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Phase I/II Trial of Ipilimumab or Nivolumab with BMS-986156 and Hypofractionated Stereotactic Radiation Therapy in Patients with Advanced Solid Malignancies

The University of Texas, MD Anderson Cancer Center

Departments: Investigational Cancer Therapeutics and Radiation Oncology

Protocol Number: 2018-0419

Protocol Phase: Phase I/II

Principal Investigator: Joe Chang, MD, PhD

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1. Treatment Scheme

Notice: Treatment schedules shall have a standing window of allowance of +/- 3 days unless patient/logistical/medical reasons intervene. Any treatment day (radiation or drug administration) that falls on a weekend or holiday will be scheduled on the next business day. For treatment or dose modification questions, please contact Joe Chang, MD, PhD by phone (713-563-2337) or e-mail (jychang@mdanderson.org), David Hong, MD by phone (713-563-5844) or e-mail (dshong@mdanderson.org). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

There will be 3 treatment groups; consisting of patients with metastatic disease in liver or lung from any primary. Safety data on Stereotactic body radiation therapy (SBRT) and ipilimumab was presented at ASTRO, 2017 (1). Based on the encouraging data on SBRT and ipilimumab, we propose to test the safety and efficacy of combination of ipilimumab or nivolumab and an anti-GITR agonistic antibody (BMS-986156) with SBRT.

The first set of subjects (group 1, 20 patients) will receive ipilimumab (3 mg/kg) plus BMS-986156 (30 or 100 mg) in order to assess safety and DLT.

The second set of subjects (group 2) will receive ipilimumab plus BMS-986156 (dose as determined in group 1) with SBRT.

Enrollment of subjects in the third set (group 3) will start at the same time as group 1.

The third set of subjects (group 3) will receive nivolumab (480 mg Q4W) plus BMS-986156 (30 mg) with SBRT.

Assessment for DLT will be done for patients enrolled on group 2; based on the outcome, dose escalation / de-escalation of ipilimumab and BMS-986156 (group 1). Treatment assignments to groups 2 and 3 will be based on disease status at enrollment and at the discretion of the PI and treating physician. In the event that a patient presents with both treatable liver and lung lesions, assignment will be based on provider preference .

All patients who achieve systemic benefit (based on physician discretion) but later progress will be given the option of receiving reinduction. Optional radiation can be administered during reinduction. If administered, radiation will be given similar to what was done in the initial treatment. After the first round of reinduction, patients may receive additional reinduction if during their most recent post cycle 4 imaging disease control is observed without severe (grade >3) toxicity. Patients with either liver or lung lesions amenable to SBRT (either 50 Gy in 4 fractions or 60 Gy in 10 fraction) will be enrolled on this trial.

Treatment group 1) Ipilimumab + BMS-986156 (30 mg / 100 mg) x 4 for safety assessment (No SBRT) → Nivolumab x 26

Treatment group 2) Sequential (late SBRT) Ipilimumab + BMS-986156 (dose as determined in group 1) x 2 → SBRT→ Ipilimumab + BMS-986156 (dose as determined in group 1) x 2 → Nivolumab x 26

Treatment group 3) Concurrent (early SBRT) Nivolumab (480 mg Q4W) + BMS-986156 (30mg) + SBRT→ Nivolumab + BMS-986156 x 3 (30mg) → Nivolumab x 22

Group 1, 20 patients: Ipilimumab + BMS-986156 (30 or 100 mg) Dose Escalation → Nivolumab x 26 (up to 2 year maintenance)
Day 1 and every 21 days: Ipilimumab therapy at 3 mg/kg as a 90 minute intravenous (IV) dose and BMS-986156 at either 30 mg or 100 mg dose as a 60 min IV dose will be given in an outpatient setting. Dose cycles will be repeated every 21 days: on days 1, 22, 43, and 64 for a total of 4 cycles. Maintenance therapy of Nivolumab (480mg Q4W) will start day 85 and continue every 28 days, for 26 cycles.

A modified 3+3 dose escalation then expansion to a total of 10 patients per arm (escalation + expansion, if applicable) will be performed on two dose levels of this combination therapy. Details on de-escalation are presented under section 7.7.1.

Group 1

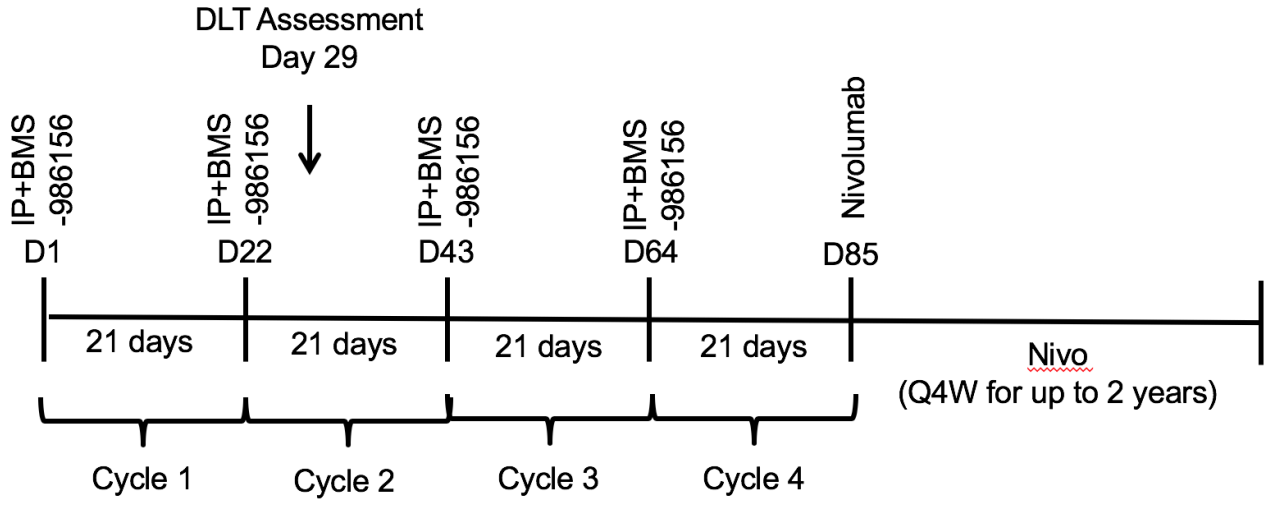

Diagram of Treatment Schedule for Ipilimumab + BMS-986156 (30 or 100 mg) Dose Escalation → Nivolumab x 26 (Treatment Group 1)

