treatment Duration

Per Protocol: Treatment should be completed within 2 week. Acceptable Variation: Treatment completing >2 but < 3 weeks Unacceptable Deviation: Treatment completed > 4 weeks

PTV Dosimetry Compliance

A single prescription, 24Gy in 3 fractions, will be used for all tumor lesions receiving SBRT. Simultaneous integrated boost planning can be utilized to achieve this dose to a partial tumor volume when near a critical organ at risk. Acceptable variation in this clinical scenario is to deliver at least 7Gy per fraction to the 95% of GTV

Organ at Risk Dosimetry Compliance

Respect spinal cord, cauda equina, sacral plexus and brachial plexus dose constraints. Any dose to spinal cord, cauda equina, sacral plexus above that listed in Tables 6.5.5-1 will be considered an unacceptable deviation. For all other OAR, when OAR dose criteria provided in Section 6.5 cannot be accomplished by following planning priorities outlined in Section 6.4, doses to serial OAR of more than 105% of the dose prescribed to the PTV will be scored as unacceptable deviations. Doses to parallel OAR exceeding 110% of the dose prescribed to the PTV will be scored as unacceptable deviations

6.8 Radiation Therapy Adverse Events

All Radiation Therapy AEs will be scored according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4. Adverse events related to SBRT for the treatment of metastases are dependent on the location of the metastases treated as well as from exposure of surrounding normal tissues. For all treated metastases, fatigue may occur and should be transient lasting < 8 weeks. Other adverse events are likely to be related to the specific metastatic location receiving SBRT:

Lung (Central and Peripheral), Mediastinal, Head and Neck Metastases:

Cardiac and Pericardial Injury

Although cardiac and pericardial injury is uncommon in the conventionally fractionated course of RT, with large doses per fraction of SBRT a number of possible side-effects can be seen.

Esophageal/Pharynx/Oral Cavity/Salivary gland Injury

The radiation effects on the oral cavity, pharynx and esophagus can be acute: esophagitis (i.e., dysphagia, causing pain on swallowing, typically relatively soon after RT course is completed, and typically resolves on its own within days to a week or longer), mucositis, altered taste, xerostomia or chronic, typically manifesting with persistence of acute symptoms, dysphagia due to stenosis, or esophageal ulceration, with perforation in the extreme cases.

Brain/Brainstem/Optic apparatus/Cochlea Injury

The radiation effects on the CNS includes visual disturbances, auditory disturbances, memory problems, and radiation necrosis. While these are rare toxicities, radiation planning should ensure avoidance of the critical structures during SBRT.

Central Airway/Bronchial Injury

This bronchial injury with subsequent focal collapse of lung may impair overall pulmonary status. It also makes further assessment of tumor response more difficult as the collapsed lung approximates the treated tumor. Because atelectatic lung and tumor have similar imaging characteristics, radiology reports will often describe the overall process as progressive disease while the actual tumor may be stable or shrinking.

The consequences of bronchial toxicity, e.g., cough, dyspnea, hypoxia, impairment of pulmonary

function test parameters, pleural effusion or pleuritic pain (associated with collapse), should all be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), v. 4; MedDRA, v. 12.0.

Lung Injury

Radiation pneumonitis is a subacute (weeks to months from treatment) inflammation of the end bronchioles and alveoli. Radiation fibrosis is a late manifestation of radiation injury to the irradiated lung. Given the small amount of lung that is typically included in the SBRT portals, lung toxicity has not been as dose-limiting as in conventionally fractionated large field RT, but it is nevertheless seen, can be symptomatic, and may be confused with other causes of respiratory deterioration, including infections, and tumor recurrence**.**

Given that larger volumes of lung may be irradiated in this protocol compared to SBRT for primary tumors, it is very important that a Radiation Oncologist participate in the care of the patient, as the clinical picture may be very similar to acute bacterial pneumonia, with fatigue, fever, shortness of breath, nonproductive cough, and a pulmonary infiltrate on chest x-ray. The infiltrate on chest x-ray should include the area treated to high dose, but may extend outside of these regions. The infiltrates may be characteristically "geometric" corresponding to the radiation portal, but may also be ill defined.

Patients reporting symptoms as above will be promptly evaluated and treated. Mild radiation pneumonitis may be treated with nonsteroidal anti-inflammatory agents or steroid inhalers. More significant pneumonitis will be treated with systemic steroids, bronchodilators, and pulmonary toilet. Supra- and concurrent infections should be treated with antibiotics. Consideration of prophylaxis of opportunistic infections should be considered in immunocompromised patients.

Liver/abdominal-pelvic metastases

Very likely (80-90%): Fatigue (which generally goes away after the radiation therapy is completed)*;* skin irritation, redness, itchiness, discomfort; temporary changes in blood work (decrease in blood counts, increase in liver enzymes), without symptoms

Less likely (30%): Nausea, vomiting (during therapy) – more common if stomach or gastrointestinal track irradiated*;* gastric, esophagus, small bowel or large bowel irritation/ulceration, bleeding, fistula, obstruction or changes in motility following therapy (may require medications or surgery) (<10% permanent changes); chest wall pain, rib fracture (< 10%)

Less likely, but serious (<20%): Radiation-induced liver disease (RILD) (<5%). Classic RILD is a clinical diagnosis of anicteric ascites, hepatomegaly and elevation of alkaline phosphatase relative to other transaminases that may occur 2 weeks to 3 months following radiation to the Liver; non-classic RILD includes elevation of liver enzymes and/or any decline in liver function within 12 weeks from start of therapy (~20%). RILD can lead to liver failure that could lead to death. There is an increased risk of liver toxicity in patients with large tumors and in patients with pre-existing liver disease; permanent thrombocytopenia (<1%); this may lead to bleeding; kidney injury (<1%); this may lead to changes on imaging and more rarely the need for medication.

Spinal metastases

Radiation Myelitis

Given the proximity and position of spinal cord in relation to the radiosurgery target, every effort should be made to minimize the radiation dose to the spinal cord. Radiation myelitis is a subacute or chronic clinical syndrome after radiation. The symptoms may include paresthesia,sensory changes, and motor weakness including paralysis. There is no active treatment for radiation myelitis; therefore, it is

important to prevent any injury to the spinal cord. Corticosteroids are used when clinical symptoms develop.

Radiation Esophagitis

Patients with thoracic spine treatment will likely develop esophageal mucositis within the first 2 weeks. These symptoms subside with time; however, adequate symptomatic treatment including hydration is advised. There are no long-term adverse events reported with spine radiosurgery.

However, it is prudent to minimize the radiation spillage in the normal esophagus. The consequences of esophageal toxicity, e.g., swallowing difficulty, dysphagia, cough, dehydration, and fistula, should be documented.

Radiation Laryngitis or Pharyngitis

Patients with cervical spine treatment will likely develop laryngopharyngeal mucositis within the first 2 weeks. These symptoms subside with time; however, adequate symptomatic treatment including hydration is advised. No long-term laryngopharyngeal toxicity has been reported with spine radiosurgery. However, it is prudent to minimize the radiation spillage in the normal larynx and pharynx. The consequences of toxicity, e.g., swallowing difficulty, dysphagia, cough, dysphonia dehydration, and fistula, should be documented.

Tracheal Injury

Although no cases of tracheal injury have been reported with spine radiosurgery, it is prudent to minimize the radiation spillage in the normal trachea. The consequences of tracheobronchial toxicity, e.g., cough, dyspnea, hypoxia, impairment of pulmonary function test parameters, pleural effusion or pleuritic pain (associated with collapse), should be documented.

Radiation Pneumonitis

There have been no reported cases of symptomatic radiation pneumonitis with spine radiosurgery. However, it is prudent to minimize the radiation spillage in the lung tissue. It is strongly recommended to use radiation beams directed from posterior to avoid passage of radiation through the lungs. Patients with symptoms of pneumonitis will be promptly evaluated and treated. Mild radiation pneumonitis may be treated with non-steroidal anti-inflammatory agents or steroid inhalers. More significant pneumonitis will be treated with systemic steroids, bronchodilators, and pulmonary toilet. Supra- and concurrent infections should be treated with antibiotics. Consideration of prophylaxis of opportunistic infections should be considered in immunocompromised patients.

Compression Fracture of Treated Vertebra

Radiation doses in excess of 19 Gy for a single fraction are associated with higher rates of vertebral body compression (Saghal 2013). In this protocol, doses per fraction this high are not used, so that the estimated rate of vertebral body compression fracture following spinal metastases treatment should be rare.

Other Adverse Events

Short-term or long-term injury to the kidney or upper airway has not been reported. If other severe adverse events occur, details should be documented.

Osseous Metastases

Erythema, desquamation and alopecia are common side effects from radiation therapy for osseous metastases; other effects are determinate on location of metastasis, and may include pain, edema and

neuralgia.

Extremities Metastases:

Erythema, desquamation and alopecia are common side effects from radiation therapy for extremities. Other effects are determinate on location of metastasis, and may include pain, lymphedema.

Skin Metastases:

Erythema, desquamation and alopecia are common side effects from radiation therapy for radiation therapy to the skin. Other effects are determinate on location of metastasis, and may include pain, edema and neuralgia.

6.8.1 Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy

6.8.2 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 Flow Chart/Time and Events Schedule

Table 7.1-1: Screening Procedural Outline

Procedure	Screening Visit (Day -28 till Day -1 prior to Randomization)	Notes
Eligibility Assessments		
Informed Consent	x	
Inclusion/Exclusion Criteria	x	All inclusion/exclusion criteria should be assessed during screening and confirmed prior to randomization.
Medical History	x	
Review of pathology report	x	
Tumor Tissue Samples	x	Sufficient tumor tissue from the resected site of the disease (a block or a minimum of 15 slides) must be available and sent to Moffitt Cancer Center for biomarker analysis. If biopsy is performed at the treatment sites, fresh tumor will be requested to biomarker studies to establish tumor cell lines.
Safety Assessments		
Physical Examination	x	Including height
Vital Signs	x	Including weight, blood pressure (BP), heart rate (HR), temperature
Oxygen saturation	x	By pulse oximetry
Performance Status (ECOG)	x	Within 14 days prior to randomization
Assessment of Signs and Symptoms	x	Within 14 days prior to randomization
Electrocardiogram (ECG)	x	Within 14 days prior to randomization
Laboratory Tests	x	On site/local complete blood count (CBC) w/differential, Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, amylase, lipase, blood urea nitrogen (BUN) or serum urea level, creatinine, uric acid, Ca, Mg, Na, K, Cl, Glucose, endocrine panel (TSH, Free T4, Free T3), Hep B/C (HBV sAG, HCV RNA), within 14 days prior to randomization.
Pregnancy Test	x	WOCBP only (within 24 hours prior to start). Serum or Urine.
Efficacy assessment		
Surveillance assessments	x	Clinical exam and/or CT scan of the involved disease sites and all known sites of resected disease and brain MRI (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions).
Other		
Randomization	x	

Table 7.1-2: On-Treatment Assessments Week 1 - Week 9

Procedure	Wk1	Wk2	Wk3	Wk5	Wk7	Wk9	Notes
Safety Assessments							
Targeted Physical Examination	x	x	x	x	x	x	To be performed within 72 hours of dosing, or while undergoing radiation therapy as an on treatment visit
Vital Signs	x	x	x	x	x	x	Including BP, HR, temperature
Oxygen saturation	x	x	x	x	x	x	By pulse oximetry prior to dosing
Weight and performance status	x	x	x	x	x	x	Within 72 hours of dosing or while undergoing radiation therapy as an on treatment visit
Adverse Events Assessment	Continuously						See Section 6.8. and Section 8
Review of concomitant medications	x	x	x	x	x	x	
Pregnancy Test	x			x		x	Every 4 weeks ± 1 week. Serum or Urine.
Laboratory Tests	x		x	x	x	x	Within 72 hrs prior to dosing/SBRT to include CBC w/differential, LFT's, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (with reflexive Free T4/T3)
Exploratory Biomarker Assessments							
Plasma	x	x	x		x		Prior to dosing/SBRT
Peripheral Blood Mononuclear Cells (PBMCs)	x	x	x		x		Prior to dosing/SBRT
Efficacy Assessments							
Surveillance Assessments	Every 12 weeks (± 7 days) from first dose of study treatment through 12 months (until distant recurrence)						Clinical exam and/or CT scan of the involved disease sites and all known sites of resected disease and brain MRI (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions). Use same imaging method as was used at screening/baseline.
Study Drug							
Randomize	x						
Study Treatment	x	RT	x	x	x	x	First dose to be administered within 14 days of randomization. See Section 5.5.
Outcome Research							
EORTC-QLQ-C30	x				x		Prior to dosing. D1W1 should be completed after randomization but prior to dosing.
EQ5D (optional)	x				x		
WPAI:GH (optional)	x				x		
Health Care Resource Utilization (optional)	x				x		