Group 2, 20 patients: Ipilimumab + BMS-986156 x 2 → SBRT → Ipilimumab + BMS-986156 x 2 → Nivolumab x 26 (up to 2 year maintenance)

Day 1 and every 21 days: Ipilimumab therapy at 3 mg/kg as a 90 minute intravenous (IV) dose and BMS-986156 (dose as determined in group 1) as a 60 min IV will be given in an outpatient setting. Dose cycles will be repeated every 21 days: on days 1, 22, 43, and 64 for a total of 4 cycles. Nivolumab (480 mg Q4W) will start day 85 and continue every 28 days for 26 cycles. Enrollment of this group will start based on the following criteria. If 2 out of 6 patients, or less, display DLTs, then, enrollment of group 2 can begin. Alternatively, if 3 out of 6 patients, or more, display DLTs, then, enrollment of group 2 cannot begin until 10 patients have been treated in group 1.

SBRT: SBRT will be given after 2 doses of ipilimumab and BMS-986156 on days 29-32 for 50 Gy in 4 fractions or on days 29-40 for 60 Gy in 10 fractions (no SBRT during weekends): SBRT will be directed at 1-4 targetable liver or lung lesion(s). To minimize treatment breaks, patients may start radiation on a Monday.

Group 2

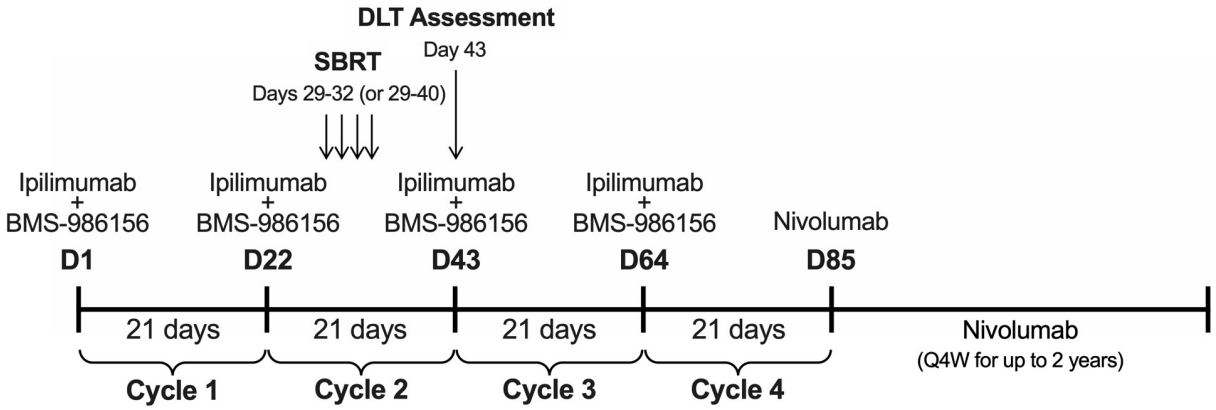

Diagram of Treatment Schedule for Ipilimumab + BMS-986156 x 2 → SBRT → Ipilimumab + BMS-986156 x 2 → Nivolumab x 26 (Treatment group 2).

Group 3, 20 patients: Nivolumab + BMS-986156 x 1 + SBRT → Nivolumab + BMS-986156 x 3 → Nivolumab x 22

First dose of Nivolumab + BMS-986156 and SBRT will be given concurrently (early) and followed by Nivolumab + BMS-986156 x 3; then, Nivolumab monotherapy for 22 cycles. Nivolumab will be administered for a total of 26 cycles, either as a combination or monotherapy, in this group. Enrollment of patients for this group will start around the same time as group 1. Choice of treatment group will be at the discretion of PI and treating physician.

Nivolumab therapy at 480 mg dose will be given on day 1 as a 30 minute IV dose and BMS-986156 at 30 mg dose will be given on day 1, 29, 57, 85 as a 60 min IV in an outpatient setting. Nivolumab monotherapy will start on day 113 and will continue for 22 cycles.

SBRT: SBRT will be given on days 1-4 (days 2-5 are acceptable if scheduling does not permit radiation to begin same day as infusions) for 50 Gy in 4 fractions or on days 1-12 for 60 Gy in 10 fractions (no SBRT during weekends). SBRT will be directed at 1-4 targetable liver or lung lesion(s). To minimize treatment breaks, patients may start radiation on a Monday.

Group 3

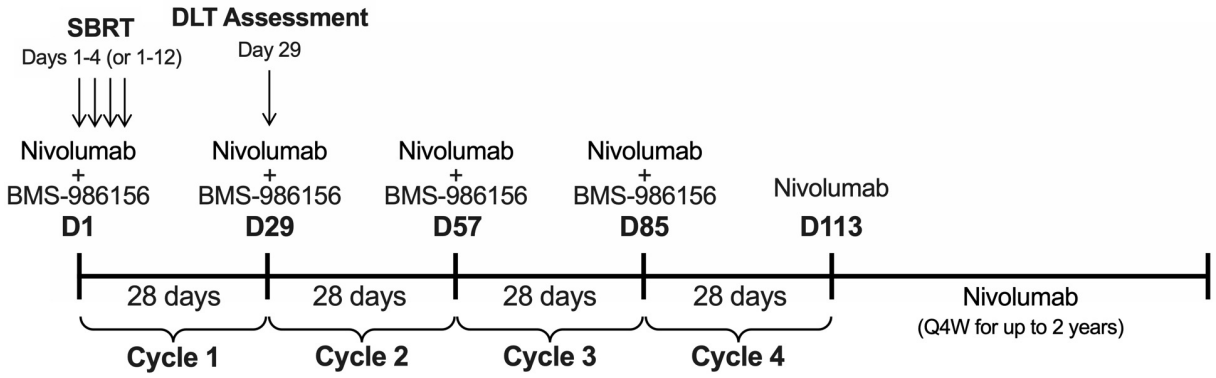

Diagram of Treatment Schedule for Nivolumab + BMS-986156 x 1 + SBRT → Nivolumab + BMS-986156 x 3 → Nivolumab x 22 (Treatment group 3)

2. Objectives

2.1. Primary Objectives

a) To determine the safe dose of BMS-986156 and Dose Limiting Toxicities (DLT) (30 mg vs 100 mg) when combined with ipilimumab (3mg/kg) for patients with metastatic cancer.

b) To evaluate the safety and toxicity profile of ipilimumab (3mg/kg) with BMS-986156 (30 or 100 mg) administered in combination with SBRT targeting 1-4 LIVER lesion(s) for patients with metastatic cancers.

c) To evaluate the safety and toxicity profile of ipilimumab (3mg/kg) with BMS-986156 (30 or 100 mg) administered in combination with SBRT targeting 1-4 LUNG lesion(s) for patients with metastatic cancer.

d) To determine safety and toxicity profile of Nivolumab (480 mg) with BMS-986156 (30 mg) administered in combination with SBRT targeting 1-4 LIVER lesion(s) for patients with metastatic cancers.

e) To determine safety and toxicity profile of Nivolumab (480 mg) with BMS-986156 (30 mg) administered in combination with SBRT targeting 1-4 LUNG lesion(s) for patients with metastatic cancers.

2.2. Secondary Objectives

a) To determine antitumor activity of ipilimumab therapy with BMS-986156 (30 or 100mg) as well as Nivolumab with BMS-986156 (30 mg) with SBRT treatment for 1-4 lung lesions in both the SBRT treated lesion and non-irradiate tumors.

b) To determine antitumor activity of ipilimumab therapy with or without BMS-986156 (30 or 100mg) as well as Nivolumab with BMS-986156 (30 mg) with SBRT treatment for 1-4 liver lesions in both the SBRT treated lesion and non-irradiate tumors.

c) To compare response and progression of the non-irradiated tumors between BMS-986156 with ipilimumab vs BMS-986156 with Nivolumab, using irRC.

d) To evaluate the predictive potential value of tumor-associated and systemic immune biomarkers for therapy effectiveness and toxicity prediction.

e) To evaluate whether skeletal mass, neutrophil, neutrophil to lymphocyte ratio, and tumor bulk are correlated with clinical outcomes and adverse events.

f) To evaluate whether tumor kinetics in combination with clinical correlates can help determine treatment response. The radiological response and clinical data will be analyzed using mathematical and statistical models to identify prognostic groups.

g) To evaluate whether tumor mutational burden correlates with improved clinical outcomes and response criteria.

3. Background

Numerous clinical trials have demonstrated the ability of ipilimumab to induce long-lasting anti-tumor effects through the generation of anti-tumor immune memory (clinical trial results reviewed in). However, such evidence also suggests that ipilimumab monotherapy is effective in a limited proportion of patients. As a result, there has been interest in combining ipilimumab with other therapies including cytotoxic chemotherapy (dacarbazine)3 and other checkpoint inhibitors (nivolumab) (2). In addition, recent interest has arisen in the combination of this drug with other treatment modalities, chief among which is radiation (3-5). Mounting preclinical evidence suggests that radiation induces a tumor antigen release that activates and primes systemic T-cells for anti-tumor immunity (6) One manifestation of this immunologic effect is term the abscopal effect, which refers to systemic disease response outside of the radiation field to control limited local disease. Given that ipilimumab acts through the promotion of T-cell activity, many preclinical trials have demonstrated the abscopal effect with the combination of radiation and checkpoint inhibitors such as ipilimumab and nivolumab (7).Exemplifying such a combination, Postow et al.(5). reported marked unexpected systemic disease regression outside of a radiation field designed to palliate a paraspinal lesion in a patient with metastatic melanoma. This study and other like it offers intriguing yet anecdotal clinical evidence of the effectiveness of this combination. As a result, several phase I/II trials have begun to systematically investigate this effect (8).

3.1. Immunotherapy

3.1.1. Ipilimumab

T-cell activation is a complex process initiated when an antigen is presented to the T cell receptor (TCR) followed by the interaction of additional T cell surface molecules with their respective ligands on the antigen presenting cell (APC). This second interaction can result in a positive or a negative costimulatory signal depending on which specific molecules are involved. CTLA-4 is a T-cell surface molecule that, on interaction with the B7 molecule of the APC, leads to the termination of the T-cell response. Blockage of CTLA-4 with the monoclonal antibody Ipilimumab has led to a remarkable enhancement of the immune response in experimental models of cancer and infection (9).