Table 7.1-3: On-Treatment Assessments Week 11 - Week 21

Procedure	Wk11	Wk13	Wk15	Wk17	Wk19	Wk21	Notes
Safety Assessments							
Targeted Physical Examination	x	x	x	x	x	x	
Vital Signs	x	x	x	x	x	x	Including BP, HR, temperature
Oxygen saturation	x	x	x	x	x	x	By pulse oximetry prior to dosing
Weight and performance status	x	x	x	x	x	x	Within 72 hours of dosing
Adverse Events Assessment	Continuously						See Section 6.8. and Section 8
Review of concomitant medications	x	x	x	x	x	x	
Laboratory Tests	x	x	x	x	x	x	Within 72 hrs prior to dosing to include CBC w/differential, LFT's, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (with reflexive Free T4 and T3)
Pregnancy Test		x		x		x	Every 4 weeks ± 1 week. Serum or Urine.
Exploratory Biomarker							
Plasma		x					Prior to dosing
Peripheral Blood Mononuclear Cells (PBMCs)		x					Prior to dosing
Efficacy Assessments							
Surveillance Assessments	Every 12 weeks (± 7 days) from first dose of study treatment through 12 months (until distant recurrence)						Clinical exam and/or CT scan of the involved disease sites and all known sites of resected disease and brain MRI (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions). Use same imaging method as was used at screening/baseline.
Study Drug							
Study Treatment	x	x	x	x	x	x	See Section 5.5.
Outcome Research							
EORTC-QLQ-C30		x			x		Prior to dosing
EQ5D (optional)		x			x		
WPAI:GH (optional)		x			x		
Health Care Resource Utilization (optional)		x			x		

Table 7.1-4: On-Treatment Assessments Week 23 - Week 33

Procedure	Wk23	Wk25	Wk27	Wk29	Wk31	Wk33	Notes
Safety Assessments							
Targeted Physical Examination	x	x	x	x	x	x	
Vital Signs	x	x	x	x	x	x	Including BP, HR, temperature
Oxygen saturation	x	x	x	x	x	x	By pulse oximetry prior to dosing
Weight and performance status	x	x	x	x	x	x	Within 72 hours of dosing
Adverse Events Assessment	Continuously						See Section 6.8. and Section 8
Review of concomitant medications	x	x	x	x	x	x	
Laboratory Tests	x	x	x	x	x	x	Within 72 hrs prior to dosing to include CBC w/differential, LFT's, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (with reflexive Free T4 and T3)
Pregnancy Test		x		x		x	Every 4 weeks ± 1 week. Serum or Urine.
Exploratory Biomarker							
Plasma		x					Prior to dosing
Peripheral Blood Mononuclear Cells (PBMCs)		x					Prior to dosing
Tumor Tissue Sample		x					Biopsy at 6 months or at the time of progression
Efficacy Assessments							
Surveillance Assessments	Every 12 weeks (± 7 days) from first dose of study treatment through 12 months (until distant recurrence)						Clinical exam and/or CT scan of the involved disease sites and all known sites of resected disease and brain MRI (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions). Use same imaging method as was used at screening/baseline.
Study Drug							
Study Treatment	x	x	x	x	x	x	See Section 5.5.
Outcome Research							
EORTC-QLQ-C30		x			x		Prior to dosing
EQ5D (optional)		x			x		
WPAI:GH (optional)		x			x		
Health Care Resource Utilization (optional)		x			x		

Table 7.1-5: On-Treatment Assessments Week 35 - Week 45

Procedure	Wk35	Wk37	Wk39	Wk41	Wk43	Wk45	Notes
Safety Assessments							
Targeted Physical Examination	x	x	x	x	x	x	
Vital Signs	x	x	x	x	x	x	Including BP, HR, temperature
Oxygen saturation	x	x	x	x	x	x	By pulse oximetry prior to dosing
Weight and performance status	x	x	x	x	x	x	Within 72 hours of dosing
Adverse Events Assessment	Continuously						See Section 6.8. and Section 8
Review of concomitant medications	x	x	x	x	x	x	
Laboratory Tests	x	x	x	x	x	x	Within 72 hrs prior to dosing to include CBC w/differential, LFT's, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (with reflexive Free T4 and T3)
Pregnancy Test		x		x		x	Every 4 weeks ± 1 week. Serum or Urine.
Exploratory Biomarker							
Plasma							Prior to dosing
Peripheral Blood Mononuclear Cells (PBMCs)							Prior to dosing
Efficacy Assessments							
Surveillance Assessments	Every 12 weeks (± 7 days) from first dose of study treatment through 12 months (until distant recurrence)						Clinical exam and/or CT scan of the involved disease sites and all known sites of resected disease and brain MRI (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions). Use same imaging method as was used at screening/baseline.
Study Drug							
Study Treatment	x	x	x	x	x	x	See Section 5.5.
Outcome Research							
EORTC-QLQ-C30		x			x		Prior to dosing
EQ5D (optional)		x			x		
WPAI:GH (optional)		x			x		
Health Care Resource Utilization (optional)		x			x		

Table 7.1-6: On-Treatment Assessments Week 47 - Week 49

Procedure	Wk47	Wk49					Notes
Safety Assessments							
Targeted Physical Examination	x	x					
Vital Signs	x	x					Including BP, HR, temperature
Oxygen saturation	x	x					By pulse oximetry prior to dosing
Weight and performance status	x	x					Within 72 hours of dosing
Adverse Events Assessment	Continuously						See Section 6.8. and Section 8
Review of concomitant medications	x	x					
Laboratory Tests	x	x					Within 72 hrs prior to dosing to include CBC w/differential, LFT's, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (with reflexive Free T4 and T3)
Pregnancy Test		x					Every 4 weeks ± 1 week. Serum or Urine.
Exploratory Biomarker							
Plasma							Prior to dosing
Peripheral Blood Mononuclear Cells (PBMCs)							Prior to dosing
Efficacy Assessments							
Surveillance Assessments	Every 12 weeks (± 7 days) from first dose of study treatment through 12 months (until distant recurrence)						Clinical exam and/or CT scan of the involved disease sites and all known sites of resected disease and brain MRI (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions). Use same imaging method as was used at screening/baseline.
Study Drug							
Study Treatment	x	x					See Section 5.5.
Outcome Research							
EORTC-QLQ-C30		x					Prior to dosing
EQ5D (optional)		x					
WPAI:GH (optional)		x					
Health Care Resource Utilization (optional)		x					

Table 7.1-7: Follow-Up Procedural Outline

Procedure	Follow-up Visits 1[a] and 2	Survival, Follow up Visits[b]	Notes
Safety Assessments			
Targeted Physical	x		
Adverse Events	x	x	See Section 6.8. and Section 8
Laboratory Tests	x		
Pregnancy Test	x		Serum or urine
Review of Concomitant Medication	x		
Outcome Research			
EORTC-QLQ-C30	x		
EQ5D	x	x	
WPAI:GH	x		
Health Care Resource	x		
Efficacy Assessments			
Surveillance Assessment	Every 12 weeks (± 7 days) < 12 months Every 12 weeks (± 14 days) > 12 months through 24 months Every 6 months (± 4 weeks) > 24 months through and up to Year 5 Until distant recurrence. All time points are relative to the first dose of study treatment.		Clinical exam and/or CT scan of the involved disease sites and all known sites of resected disease and brain MRI (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions). Use same imaging method as was used at screening/baseline.
Survival status			
Survival status	x	x	Every 3 months, maybe accomplished by visit or phone contact, to include subsequent anti-cancer therapy

[a] Follow-up visit 1 (FU1) = 30 days (± 7 days) from the last dose, Follow-up visit 2 (FU2) = 84 days (± 7 days) from follow-up visit 1.

[b] First Survival Follow-up visit 30 days (± 7 days) after FU2

7.1.1 Retesting During Screening or Lead-in Period

Retesting of laboratory parameters and/or other assessments within any single Screening will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (ie, the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

Laboratory parameters and/or assessments that are included in Section 7. Screening Procedural Outline may be repeated in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

7.2 Study Materials

- NCI CTCAE version 4.0
- Nivolumab Investigator Brochure
- Ipilimumab Investigator Brochure
- Pharmacy binder
- Laboratory manuals for collection and handling of blood (including biomarker and immunogenicity) and tissue specimens
- Site manual for enrollment/randomization worksheets
- Manual for entry of local laboratory data
- Pregnancy Surveillance Forms
- PRO instruments.

7.3 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include weight, height, ECOG Performance Status, BP, HR, temperature and oxygen saturation by pulse oximetry and should be performed as noted in Table 5.1-1 Notes. Baseline signs and symptoms are those that are assessed within 14 days prior to randomization. Concomitant medications will be collected from within 14 days prior to randomization through the study treatment period and follow-up visits 1 and 2. During the Survival Follow-up visits subsequent only anti-cancer therapy will be collected.

Baseline local laboratory assessments should be done within 14 days prior to randomization to include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH, Free T4, Free T3, and Hep B and C testing (HBV sAg, HCV RNA) (Table 5.1-1). Pregnancy testing for WOCBP (done locally) must be performed within 24 hours prior to the initial administration of study drug at baseline and then every 4 weeks (+/- 1 week) during the treatment phase.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase. During the safety follow-up phase Table 5.1-7, toxicity assessments should be done in person. Once subjects reach the survival follow-up phase either in person or documented telephone calls to assess the subject's status are acceptable.

Adverse events and laboratory values will be graded according to the NCI CTCAE version 4.0.

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

On study local laboratory assessments should be done within 72 hours of dosing to include; CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3. Additional measures including non-study required laboratory tests should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug inducted liver enzyme elevations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline or are deemed irreversible.

Oxygen saturation by pulse oximetry should be obtained prior to each dosing and at any time a subject has any new or worsening respiratory symptoms. Accurate recording and documentation of oxygen saturation at two different activity levels is important because drug-related pulmonary toxicity can present initially as lower than baseline oxygen saturation. A reading at rest and on exertion should be obtained at each time point. The extent of the exertion should be based on the judgment of the investigator, but should remain consistent for each individual subject throughout the study. If the subject's status changes, the investigator can alter the extent of exertion based on their medical judgment. If a subject shows changes on pulse oximetry or other pulmonary related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary adverse events, the subject should be immediately evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity can be found in the nivolumab Investigator's Brochure.

Some of the previously referred to assessments may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

7.3.1 Imaging Assessment for the Study

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

7.4 Efficacy Assessments

Study evaluations will take place in accordance with the flow charts in Section 5. Baseline disease assessments should be performed within 28 days prior to the first dose utilizing CT or MRI. In addition to neck, chest, abdomen, pelvis, and brain, all known sites of disease should be assessed at baseline. Subjects will be evaluated for progression of target lesions or for development of new metastases beginning 12 weeks (+/- 7 days) relative to the first dose of study treatment, and will continue to have surveillance assessment every 12 weeks (+/- 7 days) for the first 12 months. From > 12 months to 24 months after randomization, efficacy assessments should be every 12

weeks (+/- 14 days). From > 24 months until Year 5 after first dose of study treatment, efficacy assessments should be performed every 6 months (+/- 4 weeks).

7.4.1 Definitions

Progression is defined as progressive tumor lesions per immune-related RECIST (irRECIST) definition, or appearance of one or more new Merkel cell carcinoma lesions, which can be local or distant in location from the irradiated lesions.

Local Control of Irradiated Lesion:

Progression of the irradiated tumor lesion is associated with aggressive tumor biologic features and resistance to radiation therapy.

Measurable Disease per irRECIST:

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:

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

Malignant lymph nodes: to be considered pathologically enlarged and measurable per RECIST 1.1, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

If the measurable disease is restricted to a solitary lesion (visceral or nodal), its neoplastic nature must be confirmed either by cytology/histology or by lesion progression certified on the next CT/MRI examination.

Nonmeasurable Disease per irRECIST:

Nonmeasurable lesions include all other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 and < 15 mm short axis), as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

7.4.2 Methods of measurements

- CT and MRI are an essential part of the work-up to establish recurrence. Conventional CT with IV contrast and MRI gadolinium should be performed with contiguous cuts of 10 mm or less slice thickness. Spiral CT should be performed using a 3- or 5-mm contiguous reconstruction algorithm; this specification applies to the tumors of the chest, abdomen and pelvis while head & neck tumors and those of the extremities usually require specific protocols. In each institute the same technique for CT/MRI should be used to characterize each new lesion.
- PET alone will not be considered for the disease assessment. Complementary CT and/or MRI

or biopsy must be performed in such cases.

- Cytology and/or histology are mandatory to confirm progression in doubtful lesions, cutaneous, subcutaneous or lymph node lesions. Histological or cytological evidence of progression should be attempted in all cases except for brain metastases.
- Clinically detected new lesions:
  - Superficial cutaneous lesions: the neoplastic nature must be confirmed by cytology/histology.
  - Deep subcutaneous lesions and lymph node lesions should be documented by ultrasound and histological/cytological evidence should be attempted. In absence of pathology report, lesion will be documented with a CT scan/MRI.
- Tumor markers or auto-antibodies alone cannot be used to assess disease progression.

7.4.3 Date of Progression

The first date when progression was observed is taken into account regardless the method of assessment. Therefore progression will be declared for any lesion when:

- Only imaging was performed and disease progression confirmed
- Only pathology was done and a new malignancy confirmed (in solitary or in doubtful lesions, cutaneous, subcutaneous or lymph node lesions)
- Both pathology and imaging were done and progression/malignancy confirmed. In this case, whatever examination come first its date is considered the date of relapse.

Note: for documentation, the date of progression is the date that the pathology and/or imaging confirms progression--not the date that the information was communicated to the subject.

7.5 Biobanking for Exploratory Correlative Studies

A variety of factors that could potentially predict clinical response to nivolumab will be investigated in peripheral blood and in tumor specimens taken from all subjects prior to treatment and as outlined in Section 7. Data from these investigations will be evaluated for associations with RFS, OS and distant metastasis-free survival and/or safety (adverse event) data. In addition, analyses of markers between the two treatment arms will provide the necessary data to identify and validate biomarkers with predictive vs prognostic value. All samples collected may also be used for future exploratory analyses (unless restricted by local requirements) to assess biomarkers associated with MCC or immunotherapy treatment. Complete instructions on the collection, processing, handling and shipment of all samples described herein will be provided in a separate procedure manual.

Tumor tissue and blood samples are crucial for correlative science studies to determine mechanisms by which SBRT and immunotherapy impact the anti-tumoral immune responses. A planned sample collection and preparation is necessary in order for these patient tissues can preserve integrity for future correlative biomarker studies. The collected samples may be assessed for correlative research to dissect underlying mechanisms of immune activation or tolerance in MCC or to discover novel therapeutic targets to enhance anti-tumoral immune responses using a variety of methodologies inclusive of, but not limited to ex vivo culture, flow cytometry, IHC, qRT-PCR, genetic mutation detection and fluorescent in-situ hybridization (FISH). The collected tissue will be stored at the MCC Tissue Core with the exception of fresh tumor tissue that will be

utilized for Merkel cell line establishment, which will be sent to the PI's laboratory.

7.5.1 Tumor Tissue Specimens

Pre-treatment tumor tissue specimens in the form of a paraffin embedded block or a minimum of 15 unstained slides will be submitted for PD-L1 IHC assessment. These biopsy samples should be from the most recent palliative surgery or biopsy. If surgical resection or biopsy are performed at one of the treatment sites, fresh tumor tissue for cell line establishment or fresh frozen tissue for tumor cell lysate will also be requested, but not mandated. Tumor specimens not used for clinical management will be utilized for research use. Approximately half of tumor tissue from biopsy or surgery will be stored as fresh frozen tissue for future IHC or preparation of tumor cell lysate. The remaining tumor will be sent directly to the PI's laboratory in order to establish cell line.

PD-L1 stained tissue sections will be assessed by a pathologist and membranous PD-L1 expression scored in tumor and immune cells if a minimum of a hundred (100) evaluable tumor cells are present. Subjects with positive, negative or indeterminate (membrane staining is obscured by high cytoplasmic staining or melanin content) IHC already has been well established at MCC tissue core for PD-L1. The cut-off for positive PD-L1 status was defined as IHC score > 2+ in more than 5% of tumor cells.

In addition, this pre-treatment tumor sample may be used to assess other putative predictive biomarkers of SBRT, nivolumab or ipilimumab efficacy and/or to better characterize the tumor-immune microenviroment post-resection. Of note, prior studies have suggest the expression of Merkel polyomavirus in tumor correlates with better responses to PD1 blockade[37]. Therefore, Merkel polyomavirus large T antigen will be evaluated by IHC or viral load evaluated by qRT-PCR. Various other molecular markers with potential predictive value for the treatment of MCC with nivolumab, ipilimumab 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, 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. Characterization of the tumor-immune microenvironment post-resection may involve assessment of other T cell checkpoint receptors and ligands (eg, Lag-3, Tim-3) and intratumoral immune cell subsets, including but not limited to NK cell, B-cell and T-cell lymphocytes.

Tumor tissue samples may also be collected during treatment, upon disease progression or completion of treatment. This second surgical resection or biopsy will be strongly recommended for correlative biomarker studies, but also not mandated. For lesions from active disease, fresh tumor may be used for cell line establishment. Otherwise, this sample may be used for preparation of tumor cell lysate for ex vivo recall responses, or for the assessment of markers implicated in resistance to immunotherapeutic agents, including but not limited to other T cell checkpoint receptors and ligands (eg, Lag-3, Tim-3) and intratumoral immune cell subsets, including but not limited to, T regulatory cells and myeloid derived suppressor cells. These samples may also be used to investigate the effect of nivolumab or ipilimumab the expression of potentially relevant predictive and/or prognostic MCC biomarkers, including, but not limited to BRAF mutation and PD-L1. Both the pre-treatment tumor sample and the sample collected upon recurrence may be retrospectively assessed for BRAF mutation status, as well as for the expression of other immune or MCC related genes, RNAs and/or proteins, or for the presence of immune cell populations using a variety of methodologies inclusive of, but not limited to IHC, qRT-PCR, genetic mutation detection and fluorescent in-situ hybridization (FISH).

7.5.2 Plasma Biomarkers

Blood samples for exploratory serum and plasma biomarker analyses will be drawn at the time points indicated in Section 7.1. Separate blood samples will be collected and processed for serum and plasma and then put in frozen storage. Serum and plasma samples may be assessed by ELISA, seromics, microRNA profiling, circulating tumor DNA measurements, metabolomics and/or other relevant multiplex-based protein assay methods for immune or Merkel cell carcinoma-related factors that will predict for SBRT, nivolumab or ipilimumab benefit or correlate with SBRT, nivolumab or ipilimumab-related adverse events. Numerous potential serum/plasma-based biomarkers are currently under investigation for their potential to predict or correlate with safety or efficacy to radiation therapy, nivolumab, ipilimumab or other immunotherapies, including but not limited to levels of soluble PD-L1, anti-tumor antibodies, cytokines, chemokines, inflammatory factors, NKG2D ligands (e.g., soluble MICA) and microRNAs (such as, but not limited to, miR-513 and miR19b. Plasma will be prepared along with PBMC.

7.5.3 Peripheral Blood Mononuclear Cells

Myeloid derived suppressor cells (MDSCs) and regulatory T cells (Tregs) are immune cell populations capable of suppressing T cell activation and proliferation. Low pre-treatment MDSC in peripheral blood may be associated with better overall survival in Merkel cell carcinoma patients treated with the immunotherapeutic agents. Peripheral blood samples will be taken prior to initiation of study therapy and at designated timepoints on-treatment (see Section 7.1 for additional details on the blood sample collection schedule) for PBMC and MDSC preparation. PBMC and MDSC samples may be retrospectively assessed for correlative research to dissect underlying mechanisms of immune activation or tolerance in MCC or to discover novel therapeutic targets to enhance anti-tumoral immune responses using a variety of methodologies inclusive of, but not limited to ex vivo culture, flow cytometry, IHC, qRT-PCR, genetic mutation detection and fluorescent in-situ hybridization (FISH). 15cc of whole blood will be collected at week 1, 2, 3, 7, 13 and 25. PBMC from blood will be prepared with Ficoll gradient prior to freezing for future flow cytometry and ex vivo culture studies. Plasma will be stored for plasma biomarker studies (Section 7.5.2). Additional 5cc of whole blood will be collected in Cytochex for flow cytometric analysis.

7.6 Outcomes Research Assessments

HRQoL will be assessed using the EORTC QLQ-C30. The EORTC QLQ-C30 is the most commonly used QoL instrument in skin cancer clinical studies. It is a 30-item instrument that has gained wide acceptance in oncology clinical studies. The EORTC QLQ-C30 comprises 6 functional scales (physical functioning, cognitive functioning, emotional functioning, social 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 the overall health status and global quality of life items, responses for all items are 4 point categorical scales ranging from 0 (Not at all) to 4 (Very much). The overall health status/quality of life responses are 7-point Likert scales.

General health status will be measured using the EQ-5D. The EQ-5D is a standardized instrument for use as a measure of self-reported health status. The EQ-5D comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety) and a visual analog rating scale (VAS). The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'Best imaginable health state' and 'Worst imaginable health

state'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents. The utility data generated from the EQ-5D is recommended for and commonly used in cost effectiveness analysis.

Work Productivity and Activity Impairment: General Health (WPAI:GH) is a 6-item questionnaire yielding four different types of scores. The WPAI:GH was created as a patient-reported quantitative assessment of the amount of absenteeism (work time missed), presenteeism (impairment at work), work productivity (overall work impairment/absenteeism plus presenteeism) and daily activity impairment attributable to general health. WPAI:GH outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, ie, worse outcomes. The recall period in all WPAI:GH validation studies is 7 days. The general literature on recall burden suggests that a longer recall period would not be suitable for the type of information being elicited in the WPAI:GH. In theory, a shorter recall period would improve accuracy of WPAI:GH responses, but this has not been tested. Assessment of work productivity will be conducted at each site (or remotely) with the appropriately translated and validated version of the WPAI:GH. All PRO instruments will be administered during on-study, and follow-up phases as outlined in Tables of Section 5.1, respectively, to all randomized subjects. Healthcare resource utilization data (eg, hospitalizations, non-protocol specified medical visits, diagnostics, etc) will be collected for all randomized subjects. The resource utilization capture is specific to hospital admission utilization data and non-protocol specified visits related to study therapy. Resource utilization questions will be asked as outlined in Table of Section 5.1 during screening, on-study, and follow-up phases, respectively.

8 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting 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 and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

8.1 Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see
- NOTE below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.) Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Deaths due to disease progression will not be reported as an SAE.

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

Any component of a study endpoint that is considered related to study therapy (eg, death is an

endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE.

NOTE:

The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs

8.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's or the legal representative's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg. a follow-up skin biopsy).

The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

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.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

For studies capturing SAEs/pregnancies through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

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.

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 24 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.

8.2 Nonserious Adverse Events

A nonserious adverse event is an AE not classified as serious.

8.2.1 Nonserious Adverse Event Collection and Reporting

The collection of new nonserious AE information should begin at initiation of study drug and continue until 100 days from the last dose of study drug. Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause withholding 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 (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

8.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

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

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

8.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours and in accordance with SAE reporting procedures.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue 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 contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

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

8.5 Overdose

All occurrences of overdose must be reported as SAEs.

8.6 Potential Drug Induced Liver Injury (DILI)

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 is defined as:

AT (ALT or AST) elevation > 3 times ULN (5 x ULN in patients with liver metastasis) AND

Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

8.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

8.8 Protocol Monitoring Committee

A Protocol Monitoring Committee (PMC) will be established to provide oversight of safety and efficacy considerations in the protocol. The PMC meets monthly and reviews accrual, patterns and frequencies of all adverse events, protocol violations and when applicable, internal audit results.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Design

The result of Nivolumab alone clinical trial for virus-associated cancers including MCC is pending, but the estimated objective response rate with Nivolimab alone is estimated around 17% based on Avelumab and Pembrilozumab trial for patients without prior immunotherapy exposure or previously failed prior immunotherapy (refractory). Therefore, we will consider a 17% response rate as not warranting further study. We will use a 40% response rate as a promising result to pursue further study. In other words, we are interested in at least 23% improvement in treatment efficacy for either one of the two arms: Nivolimab + SBRT + Ipilimumab (Arm B) or Nivolimab + Ipilimumab (Arm A). Since both treatments are experimental therapy in this targeted population, Simon two-stage design is used to evaluate the treatment efficacy. To determine the best treatment arm, we utilize a Bayesian posterior probability with Simon two-stage design in a two-arm randomized trial in order to have objective comparison between the two arms[110]. This design has several unique features: (1) Randomization reduces selection bias and allows a greater degree of comparability, (2) The Simon two-stage design will allow for termination of an ineffective drug earlier when compared to historical control data, and (3) The Bayesian posterior probability provides additional power to detect a definitive differential treatment effect. This design has been employed in various lung cancer trials at Moffitt Cancer Center.

9.1.1 Sample Size Calculation

From historical data, we will consider 17% response rate as not warranting further study. We will use 40% response rate as a promising result to pursue further study. In other words, we are interested in at least 23% (40% vs. 17%) improvement in treatment efficacy for arms B versus A. For each arm, using a Simon Mini-Max two-stage design with 10% type I error rate and 10% type II error rate, 16 patients will be enrolled in the first stage of the trial. If 2 or fewer patients respond, the treatment will be stopped. If 3 or more patients show a response, 8 additional patients (a total of 24 patients per group) will be enrolled. If the total number responding is 6 or less, we will conclude that the treatment is not effective. If both arms fail at the first or second stage, the trial will stop. No winner will be claimed. The sample size will be 32 if both arms fail at the first stage and 40 if only one arm fails at the first stage. If only one arm pass the second stage, the arm will be the winner. If both arms pass the second stage, we will use the posterior probability, $Pr(B > A)$, (probability of the response rate in arm B higher than in arm A) to select the winner. A non-informative prior of beta distribution, beta(1,1) in both arms will be used to calculate the posterior probability. Arm B will be claimed as the winner if $Pr(B > A) > \delta = 0.8$.

Operating Characteristics

The operating characteristics of the design is evaluated by simulation (10000 times) using R software (www.r-project.org) with "clinfun" package. In particular, we are interested in the probability of (correctly) selecting an arm as superior to the other arm if it is truly superior, and conversely, the probability of (incorrectly) selecting an arm that is no better than the other arm.

Power Analysis

Power: Assuming that the true probabilities of response in arms B and A are 40% and 17%, respectively (scenario 1: 23% difference of response rate), the overall probability (power) of correctly choosing arm B as superior is 85% on the basis of superiority shown at the end of the trial.

The probability of stopping arm A early and declaring arm B superior at the end of the trial is 81%. There are 9% of both arms passing the second stage with 4% claiming arm B as the winner by the Bayesian posterior probability. In a 18% difference of response rate, the overall power is 74% and 77% for the comparison of arms B and A with 35% versus 17% (scenario 2) and 40% versus 22% (scenario 3), respectively. Proportion of both arms passing the 2nd stage is 8% in scenario 2 (scenario 3: 23%), with 2% (scenario 3: 10%) claiming arm B as the winner by the Bayesian posterior probability.

Type I error

Type I error: In the null hypothesis of a 17% response rate in both arms, there are 9% misclassifying arm B as winner (i.e., 9% type I error). Among them, only 1% has both arms passing the 2nd stage, and less than 0.01% misclassify arm B as winner.