Yervoy™ (ipilimumab) monotherapy has been approved for use in the US (March, 2011), the EU (July, 2011) and Australia (July, 2011) for the treatment of patients with unresectable advanced melanoma. Thousands of subjects with several cancer types in 90 completed and ongoing studies, have been treated during its clinical development program, which is focused in melanoma, prostate cancer, lung cancer, and renal cell carcinoma. In melanoma, two Phase 3 studies (**MDX010-20**

comparing ipilimumab 3mg/kg to a melanoma-specific vaccine gp100 in pretreated advanced melanoma (10) and **CA184024**, comparing ipilimumab 10mg/kg plus dacarbazine to dacarbazine alone in previously untreated advanced melanoma (11). In addition to one phase I study (Combination nivolumab, anti-PD-1 antibody, with ipilimumab (2) have demonstrated a survival benefit in patients treated with a combination of these two checkpoint inhibitors.

Over half of the patients treated with ipilimumab reported *immune-related adverse events* (irAE) defined as any AE associated with drug exposure and consistent with an immune-mediated event (thought to be a consequence of the intrinsic biological activity of ipilimumab). IrAEs predominantly involve the GI tract (manifested most often as diarrhea or colitis) and skin (pruritus and rash), and less commonly the liver (transaminase elevations), endocrine glands (manifested most often as hypophysitis/hypopituitarism), pulmonary system (cough and pneumonitis) and nervous system (motor neuropathy with or without sensory neuropathy). According to the Investigator's Brochure, most of these irAEs were clinically manageable and reversible with supportive care or corticosteroids.

Efficacy data from Phase I and II studies in melanoma suggest a trend of increasing durability and progression free survival (PFS) rates with increasing doses and duration of exposure to ipilimumab. However, preliminary data suggests that 10mg/kg of ipilimumab is associated with a higher frequency of SAEs and serious (Grade 3 or higher) irAEs than 3mg/kg of ipilimumab(2, 11, 12). It appears that an increased awareness and better management of these side effects has led to a decrease in their severity and an improvement in their control in recent trials. We propose to use ipilimumab at 3 mg/kg dose administered as 4 doses every 3 weeks and will implement a tight safety rule (see section 7.3) to stop the trial in case of excess toxicity.

It is important to note that because ipilimumab works indirectly through stimulation of the immune system by enhancing T-cell activation, its effect on tumor burden may take weeks to months to become apparent. The clinical activity of ipilimumab may manifest, not only as an early objective response, but also as stable disease (SD) with slow, continuous decline of tumor burden toward response and, in some cases, as a late objective response after initial tumor volume increase (12). For example, in one study (MDX010-19) the time to first response ranged from day 40 to day 441 (10). Durable responses and SD after treatment with ipilimumab have been observed in several malignancies, including melanoma, prostate and renal cell carcinoma.

3.1.2. Anti-GITR Agonistic Antibody (mAb) (BMS-986156)

T-cell costimulation integrates multiple positive and negative costimulatory signals in addition to antigen recognition by the T-cell receptor (TCR). Collectively, these signals govern the balance between T-cell activation and tolerance to antigens. CD28, a member of the immunoglobulin superfamily of costimulatory receptors, provides the second signal in the 2-signal hypothesis of T-cell activation. Other costimulators are members of the tumor necrosis factor receptor (TNFR) superfamily, including GITR (glucocorticoid-induced TNFR-related protein), CD134 (OX40), CD27, and CD137 (4-1BB). Engagement of these receptors by ligand or agonist antibody also potentiates antigen-specific T-cell responses.

GITR is a type I transmembrane costimulatory receptor that is readily detectable on naive murine T cells, with little expression on naive human T cells. GITR expression increases with activation, and its expression on Tregs is higher than on effectorl T cells. The ligand for GITR is the tumor necrosis factor (TNF) superfamily member GITR-L (TNFSF18). TCR- mediated activation of T cells can be costimulated by GITR engagement, which promotes TCR-dependent cell proliferation along with increased effector functions and reduced apoptosis.

BMS-986156 is an IgG1 agonist antibody that binds to activated human CD4+ and CD8+T cells with EC_{50}'s of 0.42-0.44 nM. EC_{50} values for binding of BMS-986156 to activated cynomolgus T cells (0.86-0.96 nM) were similar to those on human cells, being about 2-fold lower. The affinity of 28F3, the hybridoma parent molecule of BMS-986156, for binding to GITR on activated T cells was 0.7 nM as determined by Scatchard analysis. BMS-986156 is a partial ligand blocker and binds near the N-terminus of the mature GITR protein. BMS-986156 was active in two in vitro functional assays. BMS-986156 potentiated IL-2 release from the murine 3A9 T cell hybridoma upon activation in a dose-dependent manner. BMS-986156 also stimulated IFN-γ release from human CD4+ T cells cocultured with CHO cells stably expressing a single-chain anti-CD3 (OKT3) Fab. While GITR is expressed on activated T cells and on Treg cells, experiments demonstrated that agonism of BMS-986156 reduced the sensitivity of Teff cells to Treg suppression in a co-culture assay. BMS-986156 also elicited anti-tumor activity against an MC38 syngeneic tumor implanted into a mouse where the mouse GITR was replaced with that of human GITR.

BMS-986156 demonstrated ADCC and ADCP activities as well as binding to complement factor C1q in vitro, consistent with an antibody of the IgG1 subclass. As such, BMS-986156 may mediate in vivo ADCC or ADCP and complement fixation of cells expressing GITR. Because levels of GITR are highest among intratumoral Tregs, this subset of T cells is more likely to be depleted which may have a positive consequence for T cell immunity at the tumor site. A high concentration of BMS-986156, in the absence of an anti-T-cell receptor stimulus, elicited no measurable cytokine response from cultured human peripheral blood cells.

GITR is expressed not only in T cells but was also found in a subset of lung tumor cells as determined by IHC. No consequence of GITR engagement by BMS-986156 on proliferation of many GITR+ lung tumor cell lines was observed.