Summary

Summary: With δ=0.8, the design has a 85% power to detect a 23% difference of response rate. The power decreases to a range of 74-77% to differentiate a 18% difference of response rate. The type I error is controlled at 9% when both arms have a 17% response rate.

Tables of Power Analysis

Scenario 1: Arm B=0.4 versus Arm A=0.17 (Overall power of Arm B= 85%)

	B.fail.stage1	B.fail.stage2	B.pass
A.fail.stage1	0.01	0.04	0.42
A.fail.stage2	0.01	0.03	0.39
A.pass	0	0.01	0.09

Both arms passing the 2nd stage: 9%. Among them, Arm B claims 4.31% as winner

Overall power of Arm B= 85%

Scenario 2: Arm B=0.35 versus Arm A=0.17 (Overall power of Arm B= 74%)

	B.fail.stage1	B.fail.stage2	B.pass
A.fail.stage1	0.02	0.08	0.38
A.fail.stage2	0.02	0.07	0.33
A.pass	0	0.02	0.08

Both arms passing the 2nd stage: 8%. Among them, Arm B claims 2.33% as winner

Overall power of Arm B= 74%

Scenario 3: Arm B=0.4 versus Arm A=0.22 (Overall power of Arm B= 77%)

	B.fail.stage1	B.fail.stage2	B.pass
A.fail.stage1	0.01	0.03	0.25

A.fail.stage2	0.01	0.03	0.41
A.pass	0.01	0.02	0.23

Both arms passing the 2nd stage: 23%. Among them, Arm B claims 9.89% as winner

Overall power of Arm B= 77%

Scenario 4: Arm B=0.17 versus Arm A=0.17 (Type I error= 8.89%)

	B.fail.stage1	B.fail.stage2	B.pass
A.fail.stage1	0.22	0.2	0.04
A.fail.stage2	0.2	0.19	0.04
A.pass	0.05	0.04	0.01

Both arms passing the 2nd stage: 1%. Among them, Arm B claims 0.01% as winner

Type I error= 8.89%

9.1.2 Populations for Analyses

- All enrolled subjects: All subjects who signed an informed consent form and were registered.
- All randomized subjects: All subjects who were randomized to any treatment arm in the study.
- All treated subjects: All subjects who received any study drug nivolumab, ipilimumab or SBRT.
- Biomarker subjects: All randomized subjects with available biomarker data (PD-L1 expression status, Merkel cell polyomavirus expression, and other assays).

9.2 Endpoints

9.2.1 Primary Endpoint(s)

The primary endpoint is ORR. The primary endpoint of ORR will be the sum of the rate of complete response, partial response and stable disease of non-irradiated target lesions.

9.2.2 Secondary Endpoint(s)

The first secondary endpoint is PFS. PFS will be programmatically determined based on the disease progression date provided by the investigator and is defined as the time between the date of randomization and the date of first progression (local, regional or distant metastasis) or death (whatever the cause), whichever occurs first. (Note: a subject who dies without reported progression will be considered to have progressed on the date of death.) For subjects who remain alive and whose disease has not progressed, PFS will be censored on the date of last evaluable disease assessment.

The second secondary endpoint (OS) is defined as the time between the date of randomization and the date of death. For subjects without documentation of death, OS will be censored on the last

date the subject was known to be alive. OS will be followed continuously while subjects are on the study drug and every 3 months via in-person or phone contact after subjects discontinue the study drug.

To third secondary endpoint to compare the local control of irradiated tumor provided by SBRT in combination with nivolumab versus nivolumab and ipilimumab will be assessed by the local control rate of the irradiated lesion.

The fourth secondary endpoint (to assess the safety and tolerability of nivolumab, SBRT and ipilimumab) will be measured by the incidence of adverse events, serious adverse events, deaths, and laboratory abnormalities.

The fifth secondary endpoint (to evaluate PD-L1 expression as a predictive biomarker) will be measured by the endpoint RFS based on PD-L1 expression level.

The sixth secondary objective (to evaluate HRQoL) will be measured by mean changes from baseline in the EORTC-QLQ-C30 global health status/QoL composite scale and by mean changes from baseline in the remaining EORTC QLQ-C30 scales in all randomized subjects.

9.3 Analyses

9.3.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment arm as randomized using descriptive statistics for all randomized subjects.

9.3.2 Efficacy Analyses

9.3.2.1 Primary Endpoint Methods

Objective-response rate (ORR) including Complete Response (CR) rate, Partial Response (PR) rate, and Stable Disease (SD) rate will be calculated through exact binomial distribution with a 2-sided 95% confidence interval among patients who obtain a least one dose of study drug.

9.3.2.2 Secondary Endpoint Methods

The PFS analyses will be conducted using a two-sided log-rank test stratified by prior immunotherapy exposure in randomized subjects. The hazard ratio and corresponding two-sided 95% CI will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors. PFS curves, PFS medians with 95% CIs, and PFS rates at 6, 12, 24 and 36 months with 95% CIs will be estimated using Kaplan-Meier methodology.

The OS analysis will be conducted using a two-sided log-rank test stratified by prior immunotherapy exposure at screening in randomized subjects. The hazard ratio and corresponding two-sided (1-adjusted α)% CI will be estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by the above factors. OS curves, OS medians with 95% CIs and OS rates at 12 and 24 months with 95% CIs will be estimated using Kaplan-Meier methodology.

The local control (LC) of irradiated lesions will be conducted using a two-sided log-rank test stratified by prior immunotherapy exposure at screening in randomized subjects. The hazard ratio and corresponding two-sided (1-adjusted α)% CI will be estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by the above factors. LC curves,

LC medians with 95% CIs and LC rates at 12 and 24 months with 95% CIs will be estimated using Kaplan-Meier methodology.

To evaluate PD-L1 expression as a predictive biomarker, a Cox proportional hazards model will be used to test the interaction between PD-L1 expression (positive vs negative) and treatment arm for the primary and secondary endpoint. Additionally, ORR will be analyzed within each PD-L1 expression subgroup (positive and negative) including log-rank tests and hazard ratios with corresponding confidence intervals. PFS curves and medians will be estimated using Kaplan-Meier methodology. These analyses will be descriptive and not adjusted for multiplicity.

9.3.3 Safety Analyses

Safety analyses will be performed in all treated subjects. Descriptive statistics of safety will be presented using NCI CTCAE version 4.0 by treatment group. All on-study AEs, treatment-related AEs, SAEs, and treatment-related SAEs will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade NCI CTCAE v 4.0 criteria.

9.3.4 Outcomes Research Analyses

EORTC QLQ C-30

The analysis of EORTC QLQ C-30 will be performed in all randomized who have an assessment at baseline and at least one follow-up assessment.

All scales and single items are scored on a categorical scales and linearly transformed to 0-to-100 scales with higher scores for a functional scale representing higher levels of functioning, higher scores for the global health status/quality of life representing higher levels of global health status/quality of life and higher scores for a symptom scale representing higher level of symptoms.

EORTC QLQ C-30 global health status/QoL composite scale data and the remaining EORTC QLQ C-30 scale data will be summarized by timepoint using descriptive statistics for each treatment arm. Exploratory analyses may be performed to examine differences between the 2 arms.

10 STUDY MANAGEMENT

10.1 Compliance

10.1.1 Compliance with the Protocol and Protocol Revisions

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

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

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

10.1.2 Required Documentation

Before the study can be initiated at any site, the site will be required to provide regulatory documentation to the Moffitt Clinical Research Network (MCRN) at Moffitt Cancer Center. Sites must provide a copy of their informed consent to the MCRN Coordinating Center for review and approval prior to submission of any documents to the site's IRB. Any changes re- quested by the site's IRB must be provided to the MCRN staff for review and approval prior to resubmission to the IRB.

The MCRN Coordinating Center must receive the following trial specific documents either by hardcopy, fax, or email before a site can be activated for any trial:

1. IRB Approval Letter that includes the protocol version and date
2. FDA Related Forms 1572/1571/310 as appropriate
3. Signed Protocol Title Page
4. IRB Approved Consent Form
5. Site Delegation of Responsibility Log
6. Signed Financial Interest Disclosure Forms (principal and sub investigators)
7. Updated Investigator/Personnel documents (CVs, licenses, Conflict of Interest statements, etc.) as needed
8. Updated Laboratory Documents (certifications, normal ranges, etc.) as needed
9. Signed protocol specific Task Order

A study initiation visit (or teleconference) will be held prior to the start of any study related activity at the site. Attendance is required for:

- The site PI and appropriate research staff
- Moffitt PI and MCRN research coordinator

The requirements of the protocol and all associated procedures and processes will be reviewed and agreed upon prior to the activation of the study. The MCRN utilizes the EDC system, OnCore. OnCore training will be scheduled if indicated with the appropriate staff from the site.

10.1.3 Registration Procedure

All subjects must be registered with the MCRN Coordinating Center to be able to participate in a trial. The participating site must fax or email the completed study specific eligibility checklist and registration forms, supporting documents and signed informed consent to the Coordinating Center. Unsigned or incomplete forms will be returned to the site. Once documents are received, the MCRN Research Coordinator will review them to confirm eligibility and to complete the registration process. If eligibility cannot be confirmed, the research coordinator will query the site for clarification or additional documents as needed. Subjects failing to meet all study eligibility requirements will not be registered and will be unable to participate in the trial.

Upon completion of registration, the MCRN Research Coordinator will provide the participating site with the study sequence number. Within 24-48 hours after registration, it is the site's responsibility to:

- Enter the demographic and on-study patient information into the OnCore database.
- Order investigational agent(s) if indicated per protocol.

It is the responsibility of the participating Investigator or designee to inform the subject of the research treatment plan and to conduct the study in compliance with the protocol as agreed upon with Moffitt Cancer Center and approved by the site's IRB.

To register a patient send the completed signed eligibility checklist along with supporting documentation to the MCRN via email at affiliate.research@moffitt.org or via fax at 813-745-5666, Monday through Friday between 8:00AM and 5:00PM(EST).

10.1.4 Adherence to Protocol

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

10.1.5 Emergency Modifications

Moffitt Cancer Center and Affiliate investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior H. Lee Moffitt Cancer Center or their respective institution's approval/favorable opinion.

For Institutions Relying on Moffitt's IRB:

For any such emergency modification implemented, a Moffitt IRB modification form must be completed by Moffitt Research Personnel within five (5) business days of making the change.

For Institutions Relying on Their Own IRB:

For Affiliate investigators relying on their own instution's IRB, as soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to Moffitt Principal Investigator for agreement and the Affiliate institution's IRB for review and approval. (Once IRB's response is received, this should be forwarded to the MCRN.)

10.2 Data Management and Monitoring

Data will be captured in OnCore, Moffitt's Clinical Trials Database. Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly to verify data is accurate, complete, and verifiable from source documents; and the conduct of the trial is in compliance with the currently approved protocol/ amendments, Good Clinical Practice (GCP), and applicable regulatory requirements.

To obtain access to OnCore, the site research staff must complete an OnCore Access Request Form and a Moffitt Information Systems Confidentiality Agreement (provided in the MCRN Handbook at the site initiation visit) and submit both to the Coordinating Center. Once the completed forms are received, the site coordinator will receive VPN access, logon/password, and information on how to access OnCore using the VPN. The MCRN Coordinating Center will provide OnCore training to the site once initial access is granted and on an ongoing basis, as needed.

10.2.1 Record Retention

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

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

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

10.2.2 Obligations of Investigators

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

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the eCRFs. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by

the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

10.3 Ethical and Legal Aspects

10.3.1 Ethical and Legal Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the investigator abide by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the EC/IRB approval must be obtained and also forwarded to Bristol-Myers-Squibb.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by the investigator without discussion and agreement by Bristol-Myers-Squibb. However, the investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC/IRB/Bristol-Myers-Squibb approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and, if appropriate, the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution. Any deviations from the protocol must be explained and documented by the investigator.

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

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and properly documented.

10.3.2 Subject Information and Consent

Each subject/legal representative or proxy consenter will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the subject/legal representative or proxy consenter voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The subject/legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject's clinical record must clearly show that informed consent was obtained prior to these procedures.

1. If the patient is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of Bristol-Myers-Squibb and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

2. For minors or adults under legal protection, consent shall be given by the legal guardian(s). The consent of a minor or adult under legal protection shall also be requested where such a person is able to express his/her own will. His/her refusal or the withdrawal of his/her consent may not be disregarded.

3. In emergency situations, when prior consent of the patient is not possible, the consent of the patient's legal representative(s) or proxy consenter, if present, should be requested. The patient should be informed about the study as soon as possible and his/her consent to continue the study should be requested.

The informed consent form and any other written information provided to subjects/legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and/or the written informed consent form. The investigator will inform the subject/legal representative or proxy consenter of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB`s approval/favorable opinion in advance of use.

10.4 Publication Policy

Bristol-Myers-Squibb recognizes the right of the investigator to publish results upon completion of the study. However, the investigator must send a draft manuscript of the publication or abstract to Bristol-Myers-Squibb at least thirty days in advance of submission in order to obtain approval prior to submission of the final version for publication or congress presentation. This will be reviewed promptly and approval will not be withheld unreasonably. In case of a difference of opinion between Bristol-Myers-Squibb and the investigator(s), the contents of the publication will be discussed in order to find a solution which satisfies both parties. All relevant aspects regarding data reporting and publication will be part of the contract between Bristol-Myers-Squibb and the investigator/institution.

The Principal Investigator should ensure that the information regarding the study be publicly available on the internet at www.clinicaltrials.gov.

10.5 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

11 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. **Expanded definition** Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (e.g., calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

12 LIST OF ABBREVIATIONS

Term	Definition
ADA	anti-drug antibody
AE	adverse event
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	aminotransaminases
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
HCG	human chorionic gonadotrophin
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CL	clearance
cm	centimeter
Cmax	maximum observed concentration
CMV	cytomegalovirus
CNS	central nervous system
CR	Complete response
CRF	Case Report Form, paper or electronic
CT	computed tomography
CTA	Clinical trial agreement
CTCAE	common terminology criteria for adverse events
CTLA-4	cytotoxic T lymphocyte associated antigen-4
CTV	Clinical Target Volume
DILI	drug-induced liver injury
dL	deciliter
DLT	dose limiting toxicity
DMC	data monitoring committee

DMFS	distant metastases-free survival
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EFS	Event-free survival
ELISA	enzyme-linked immunosorbent assay
EOI	end of infusion
EORTC	European Organization for Research and Treatment of Cancer
EDC	Electronic Data Capture
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GTV	Gross Tumor Volume
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	heart rate or hazard ratio
HRQoL	Health Related Quality of Life
HRT	hormone replacement therapy
IB	Investigator Brochure
irAE	immune-related adverse event
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	Interferon
IHC	immunohistochemistry
IMP	investigational medicinal product
IP	Investigational product
IRB	Institutional Review Board
ITSM	immunoreceptor tyrosine-based switch motif
ITV	Internal Target Volume
IU	International Unit
IV	intravenous
IVRS	Interactive Voice Response System
kg	kilogram

L	liter
LDH	lactate dehydrogenase
LFT	liver function test
MDSC	Myeloid derived suppressor cells
mg	milligram
mL	milliliter
MLR	mixed lymphocyte reaction
MRI	Magnetic resonance imaging
MTD	maximum tolerated dose
MU	million units
µg	microgram
N	number of subjects or observations
N/A	not applicable
NSCLC	non-small cell lung cancer
NED	no evidence of disease
ng	nanogram
NIMP	non-investigational medicinal products
OAR	Organs at Risk
Obs.	Observation
ORR	Objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD-1	programmed death receptor-1
PFS	Progression free survival
PK	pharmacokinetics
PPK	Population pharmacokinetic
PR	Partial response
PRO	Patient Reported Outcome
PTV	Planning Target Volume
QoL	Quality of Life
QLQ-C30	Quality of Life Questionnaire-Core
RCC	renal cell carcinoma

RT	radiation therapy
TCR	T-cell receptor
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBRT	Stereotactic Body Radiation Therapy
SNP	single nucleotide polymorphism
T-HALF	Half life
Tmax	time of maximum observed concentration
ULN	upper limit of normal
US	United States
VAS	visual analog rating scale
Vz	Volume of distribution of terminal phase (if IV and if multi-exponential decline)
WBC	white blood cell
WOCBP	women of childbearing potential
WPAI:GH	Work Productivity and Activity Impairment : General Health

13 REFERENCES

1 Hodgson, N. C. Merkel cell carcinoma: changing incidence trends. *Journal of surgical oncology* **89**, 1-4, doi:10.1002/jso.20167 (2005).

2 Lebbe, C. *et al.* Diagnosis and treatment of Merkel Cell Carcinoma. European consensus-based interdisciplinary guideline. *European journal of cancer* **51**, 2396-2403, doi:10.1016/j.ejca.2015.06.131 (2015).

3 Veness, M. J. & Harris, D. Role of radiotherapy in the management of organ transplant recipients diagnosed with non-melanoma skin cancers. *Australasian radiology* **51**, 12-20, doi:10.1111/j.1440-1673.2006.01649.x (2007).

4 Feng, H., Shuda, M., Chang, Y. & Moore, P. S. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science* **319**, 1096-1100, doi:10.1126/science.1152586 (2008).

5 Houben, R. *et al.* Merkel cell polyomavirus-infected Merkel cell carcinoma cells require expression of viral T antigens. *Journal of virology* **84**, 7064-7072, doi:10.1128/JVI.02400-09 (2010).

6 Aldabagh, B., Joo, J. & Yu, S. S. Merkel cell carcinoma: current status of targeted and future potential for immunotherapies. *Seminars in cutaneous medicine and surgery* **33**, 76-82 (2014).

7 Chapuis, A. G. *et al.* Regression of metastatic Merkel cell carcinoma following transfer of polyomavirus-specific T cells and therapies capable of re-inducing HLA class-I. *Cancer immunology research* **2**, 27-36, doi:10.1158/2326-6066.CIR-13-0087 (2014).

8 Weber, J. S. *et al.* Safety, efficacy, and biomarkers of nivolumab with vaccine in ipilimumab-refractory or -naive melanoma. *J Clin Oncol* **31**, 4311-4318, doi:10.1200/JCO.2013.51.4802 (2013).

9 Lipson, E. J. *et al.* PD-L1 expression in the Merkel cell carcinoma microenvironment: association with inflammation, Merkel cell polyomavirus and overall survival. *Cancer immunology research* **1**, 54-63, doi:10.1158/2326-6066.CIR-13-0034 (2013).

10 Nghiem P, B. S., Daud A, et al. Activity of PD-1 blockade with pembrolizumab as first systemic therapy in patients with advanced Merkel cell carcinoma. *2015 European Cancer Congress* (2015).

11 Demaria, S. *et al.* Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research* **11**, 728-734 (2005).

12 Hiniker, S. M., Chen, D. S. & Knox, S. J. Abscopal effect in a patient with melanoma. *N Engl J Med* **366**, 2035; author reply 2035-2036, doi:10.1056/NEJMc1203984#SA1 (2012).

13 Liao, Y. P., Wang, C. C., Schaue, D., Iwamoto, K. S. & McBride, W. H. Local irradiation of murine melanoma affects the development of tumour-specific immunity. *Immunology* **128**, e797-804, doi:10.1111/j.1365-2567.2009.03084.x (2009).

14 Abuodeh, Y., Venkat, P. & Kim, S. Systematic review of case reports on the abscopal effect. *Current problems in cancer*, doi:10.1016/j.currproblcancer.2015.10.001 (2015).

15 Grass, G. D., Krishna, N. & Kim, S. The immune mechanisms of abscopal effect in radiation therapy. *Current problems in cancer*, doi:10.1016/j.currproblcancer.2015.10.003 (2015).

16 Deng, L. *et al.* Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest* **124**, 687-695, doi:10.1172/JCI67313 (2014).

17 Kim, S. *et al.* Radiation-induced autophagy potentiates immunotherapy of cancer via up-regulation of mannose 6-phosphate receptor on tumor cells in mice. *Cancer Immunol Immunother* **63**, 1009-1021, doi:10.1007/s00262-014-1573-4 (2014).

18 Victor, C. T. *et al.* Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. *Nature*, doi:10.1038/nature14292 (2015).

19 Cotter, S. E. *et al.* Abscopal effect in a patient with metastatic Merkel cell carcinoma following radiation therapy: potential role of induced antitumor immunity. *Archives of dermatology* **147**, 870-872, doi:10.1001/archdermatol.2011.176 (2011).

20 Strom T, N. A., Messina J, Kim S, Torres-Roca J, Sondak V, Padhya T, Trotti A, Caudell J, Harrison L. Improved Local and Regional Control with Radiation Therapy for Merkel Cell Carcinoma of the Head

and Neck. *Annals of surgical oncology* **In Press** (2016).

21 Twyman-Saint Victor, C. *et al.* Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. *Nature* **520**, 373-377, doi:10.1038/nature14292 (2015).

22 Dewan, M. Z. *et al.* Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. *Clinical cancer research : an official journal of the American Association for Cancer Research* **15**, 5379-5388, doi:10.1158/1078-0432.CCR-09-0265 (2009).

23 Schaue, D., Ratikan, J. A., Iwamoto, K. S. & McBride, W. H. Maximizing tumor immunity with fractionated radiation. *International journal of radiation oncology, biology, physics* **83**, 1306-1310, doi:10.1016/j.ijrobp.2011.09.049 (2012).

24 Iyer, J. G. *et al.* Single-fraction radiation therapy in patients with metastatic Merkel cell carcinoma. *Cancer medicine* **4**, 1161-1170, doi:10.1002/cam4.458 (2015).

25 Larkin, J., Hodi, F. S. & Wolchok, J. D. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med* **373**, 1270-1271, doi:10.1056/NEJMc1509660 (2015).

26 Postow, M. A. *et al.* Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med* **372**, 2006-2017, doi:10.1056/NEJMoa1414428 (2015).

27 Wolchok, J. D. *et al.* Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med* **369**, 122-133, doi:10.1056/NEJMoa1302369 (2013).

28 Rizvi NA, G. S., Goldman JW, et al. Safety and efficacy of first-line nivolumab and ipilimumab in non-small cell lung cancer. . *16th World Conference on Lung Cancer.* (2015).

29 Hiniker SM, R. S., Maecker HT, et al. . A prospective clinical trial combining radiation therapy with systemic immunotherapy in metastatic melanoma. *ASTRO 2015* (2015).

30 Hodi, F. S. *et al.* Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* **363**, 711-723, doi:NEJMoa1003466 [pii]
10.1056/NEJMoa1003466 (2010).

31 Agelli, M. & Clegg, L. X. Epidemiology of primary Merkel cell carcinoma in the United States. *Journal of the American Academy of Dermatology* **49**, 832-841, doi:10.1067/S0190 (2003).

32 Samlowski, W. E. *et al.* A phase II trial of imatinib mesylate in merkel cell carcinoma (neuroendocrine carcinoma of the skin): A Southwest Oncology Group study (S0331). *American journal of clinical oncology* **33**, 495-499, doi:10.1097/COC.0b013e3181b9cf04 (2010).

33 Samimi, M. *et al.* Prognostic value of antibodies to Merkel cell polyomavirus T-Antigens and VP1 protein in Merkel cell carcinoma patients. *The British journal of dermatology*, doi:10.1111/bjd.14313 (2015).

34 Leroux-Kozal, V. *et al.* Merkel cell carcinoma: histopathologic and prognostic features according to the immunohistochemical expression of Merkel cell polyomavirus large T antigen correlated with viral load. *Human pathology* **46**, 443-453, doi:10.1016/j.humpath.2014.12.001 (2015).

35 Lyngaa, R. *et al.* T-cell responses to oncogenic merkel cell polyomavirus proteins distinguish patients with merkel cell carcinoma from healthy donors. *Clinical cancer research : an official journal of the American Association for Cancer Research* **20**, 1768-1778, doi:10.1158/1078-0432.CCR-13-2697 (2014).

36 Kaufman H, R. J., Hamid O, Bhatia S, Terheyden P, D'Angelo S, Shih K, Lebbe C, Linette G, Milella M, Brownell I, Lewis K, Lorch J, Chin K, Mahnke L, von Heydebreck A, Cuillerot J, Nghiem Avelumab (MSB0010718C; anti-PD-L1) in patients with metastatic Merkel cell carcinoma previously treated with chemotherapy: Results of the phase 2 JAVELIN Merkel 200 trial. *J Clin Oncol* (2016).

37 Nghiem, P. T. *et al.* PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. *N Engl J Med* **374**, 2542-2552, doi:10.1056/NEJMoa1603702 (2016).

38 Company, B.-M. S. Final Clinical Study Report for CA209003: A Phase 1, Open-label, Multicenter, Multidose, Dose Escalation Study of BMS-936558 (MDX-1106) in Subjects with Selected Advanced or Recurrent Malignancies (Study MDX-1106-03). *Document Control No. 930044417* (2013).

39 Larkin, J. *et al.* Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *New*

England Journal of Medicine **373**, 23-34 (2015).

40 Hellmann M, G. S., Goldman J, Brahmer J, Borghaei H, Chow L, Ready N, Gerber D, Juergens R, Shepherd F, Laurie S, Zhou Y, Geese W, Agrawal S, Li X, Antonia S. CheckMate 012: Safety and efficacy of first-line (1L) nivolumab (nivo; N) and ipilimumab (ipi; I) in advanced (adv) NSCLC. *2016 ASCO Annual Meeting* **J Clin Oncol 34, 2016 (suppl; abstr 3001)** (2016).

41 Eggermont, A. M. *et al.* in *ASCO Annual Meeting Proceedings.* LBA9008.

42 Company, B.-M. S. Final Clinical Study Report for Study CA184-029: Adjuvant immunotherapy with anti- CTLA-4 monoclonal antibody (ipilimumab) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, double-blind Phase 3 trial of the EORTC Melanoma Group (Study CA184-029). *Document Control No. 930078161.* (2014).

43 Taube, J. M. *et al.* Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. *Science translational medicine* **4**, 127ra137-127ra137 (2012).

44 Topalian, S. L. *et al.* Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. *New England Journal of Medicine* **366**, 2443-2454 (2012).

45 Gibney, G. T. *et al.* Safety, correlative markers, and clinical results of adjuvant nivolumab in combination with vaccine in resected high-risk metastatic melanoma. *Clinical Cancer Research* **21**, 712-720 (2015).

46 Hodi, F. S. *et al.* in *ASCO Annual Meeting Proceedings.* 9002.

47 Sznol, M. *et al.* in *ASCO Annual Meeting Proceedings.* LBA9003.

48 Greenwald, R. J., Freeman, G. J. & Sharpe, A. H. The B7 family revisited. *Annu. Rev. Immunol.* **23**, 515-548 (2005).

49 Freeman, G. J. *et al.* Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *The Journal of experimental medicine* **192**, 1027-1034 (2000).