BMS-986156 monotherapy has been evaluated during the dose escalation phase and cohort expansion phase at 10 mg (4 subjects), 30 mg (6 subjects), 100 mg (4 subjects), 240 mg (9 subjects), and 800 mg (11 subjects) of BMS-986156. The majority of the subjects were Caucasian (88.2%) with a median age of 56.5 years. All 34 subjects that have received at least 1 dose of BMS-986156 as monotherapy experienced adverse events (AEs), which were mostly Grade 1 and Grade 2. The most frequently reported AEs (>10% of subjects) were fatigue, nausea, malignant neoplasm progression, constipation, abdominal pain, decreased appetite, pyrexia, back pain, diarrhea, vomiting, dyspnea, headache, peripheral edema, and pain. AEs reported for 20 subjects were considered related to study drug because no other potential cause for the events could be identified. There were no dose-limiting toxicities (DLTs). The 5 most frequent drug-related AEs included pyrexia, nausea, fatigue, chills, and diarrhea.

Overall, the safety profile of BMS-986156 monotherapy is manageable with the MTD not being reached at 800 mg. The safety profile of monotherapy BMS-986156 allowed for dose escalation up to 800 mg. However, monotherapy expansion was discontinued as a result of a decision to develop the drug in combination with nivolumab.

Detailed information about BMS-986156 can be found in the current version of the BMS-986156 Investigator's Brochure (IB) v03.

3.1.3. Nivolumab

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.1 Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition

of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

OPDIVO™ (nivolumab) is approved for use in multiple countries including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014) and has demonstrated clinical activity in NSCLC, melanoma, RCC, and cHL (approved indications) and other tumor types as monotherapy or in combination with ipilimumab. The majority of responses were durable and exceeded 6 months. In randomized, controlled studies, nivolumab monotherapy demonstrated statistically significant improvement in OS over standard of care in subjects with advanced or metastatic melanoma, in subjects with advanced or metastatic NSCLC, and in subjects with advanced RCC (see Investigator's Brochure for nivolumab).

All available data suggest that nivolumab monotherapy has a consistent AE profile across tumor types. The safety profile is generally consistent across completed and ongoing clinical trials, with no maximum tolerated dose (MTD) reached at any monotherapy dose tested up to 10 mg/kg. There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. Across all studies conducted to date, drug-related AEs have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, GI toxicity, dermatologic toxicity (including rash), and hepatotoxicity. For nivolumab monotherapy and combination therapy, the majority of these AEs have been managed successfully with supportive care and, in more severe cases, a combination of dose delay, permanent discontinuation, and/or use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in the management guidelines provided in the nivolumab IB v16.

Additional details are provided in the current version of the nivolumab IB v16.

3.1.4. Nivolumab Plus Anti-GITR mAb (BMS-986156)

CA009002 "A Phase 1/2a Dose Escalation and Cohort Expansion Study for Safety, Tolerability, and Efficacy of BMS-986156 Administered Alone and in Combination with Nivolumab (BMS-936558, anti PD-1 Monoclonal Antibody) in Advanced Solid Tumors" is an ongoing Phase 1/2a open-label first-in-human (FIH) study of BMS-986156 administered Q2W as a monotherapy and in combination with nivolumab in subjects with advanced solid tumors, evaluating the safety profile, tolerability, preliminary efficacy, PK, and PD of IV doses of BMS-986156. The study is expected to determine the maximum tolerated dose (MTD)/maximum administered dose (MAD) or an alternate dose of BMS-986156 and to establish its safety and tolerability in patients with cancer. Preliminary safety data from Study CA009002 are consistent with a manageable safety profile, with no signals observed.

The monotherapy safety profile supported initiation of the combination dosing at dose level 2 (30 mg BMS-986156). As of 15 Jun 2017, 225 subjects (100 male and 125 female) have received at least 1 dose of BMS-986156 in combination with nivolumab. BMS-986156 in combination with nivolumab has been tested in a dose escalation phase, with 3 subjects at 30 mg BMS-986156/240 mg nivolumab Q2W, 9 subjects at 100 mg BMS-986156/240 mg nivolumab,14 subjects at 240 mg BMS-986156/240 mg nivolumab Q2W, and 11 subjects at 800 mg BMS-986156/240 mg nivolumab Q2W. The dose for Q2W schedule expansion phase was 240 mg BMS-986156/240 mg nivolumab; 176 subjects were treated as of the data cut-off date. Additionally, BMS-986156 in combination with nivolumab was evaluated in a more convenient schedule of Q4W, with a dose of 480 mg BMS-986156/480 mg nivolumab; 12 subjects were treated as of the data cut-off date. The majority of the

subjects treated with BMS-986156 in combination with nivolumab were Caucasian (91.1%), with a median age of 60.0 years.

Overall, the safety profile of BMS-986156 combination therapy is manageable with no MTD reached. Two hundred and four out of 225 subjects treated with BMS-986156 in combination with nivolumab experienced AEs. AEs were mainly Grade 1 and Grade 2. The most frequently reported AEs (>10% of subjects) were fatigue, nausea, pyrexia, decreased appetite, diarrhea, malignant neoplasm progression, cough, anemia, vomiting, chills, abdominal pain, constipation, and dyspnea. AEs reported for 133 subjects were considered related to study drug because no other potential cause for the event could be identified. One DLT (Grade 4 creatine phosphokinase [CPK] increased) was reported for 1 subject receiving 800 mg of BMS-986156 in combination with 240 mg nivolumab Q2W, but the subject did not display any clinical signs or symptoms. The 5 most frequent drug-related AEs included fatigue, pyrexia, chills, infusion related reaction, and nausea. One hundred and two subjects experienced SAEs and 14 SAEs were considered related to study drug. Forty-five subjects died due to disease progression. There were no deaths related to study drug reported during combination therapy. There were 5 events leading to discontinuation due to disease progression (4 reported as malignant neoplasm progression, and 1 reported as disease progression). There were 4 related AEs that led to discontinuation from study drug for the combination therapy treatment group. The safety profile of combination therapy was comparable to Nivolumab monotherapy.

In summary, 213 subjects have been treated with BMS-986156 in combination with nivolumab Q2W; 190 of those received 240 mg BMS-986156/240 mg nivolumab, which was the dose chosen for expansion. Overall, BMS-986156 administered in combination with nivolumab in a Q2W schedule showed a safe profile. An additional 12 subjects were treated with 480 mg BMS-986156 in combination with nivolumab. BMS-986156 dosing in the monotherapy arm, ranged from 10 up to 800 mg Q2W. The safety profile supported initiation of the combination dosing of 30 mg BMS-986156 with 240 mg nivolumab Q2W in Part B. Combination of BMS 986156 and nivolumab has been tested in a dose escalation from 30 mg BMS 986156/240 mg nivolumab Q2W up to 800 mg BMS 986156/240 mg nivolumab Q2W, which were found to be safe. In expansion phase, 240 mg BMS 986156/240 mg nivolumab Q2W is being evaluated in part D, and a Q4W schedule of 480 mg BMS-986156/480 mg nivolumab is being tested in Part E of the study.

In the CA009002 study, a flat dose of 240 mg nivolumab Q2W or 480 mg Q4W, was administered in combination with BMS-986156. The nivolumab dose of 240 mg Q2W or 480 mg Q4W were selected based on clinical data and modeling and simulation approaches using population PK and exposure-response analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) where body weight-normalized dosing (mg/kg) has been used. The safety and efficacy of 240 mg Q2W or 480 mg Q4W flat dose of nivolumab is expected to be similar to the approved dose of 3 mg/kg Q2W.

Detailed information about Nivolumab/BMS-986156 combination therapy can be found in the current version of the BMS-986156 IB v03.

3.2. Stereotactic Body Radiation Therapy

The development of precise radiation beam-shaping along with improved algorithms/computing power for target tracking and radiation dosimetry, and new techniques to minimize setup variations has facilitated the implementation of stereotactic body radiation therapy (SBRT). This modality allows for highly conformal treatment with markedly increased radiation doses (>10 Gy per dose). SBRT has been shown to achieve high levels of tumor control with relatively large total doses given over a small number of fractions. This process, termed hypofractionation, results in the delivery of high biological effective dose (BED) while sparing normal tissue toxicities.

In the setting of numerous prospective single arm trials, SBRT has shown efficacy in the control various metastatic disease sites. Herfrath et al reported on a phase I/II clinical trial that achieved local tumor control rates of 81% 18 months following SBRT (14-26 Gy total dose) with no major side effects (8). More contemporary trials have reported even better rates of local control with higher SBRT doses. Rusthoven et al. reported local control rates of 92% at 2 years following SBRT (36-60 Gy)(13). Similar results have been reported in the control of pulmonary metastases, with prospective trials reporting 96% local control in 1-3 pulmonary lesions 2 years following SBRT treatment (48-60 Gy)(14).

In addition to palliation of metastatic disease, SBRT has demonstrated efficacy in the definitive management of early stage I NSCLC. Although the standard of care has been surgical resection, a significant portion of the population is unable to tolerate surgery due to medical comorbidities or refusal due to personal preference. The predominant non-surgical intervention is SBRT in these cases. In a multi-institutional retrospective series, Onishi reported low rates (14.5%) of local progression 2 years following 18-75 Gy definitive SBRT for stage I NSCLC (15). Furthermore, greater control was shown with higher doses. Patients receiving BED ≥100 Gy achieved lower rates of local failure (8.1%) and better 3-year overall survival (88.4%) compared with those receiving BED <100 Gy (local failure: 26.4% and overall survival: 69.4%, both $p<0.05$).
In addition to achieving high rates of local control, radiation therapy has also been shown to promote a potent immunogenic release of tumor antigen and local cytokine release, priming the adaptive immune system towards tumor control (4). Nowhere is this more evident than with SBRT. Complementary to the ability of SBRT to achieve local control, preclinical studies have demonstrated that such high BEDs promote tumor-antigen release, achieving T-cell priming in a manner superior to that seen with conventional fractionation (16). Such immune education has been shown to promote distal disease control (also known as the abscopal effect) both in pre-clinical models and in clinical cases. Clinical descriptions of this phenomenon has been predominately through limited and often sporadic case reports where unexpected and pronounced distal tumor regression is observed outside of SBRT radiation fields (17, 18).

3.3. Rationale and Scientific Impact

Encouraged by mounting evidence, a number of early phase I trials have begun to prospectively investigate the pairing of immune stimulants with radiation to achieve ever more instances of the abscopal effect. Brody et al. reported on 15 patients with advanced stage low-grade lymphomas. Objective responses in non-irradiated sites were observed in 6 patients following 4 Gy radiation coupled with the injection of a C-G enriched synthetic oligodeoxynucleotide, an established toll-like receptor agonist meant to produce immunostimulation (16, 19). Similar results were observed applying this strategy to treat cutaneous lymphomas(20). Furthermore, Seung et al. treated 11 metastatic melanoma and renal cell carcinoma patients with 60 Gy SBRT given in 3 fractions followed by adjuvant systemic IL-2 administration (21). In this study, complete metabolic resolution in non-irradiated sites was observed in 6 patients with partial responses in 2 others. Assessment of responders found that they exhibited significantly greater frequencies of proliferating CD4+ T-cells expressing an early activated phenotype, providing further evidence of an immune-mediated phenomenon (21).