50 Carter, L. L. *et al.* PD-1: PD-L inhibitory pathway affects both CD4+ and CD8+ T cells and is overcome by IL-2. *European journal of immunology* **32**, 634-643 (2002).

51 Latchman, Y. *et al.* PD-L2 is a second ligand for PD-1 and inhibits T cell activation. *Nature immunology* **2**, 261-268 (2001).

52 Chemnitz, J. M., Parry, R. V., Nichols, K. E., June, C. H. & Riley, J. L. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. *The Journal of Immunology* **173**, 945-954 (2004).

53 Sheppard, K.-A. *et al.* PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3ζ signalosome and downstream signaling to PKCθ. *FEBS letters* **574**, 37-41 (2004).

54 Nishimura, H. & Honjo, T. PD-1: an inhibitory immunoreceptor involved in peripheral tolerance. *Trends in immunology* **22**, 265-268 (2001).

55 Nishimura, H., Nose, M., Hiai, H., Minato, N. & Honjo, T. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity* **11**, 141-151 (1999).

56 Nishimura, H. *et al.* Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. *Science* **291**, 319-322 (2001).

57 Okazaki, T. *et al.* Autoantibodies against cardiac troponin I are responsible for dilated cardiomyopathy in PD-1-deficient mice. *Nature medicine* **9**, 1477-1483 (2003).

58 Blazar, B. R. *et al.* Blockade of programmed death-1 engagement accelerates graft-versus-host disease lethality by an IFN-γ-dependent mechanism. *The Journal of Immunology* **171**, 1272-1277 (2003).

59 Salama, A. D. *et al.* Critical role of the programmed death-1 (PD-1) pathway in regulation of experimental autoimmune encephalomyelitis. *The Journal of experimental medicine* **198**, 71-78 (2003).

60 Blank, C. *et al.* PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells. *Cancer research* **64**, 1140-1145 (2004).

61 Dong, H. *et al.* Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nature medicine* **8**, 793-800 (2002).

62 Hirano, F. *et al.* Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. *Cancer research* **65**, 1089-1096 (2005).

63 Iwai, Y. *et al.* Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proceedings of the National Academy of Sciences* **99**, 12293-12297 (2002).

64 Iwai, Y., Terawaki, S. & Honjo, T. PD-1 blockade inhibits hematogenous spread of poorly immunogenic tumor cells by enhanced recruitment of effector T cells. *International immunology* **17**, 133-144 (2005).

65 Strome, S. E. *et al.* B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. *Cancer research* **63**, 6501-6505 (2003).

66 Dong, H. & Chen, L. B7-H1 pathway and its role in the evasion of tumor immunity. *Journal of molecular medicine* **81**, 281-287 (2003).

67 Konishi, J. *et al.* B7-H1 expression on non-small cell lung cancer cells and its relationship with tumor-infiltrating lymphocytes and their PD-1 expression. *Clinical Cancer Research* **10**, 5094-5100 (2004).

68 Ohigashi, Y. *et al.* Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. *Clinical Cancer Research* **11**, 2947-2953 (2005).

69 Thompson, R. H. *et al.* Costimulatory molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma. *Cancer* **104**, 2084-2091 (2005).

70 Thompson, R. H. *et al.* Costimulatory B7-H1 in renal cell carcinoma patients: Indicator of tumor aggressiveness and potential therapeutic target. *Proceedings of the National Academy of Sciences of the United States of America* **101**, 17174-17179 (2004).

71 Thompson, R. H. *et al.* B7-H1 glycoprotein blockade: a novel strategy to enhance immunotherapy in patients with renal cell carcinoma. *Urology* **66**, 10-14 (2005).

72 Tsushima, F. *et al.* Predominant expression of B7-H1 and its immunoregulatory roles in oral squamous cell carcinoma. *Oral oncology* **42**, 268-274 (2006).

73 Azuma, T. *et al.* B7-H1 is a ubiquitous antiapoptotic receptor on cancer cells. *Blood* **111**, 3635-3643 (2008).

74 Hino, R. *et al.* Tumor cell expression of programmed cell death-1 ligand 1 is a prognostic factor for malignant melanoma. *Cancer* **116**, 1757-1766, doi:10.1002/cncr.24899 (2010).

75 Institute, B.-M. S. P. R. Effect of MDX-1106 on CD4+ T cells during an allogeneic mixed lymphocyte reaction (MLR) (Medarex Study No. MDX-1106-026-R). . *Document Control No. 930046581.* (2006).

76 Lenschow, D. J., Walunas, T. L. & Bluestone, J. A. CD28/B7 system of T cell costimulation. *Annual review of immunology* **14**, 233-258 (1996).

77 Kearney, E. R. *et al.* Antigen-dependent clonal expansion of a trace population of antigen-specific CD4+ T cells in vivo is dependent on CD28 costimulation and inhibited by CTLA-4. *The Journal of Immunology* **155**, 1032-1036 (1995).

78 Krummel, M. F. & Allison, J. P. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. *The journal of experimental medicine* **182**, 459-465 (1995).

79 Krummel, M. F., Sullivan, T. J. & Allison, J. P. Superantigen responses and co-stimulation: CD28 and CTLA-4 have opposing effects on T cell expansion in vitro and in vivo. *International immunology* **8**, 519-523 (1996).

80 Walunas, T. L. *et al.* CTLA-4 can function as a negative regulator of T cell activation. *Immunity* **1**, 405-413 (1994).

81 Perez, V. L. *et al.* Induction of peripheral T cell tolerance in vivo requires CTLA-4 engagement. *Immunity* **6**, 411-417 (1997).

82 Korman, A., Yellin, M. & Keler, T. Tumor immunotherapy: preclinical and clinical activity of anti-CTLA4 antibodies. *Current opinion in investigational drugs (London, England: 2000)* **6**, 582-591 (2005).

83 Chambers, C. A., Sullivan, T. J. & Allison, J. P. Lymphoproliferation in CTLA-4–deficient mice is mediated by costimulation-dependent activation of CD4+ T cells. *Immunity* **7**, 885-895 (1997).

84 Tivol, E. A. *et al.* Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. *Immunity* **3**, 541-547 (1995).

85 Waterhouse, P. *et al.* Lymphoproliferative disorders with early lethality in mice deficient in Ctla-4. *Science* **270**, 985-988 (1995).

86 Egen, J. G., Kuhns, M. S. & Allison, J. P. CTLA-4: new insights into its biological function and use in tumor immunotherapy. *Nature immunology* **3**, 611-618 (2002).

87 Yang, Y.-F. *et al.* Enhanced induction of antitumor T-cell responses by cytotoxic T lymphocyte-associated molecule-4 blockade: the effect is manifested only at the restricted tumor-bearing stages. *Cancer research* **57**, 4036-4041 (1997).

88 McGaha, T. & Murphy, J. W. CTLA-4 down-regulates the protective anticryptococcal cell-mediated immune response. *Infection and immunity* **68**, 4624-4630 (2000).

89 Gomes, N. A., Barreto-de-Souza, V., Wilson, M. E. & DosReis, G. A. Unresponsive CD4+ T Lymphocytes from Leishmania chagasi—Infected Mice Increase Cytokine Production and Mediate Parasite Killing after Blockade of B7-1/CTLA-4 Molecular Pathway. *Journal of Infectious Diseases* **178**, 1847-1851 (1998).

90 Riley, J. L. *et al.* Modulation of susceptibility to HIV-1 infection by the cytotoxic T lymphocyte antigen 4 costimulatory molecule. *The Journal of experimental medicine* **191**, 1987-1998 (2000).

91 Salama, J. K. *et al.* Stereotactic body radiotherapy for multisite extracranial oligometastases. *Cancer* **118**, 2962-2970 (2012).

92 Salama, J. K., Kirkpatrick, J. P. & Yin, F.-F. Stereotactic body radiotherapy treatment of extracranial metastases. *Nature Reviews Clinical Oncology* **9**, 654-665 (2012).

93 Squibb, B.-M. Clinical Study Report MDX010-20: A randomized, double-blind, multicenter study comparing MDX-010 monotherapy, MDX-010 in combination with a melanoma peptide vaccine, and melanoma vaccine monotherapy in HLA-A*0201-positive patients with previously treated unresectable stage III or IV melanoma. . *Document Control No. 930041541.* (2010).

94 Antonia, S. J. *et al.* Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol* **17**, 883-895, doi:10.1016/S1470-2045(16)30098-5 (2016).

95 Atkins M, C. T., Hodi S, Thompson J, Hwu W, McDermott D, Brookes M, Tosolini A, Ebbinghaus S, Yang Z, Gause C, Perini R, Ribas A. Pembrolizumab (MK-3475) plus low-dose ipilimumab (IPI) in patients (pts) with advanced melanoma (MEL) or renal cell carcinoma (RCC): Data from the KEYNOTE-029 phase 1 study. *J Clin Oncol*, suppl; abstr 3009 (2015).

96 Timmerman, R. *et al.* Stereotactic body radiation therapy for inoperable early stage lung cancer. *Jama* **303**, 1070-1076, doi:10.1001/jama.2010.261 (2010).

97 Scorsetti, M. *et al.* Final results of a phase II trial for stereotactic body radiation therapy for patients with inoperable liver metastases from colorectal cancer. *Journal of cancer research and clinical oncology* **141**, 543-553, doi:10.1007/s00432-014-1833-x (2015).

98 Ryu, S. *et al.* RTOG 0631 Phase II/III Study of Image-Guided Stereotactic Radiosurgery for Localized (1-3) Spine Metastases: Phase II Results. *International journal of radiation oncology, biology, physics* **81**, S131-S132, doi:10.1016/j.prro.2013.05.001 (2011).

99 Vargo, J. A. *et al.* A prospective phase 2 trial of reirradiation with stereotactic body radiation therapy plus cetuximab in patients with previously irradiated recurrent squamous cell carcinoma of the head and neck. *International journal of radiation oncology, biology, physics* **91**, 480-488, doi:10.1016/j.ijrobp.2014.11.023 (2015).

100 Chuong, M. D. *et al.* Stereotactic body radiation therapy for locally advanced and borderline

resectable pancreatic cancer is effective and well tolerated. *International journal of radiation oncology, biology, physics* **86**, 516-522, doi:10.1016/j.ijrobp.2013.02.022 (2013).

101 Naghavi, A., Johnstone, P. & Kim, S. Clinical trials exploring the benefit of immunotherapy and radiation in cancer treatment: A review of the past and a look into the future. *Curr Probl Cancer*, doi:10.1016/j.currproblcancer.2015.10.002 (2015).

102 Squibb, B.-M. Ipilimumab population pharmacokinetics and exposure-response analyses in subjects with advanced melanoma (CA184004, CA184007, CA184008, and CA184022). *Document Control No. 930043857.* (2010).

103 Company, B.-M. S. Final Clinical Study Report for MDX1106-01: A Phase 1, Open label, Dose Escalation, Safety and Pharmacokinetic Study of MDX-1106 in Patients with selected Refractory or Relapsed Malignancies. . *Document Control Number 930044418.* (2011).

104 Company, B.-M. S. Phase I Clinical Study of ONO-4538 Single- and Multiple-dose Study in Patients with Malignant Tumors (Protocol No. ONO-4538-01) *Clinical Study Report (Interim report to extended treatment phase).*

105 Company, B.-M. S. Phase II Clinical Study of ONO-4538 Multicenter, Open-label, Uncontrolled Study in Malignant Melanoma (Protocol No. ONO-4538-02) *Clinical Study Report (Interim report).*

106 Company, B.-M. S. Final Clinical Study Report for CA209010: A Randomized, Blinded, Phase 2 Dose-Ranging Study of Nivolumab (MDX-1106, BMS-936558) in Subjects With Progressive Advanced/Metastatic Clear-Cell Renal Cell Carcinoma (RCC) Who Have Received Prior Anti-Angiogenic Therapy. *Document Control No. 930074316.* (2011).

107 Company, B.-M. S. Final Clinical Study Report for CA209063: A Single-Arm Phase 2 Study of Nivolumab (BMS-936558) in Subjects with Advanced or Metastatic Squamous Cell Non-Small Cell Lung Cancer Who Have Received at Least Two Prior Systemic Regimens. *Document Control No. 930075122.* (2014).

108 Company, B.-M. S. Final Clinical Study Report for CA209037: A Randomized, Open-Label, Phase 3 Trial of BMS-936558 (Nivolumab) Versus Investigator's Choice in Advanced (Unresectable or Metastatic) Melanoma Patients Progressing Post Anti-CTLA-4 Therapy. . *Document Control No. 930081508.* (2014).

109 Barriger, R. B. *et al.* A dose-volume analysis of radiation pneumonitis in non-small cell lung cancer patients treated with stereotactic body radiation therapy. *International journal of radiation oncology, biology, physics* **82**, 457-462, doi:10.1016/j.ijrobp.2010.08.056 (2012).

110 Chen, D. T. *et al.* A Bayesian pick-the-winner design in a randomized phase II clinical trial. *Oncotarget* **8**, 88376-88385, doi:10.18632/oncotarget.19088 (2017).

APPENDIX 1 AJCC MERKEL CELL CARCINOMA STAGING

T	N	M
Tx, Primary tumor cannot be assessed **T0**, No primary tumor **Tis**, In situ primary tumor **T1**, Primary tumor ≤2 cm **T2**, Primary tumor >2 but ≤5 cm **T3**, Primary tumor >5 cm **T4**, Primary tumor invades bone, muscle, fascia, or cartilage	**Nx**, Regional nodes cannot be assessed **N0**, No regional node metastasis* **cN0**, Nodes not clinically detectable* **cN1**, Nodes clinically detectable* **pN0**, Nodes negative by pathologic examination **pNx**, Nodes not examined pathologically **N1a**, Micrometastasis† **N1b**, Macrometastasis‡ **N2**, In-transit metastasis§	**Mx**, Distant metastasis cannot be assessed **M0**, No distant metastasis **M1**, Distant metastasis// -**M1a**, distant skin, distant subcutaneous tissues, or distant lymph nodes -**M1b**, lung -**M1c**, all other visceral sites

Stage	Stage grouping		
0	Tis	N0	M0
IA	T1	pN0	M0
IB	T1	cN0	M0
IIA	T2/T3	pN0	M0
IIB	T2/T3	cN0	M0
IIC	T4	N0	M0
IIIA	Any T	N1a	M0
IIIB	Any T	N1b/N2	M0
IV	Any T	Any N	M1

*"N0" denotes negative nodes by clinical, pathologic, or both types of examination. Clinical detection of nodal disease may be via inspection, palpation, and/or imaging; cN0 is used only for patients who did not undergo pathologic node staging.
†Micrometastases are diagnosed after sentinel or elective lymphadenectomy.
‡Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically by biopsy or therapeutic lymphadenectomy.
§In-transit metastasis is tumor distinct from primary lesion and located either: (1) between primary lesion and draining regional lymph nodes; or (2) distal to primary lesion.
//Because there are no data to suggest significant effect of M categories on survival in Merkel cell carcinoma, M1a-c are included in same stage grouping.

Source: Lemos, B. D. et al. Pathologic nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: analysis of 5823 cases as the basis of the first consensus staging system. Journal of the American Academy of Dermatology 63, 751-761 (2010)

APPENDIX 2 PERFORMANCE STATUS SCALES

STATUS	SCALES		STATUS
	KARNOFSKY	ZUBROD-ECOG-	
Normal, no complaints	100	0	Normal activity
Able to carry on normal activities Minor signs or	90	0	Symptoms, but fully ambulatory
Normal activity with effort	80	1	
Cares for self. Unable to carry on normal	70	1	Symptomatic, but in bed < 50% of the day.
Requires occasional assistance, but able to care	60	2	
Requires considerable assistance and frequent medical care	50	2	Needs to be in bed > 50% of the day, but not bedridden
Disabled. Requires special	40	3	
Severely disabled. Hospitalization indicated	30	3	
Very sick. Hospitalization	20	4	Unable to get out of bed
Moribund	10	4	
Dead	0	5	Dead

APPENDIX 3 METHODS OF CONTRACEPTION

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide[1,2]
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- Nonhormonal IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy.
- Complete Abstinence*

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

LESS EFFECTIVE METHODS OF CONTRACEPTION

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

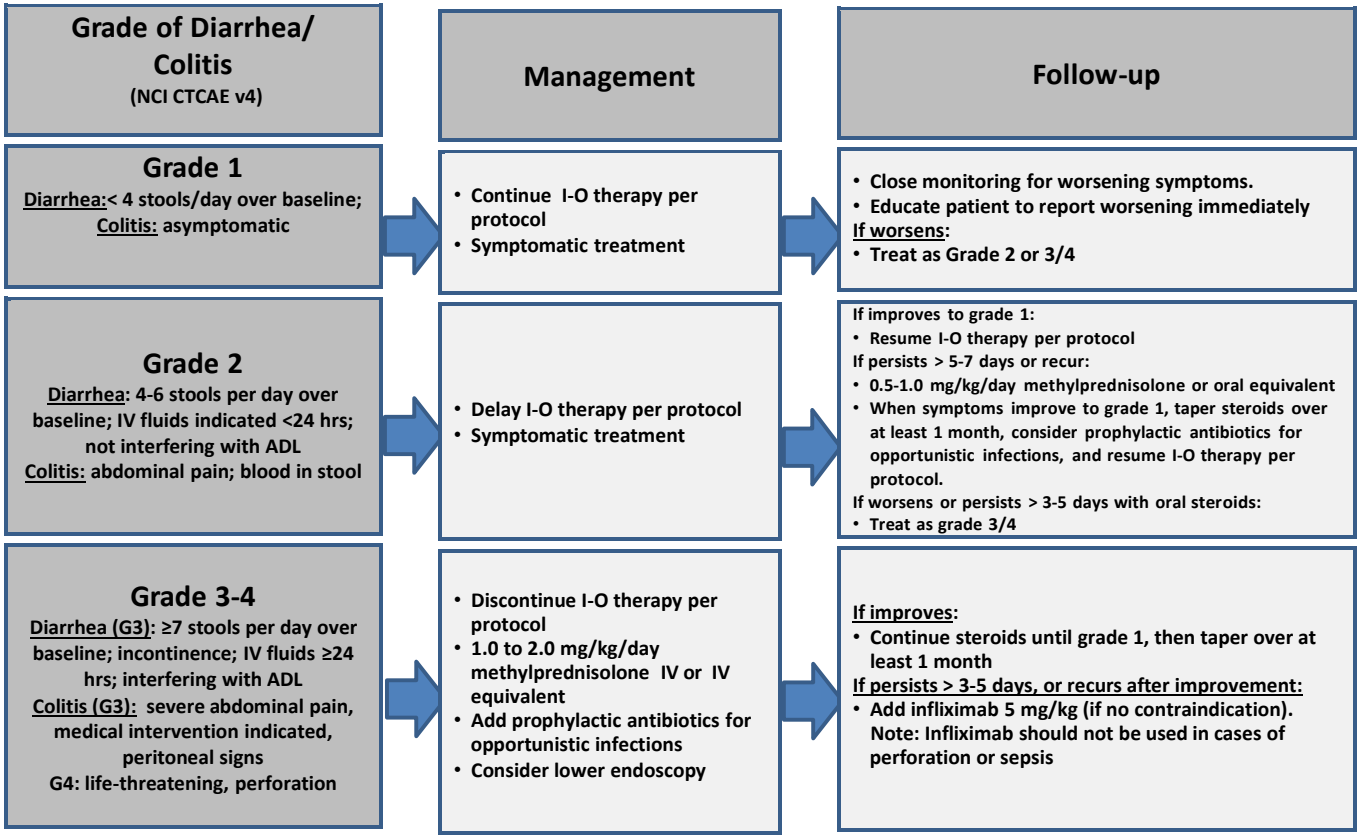
  * A male and female condom must not be used together

[1] Kestelman P. et. al., Efficacy of the Simultaneous Use of Condoms and Spermicides Family Planning Perspectives.Vol 23 (5); October 1991.
[2] Gabbay MB, Thomas J, Gibbs A, Hold P. A Randomized Crossover Trial of The Impact of Additional Spermicide on Condom Failure Rates. Sex Transm Dis 2008; 35: 862-8.Date: 22-Feb-2016

APPENDIX 4 IMMUNE ADVERSE EVENT MANAGEMENT ALGORITHMS

GI Adverse Event Management Algorithm

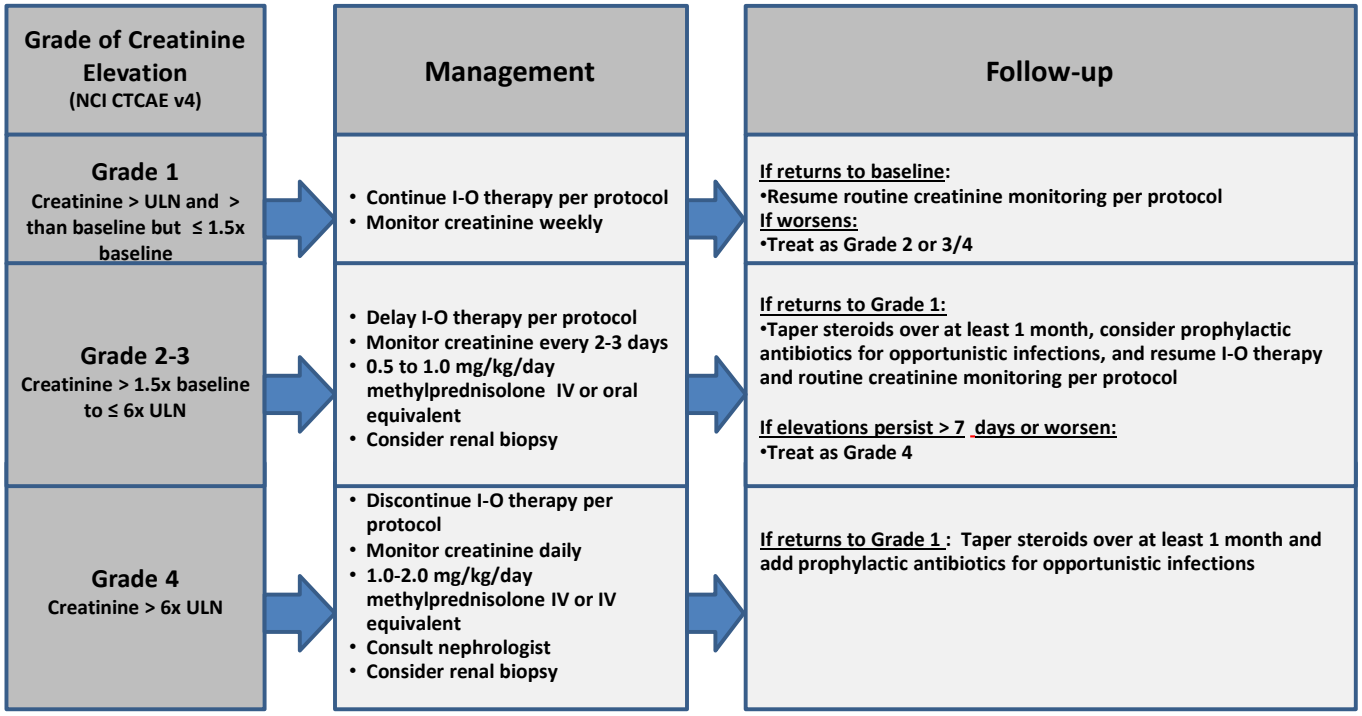
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



Patients on IV steroids may be switched to an equivalent dose of oralcorticosteroids (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

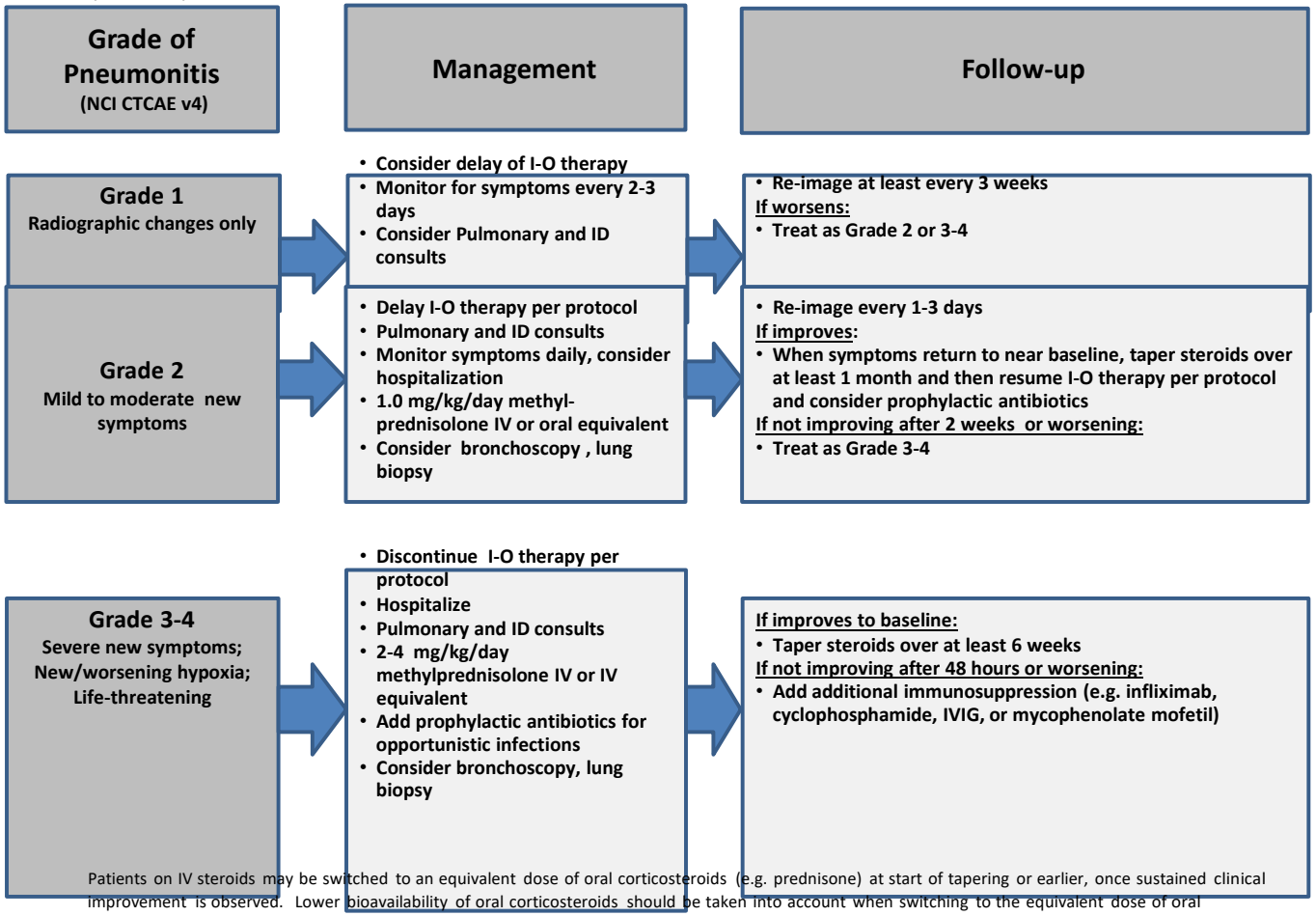
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