Focus has increasingly shifted towards combining radiation with the new emerging class of checkpoint inhibitors, chief among these has been ipilimumab, which has recently been approved for melanoma. In murine models featuring relatively immunogenic tumors, anti-CTLA-4 monoclonal antibodies have been shown to induce immune-mediated regression and specific T-cell memory (22). However, additional immune conditioning in the form of vaccinations or chemotherapy were required to induce anti-tumor immunity in poorly immunogenic tumors , a finding corroborated by clinical studies which show a relatively low proportion of patients achieving lasting clinical responses . To this end, radiation when coupled with anti-CTLA-4 monoclonal antibody was found

to induce a potent immune response in non-immunogenic tumor that were previously unresponsive to anti-CTLA-4 monotherapy(23). A number of preclinical studies conducted by Dr. Demaria's group and others have provided evidence that radiation induced antigen release is a potent immune adjuvant that when combined with anti-CTLA-4 therapy results in profound immune-mediated systemic disease control outside of the radiation field (24).

At least two clinical cases of systemic disease regression have been reported following the combination of ipilimumab with SBRT. Postow et al. reported on a patient with metastatic melanoma who was previously enrolled on a trial with ipilimumab. While receiving maintenance ipilimumab therapy, the patient was treated with SBRT to 28.5 Gy in 3 fractions to palliate a symptomatic paraspinal mass (5). Following 1 month after SBRT, metastatic foci in the right hilum and spleen showed marked regression. A similar report by Hiniker et al. detailed another patient with metastatic melanoma who received SBRT to 54 Gy in 3 fractions to two out of five metastatic liver lesions (6). Follow up imaging noted metabolic resolution of all liver lesions in addition to a left axillary lesion well outside of the radiation field. In light of these pre-clinical and clinical studies, we are optimistic that our study, combining CTLA-4 blockade (ipilimumab) with SBRT, will result in increased anti-tumors responses in both locally irradiated and systemic non-irradiated disease sites.

This phase I/II clinical trial is designed to test the effectiveness of SBRT targeting 1-4 lung or liver lesions with systemic ipilimumab and BMS-986156 in patients with metastatic disease. For all arms of this trial, ipilimumab will be administered at 3 mg/kg every 21 days for 4 cycles. The rational for adding in SBRT after two cycles of Ipilimumab is based on the observation that Ipilimumab can take a few cycles of treatment to induce an immune responses. This is supported by the work of Wolchok et al (12), which demonstrated that lymphocyte infiltration can take weeks to happen which is one of the reasons that the standard RECIST criteria are not adequate for assessing responses to checkpoint inhibitors. The development of irRC is to better assess the delayed immunologic responses seen with Ipilimumab. Based on this work and others we feel that having an arm that gives 2 cycles of Ipilimumab prior to SBRT provides a rational way of combining with radiation.

Preliminary safety data on ipilimumab and SBRT: Combining ipilimumab and SBRT was safe with signs of efficacy (1, 25). In this phase I trial, treatments combining liver or lung SBRT at 50 Gy in 4 fractions or 60 Gy in 10 fractions concurrently or sequentially with ipilimumab at 3 mg/kg for 4 doses were considered safe. Two patients (6%) had DLTs, and even though rates of grade 3 treatment-related toxicity were 34% of treated patients, most were self-limiting and managed as an outpatient. Data on efficacy is encouraging, with 10% out-of-field irPR and 23% clinical benefit. Though these data are encouraging, the outcome may be improved by adding another I-O agent to the treatment regimen: we propose to test the safety and efficacy of combining BMS-986156 with ipilimumab + SBRT. However, there are no clinical data available on the safety of BMS-986156 + Ipilimumab. Treatment group 1 will be initiated to determine the safety of combining BMS-986156 (30 or 100 mg) and ipilimumab (3 mg/kg). After BMS-986156 dose determination in group 1, group 2 will be initiated with BMS-986156 (dose as determined in group 1) and ipilimumab plus SBRT. Recently, in our preclinical model of PD-1 resistance we have shown a dramatic improvement in radiation-induced abscopal responses with the addition of anti-GITR antibody. Moreover, an ongoing study (CA009-002) has recently provided human safety data following administration of a flat dose of nivolumab, another checkpoint inhibitor, in combination with BMS-986156, an anti-GITR monoclonal antibody (26). Altogether, these studies suggest that anti-GITR, a T-cell agonist, may potentiate a T cell mediated response and may contribute to abscopal responses observed when SBRT is administered with checkpoint inhibitors such as ipilimumab or nivolumab. These findings likewise prompted us to include additional arms involving concurrent SBRT administration with anti-GITR plus either ipilimumab or nivolumab in this study. Treatment group 3 will be initiated with nivolumab (480mg) plus BMS-986156 (30mg) and SBRT combination therapy.

Our hypotheses are as follows:

1) SBRT targeting a limited number of liver or lung metastasis in conjunction with ipilimumab and BMS-986156 or nivolumab and BMS-986156 combination therapy will result in improved local and systemic disease control.

2) that the underlying mechanism of action is through the SBRT mediated release of immunogenic tumor antigens that promote systemic immune-mediated tumor response that is further potentiated by systemic checkpoint inhibitor therapy.

4. Eligibility Criteria

To be eligible for this trial, patients must meet all of the following criteria.

4.1. Inclusion Criteria

1. Patients must have histological confirmation of solid metastatic cancer (all groups) with at least one metastatic or primary lesion in the liver or lung/chest (groups 2 and 3). All Groups must have measureable disease per irRC criteria.
2. Patients who have completed prior systemic anti-cancer therapies, an interval of 5 drug half-lives or 4-weeks whichever is shorter, is required, prior to enrollment on study. Note: patients with anaplastic thyroid will be waived from this inclusion criteria given the rapid trajectory of their disease.
    - Patients that have previously progressed on immunotherapy such as ipilimumab, anti-PD-I, anti-PDL-1 or talimogene laherparepvec (T-VEC) will be eligible.
3. All patients must have at least one metastatic or primary lesion within the lung/chest or liver located in an anatomical location amenable to SBRT treatment with 50 Gy in 4 fractions or with 60 Gy in 10 fractions, except for group 1.
4. Repeat radiation in fields previously radiated will be allowed at the discretion of the treating physician.
5. Age ≥18 years
6. ECOG performance status ≤2 (Karnofsky >60%).
7. Patients must have normal organ and marrow function as defined below: (use of growth factors or blood transfusion to achieve these requirements is not allowed 2 weeks prior to study enrollment)
    - Total bilirubin ≤ 2.0 mg/dL. (Does NOT apply to patients with Gilbert's Syndrome)
    - AST(SGOT)/ALT(SGPT) <2.5 X institutional upper limit of normal.
    - WBC ≥ 2500/uL, ANC ≥ 1000/uL
    - Platelets ≥ 75K
    - Hemoglobin ≥ 9g/dL
    - Creatinine ≤ 2.0 x ULN
8. Patients must be willing and able to review, understand, and provide written consent before starting therapy.
9. Patients with brain metastasis will be included as long as they are free of neurologic symptoms related to metastatic brain lesions and who do not require or receive systemic corticosteroid therapy, > 10 mg/day in the 14 days prior to beginning the trial (≤ 10 mg steroid, e.g.: prednisone, is allowed). We will allow patients with stable brain metastases (clinically and radiographically) for ≥ 4 weeks to enroll on the protocol.

4.2. Exclusion Criteria

1. Serious autoimmune disease at the discretion of the treating attending: Patients with a history of active serious inflammatory bowel disease (including Crohn's disease and ulcerative colitis) and autoimmune disorders such as rheumatoid arthritis, systemic progressive sclerosis [scleroderma], Systemic Lupus Erythematosus or autoimmune vasculitis [e.g., Wegener's Granulomatosis] are excluded from this study.
2. Active diverticulitis, intra-abdominal abscess, GI obstruction, abdominal carcinomatosis or other known risk factors for bowel perforation.
3. Any underlying medical or psychiatric condition, which in the opinion of the Investigator, will make the administration of study drug hazardous or obscure the interpretation of AEs: e.g. a condition associated with frequent diarrhea or chronic skin conditions, recent surgery or colonic biopsy from which the patient has not recovered, or partial endocrine organ deficiencies.
4. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, history of congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
5. Known active HIV, Hepatitis B, or Hepatitis C that has not been documented to be stable.
6. Any non-oncology vaccine therapy used for prevention of infectious diseases (for up to one month prior to or after any dose of ipilimumab).
7. Concomitant therapy with any of the following: IL-2, interferon or other non-study immunotherapy regimens; cytotoxic chemotherapy; immunosuppressive agents; other investigational therapies; or chronic use of systemic corticosteroids while receiving ipilimumab (as long as steroid replacement is significantly greater than what is required for physiologic replacement, i.e. in hypothyroidism).
8. Pregnant women are excluded from this study. Women of child-bearing potential (WOCBP) must have a negative urine or serum pregnancy within 7 days of study enrollment up to administration of the dose of study drug.During the course of the treatment and **160 days** AFTER the last dose of study drug you should not get pregnant or breast feed. In the case of male participants, during the course of treatment and **220 days** AFTER the last dose of immunotherapy you should not father a child (condom use is mandatory, even if vasectomized) or donate sperm. For contraception guidelines please see section 9 of this protocol.
9. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 31 weeks after the last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year. History of or current immunodeficiency disease or prior treatment compromising immune function at the discretion of the treating physician.
10. Prior allogeneic stem cell transplantation;
11. Patients who were intolerant to previous immuno-oncology (IO) drugs should be excluded.

4.3. Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial. The patient population screened for this study adheres to the referral patterns reported at M.D. Anderson Cancer Center.

5. Immunotherapy Information

5.1. Ipilimumab (Yervoy™): manufactured by Bristol-Myers Squibb Co (BMY)

5.1.1. Physical/Chemical Properties*:*

Ipilimumab is an IgG1 monoclonal antibody. It is a soluble protein consisting of 4 polypeptide chains, 2 identical heavy chains consisting of 477 amino acids and 2 identical kappa light chains consisting of 215 amino acids each linked through inter-chain disulfide bonds. It has a molecular weight of 147,991 daltons (d) and it is a clear to slightly opalescent, colorless to pale yellow liquid, may contain particles, with a pH of 7.0. The isoelectric focusing analysis generates a banding pattern in the isoelectric point (pI) range of 8.5 to 8.8, with the major isoform at an approximate pI of 8.7.

5.1.2. Mechanism of Action*:*

Ipilimumab is a human immunoglobulin G (IgG1)κ anti-CTLA-4 monoclonal antibody (mAb) that binds to CTLA-4 antigen expressed on the plasma membrane of T cells and blocks the interaction of CTLA-4 with its natural ligands, B7.1 (CD80) and B7.2 (CD86). *In vitro* studies were performed with ipilimumab to demonstrate that it is specific for CTLA-4, actively inhibits CTLA-4 interactions with B7.1 and B7.2, and does not show any binding to human B7.1, B7.2 negative cell lines, demonstrating by immunohistochemistry that ipilimumab is specific and non-cross reactive in non-human primate tissues.

5.1.3. Pharmacology:

Ipilimumab is a human immunoglobulin G (IgG1)κ anti-CTLA-4 monoclonal antibody (mAb). In vitro studies were performed with ipilimumab to demonstrate that it is specific for CTLA-4, actively inhibits CTLA-4 interactions with B7.1 and B7.2, does not show any cross-reactivity with human B7.1, B7.2 negative cell lines, and stains the appropriate cells without non-specific cross-reactivity in normal human tissues, as demonstrated by immunohistochemistry. Ipilimumab does cross-react with