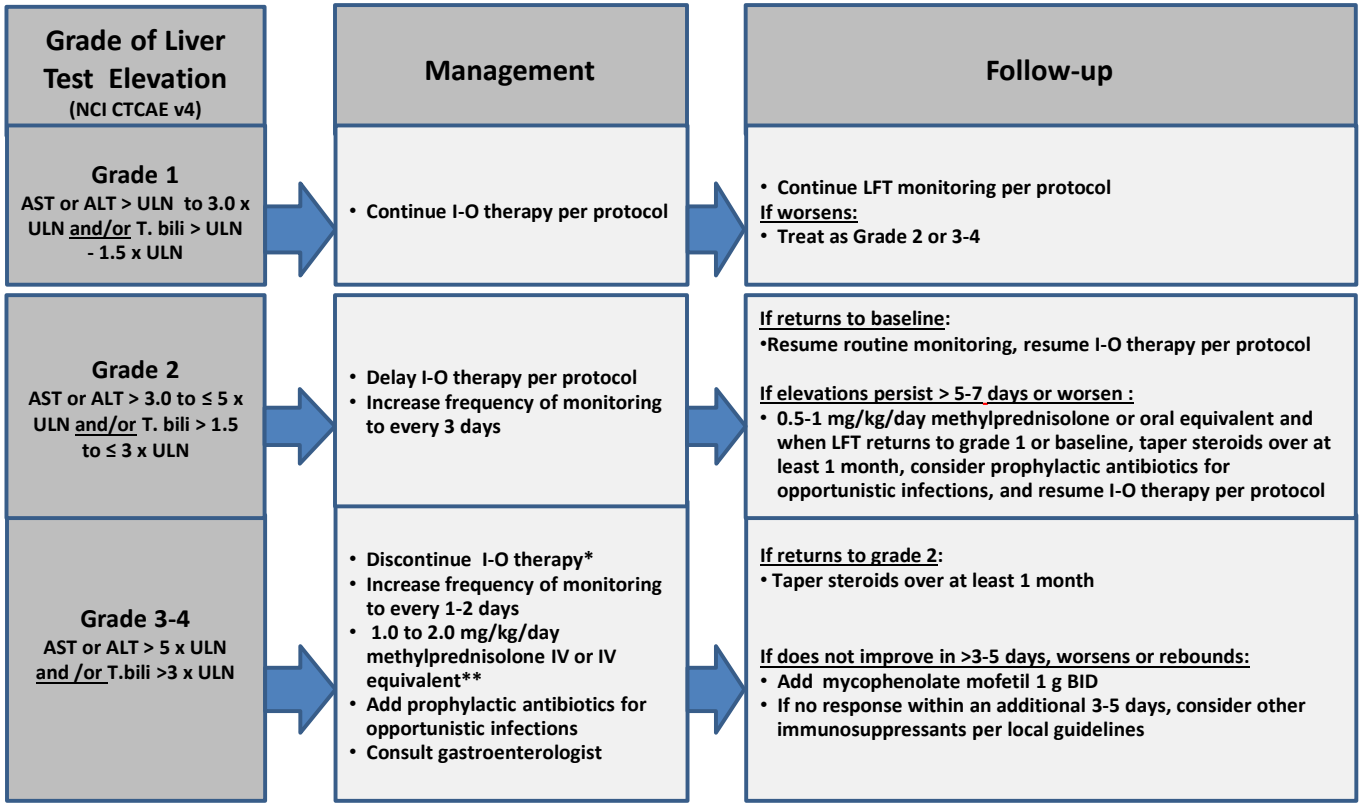
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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.

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.



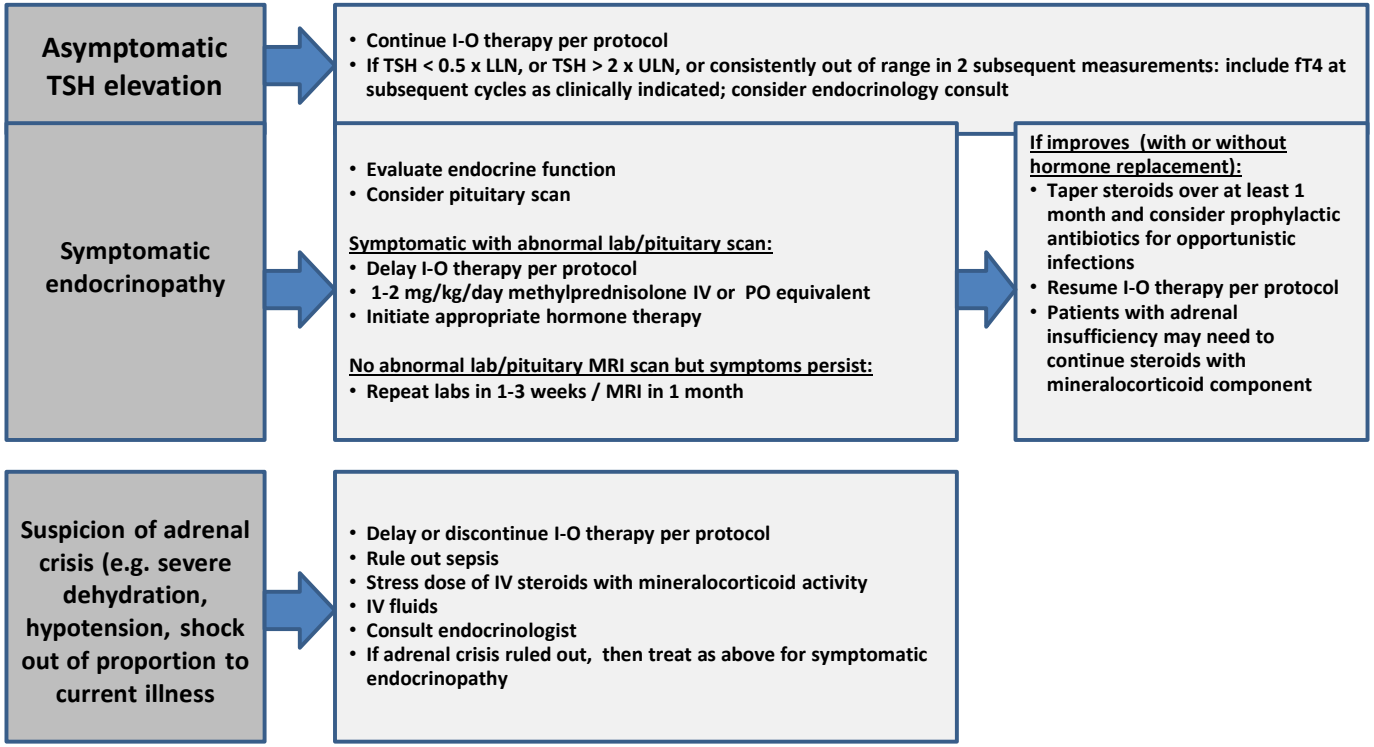
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Endocrinopathy Management Algorithm

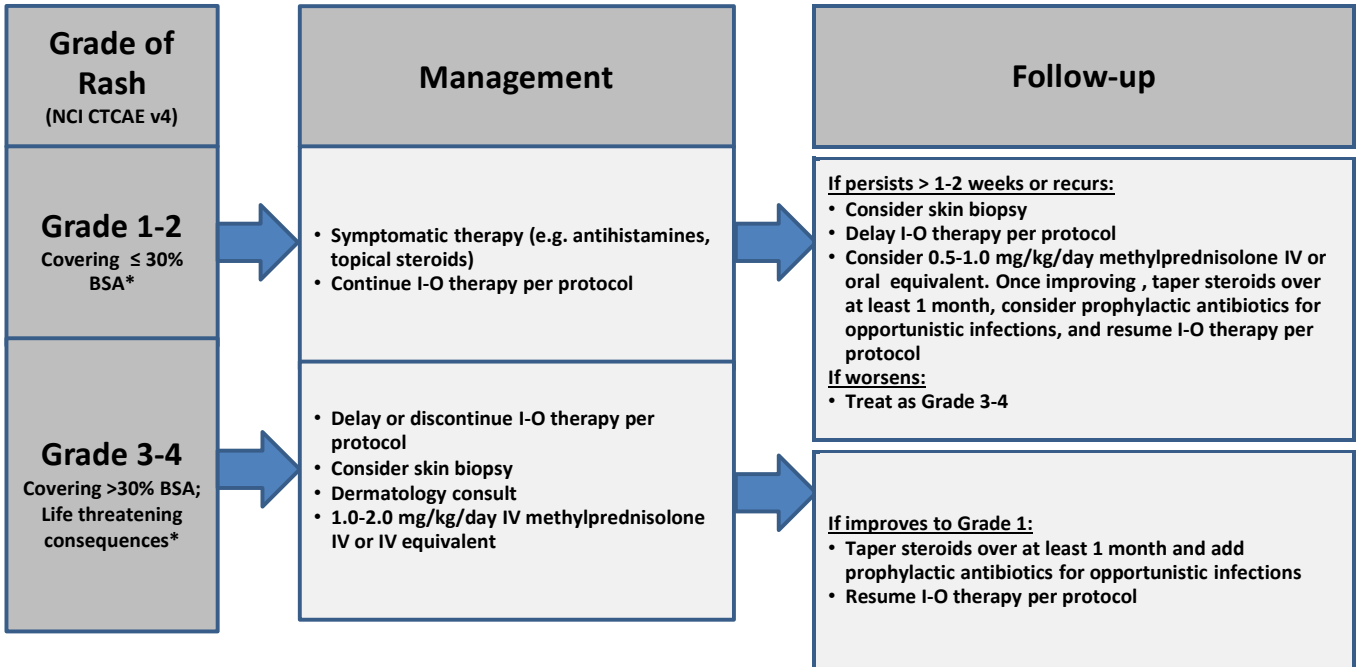
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

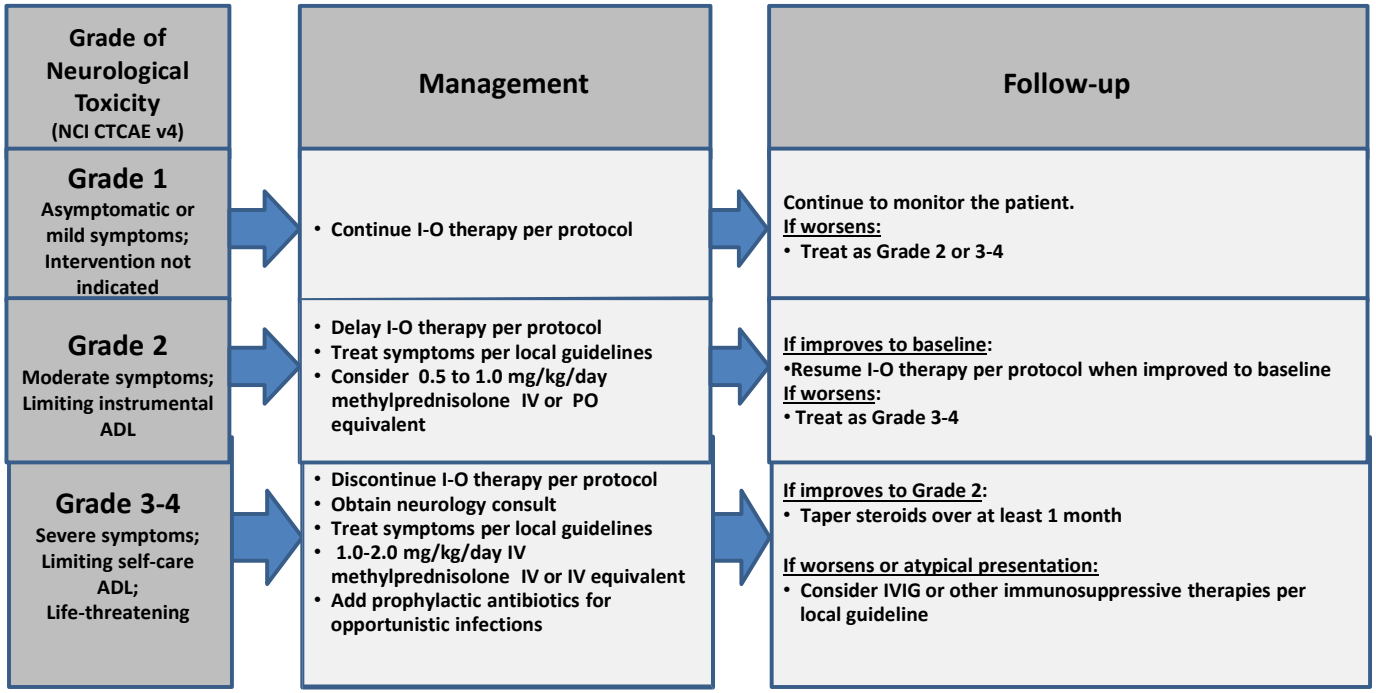
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.

Neurological 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.

APPENDIX 5 EORTC QLQ-C30 (VER 3) FORM

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
□□□□

Your birthdate (Day, Month, Year):
□□□□□□□□

Today's date (Day, Month, Year): 31
□□□□□□□□

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4

16. Have you been constipated?	1	2	3	4

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent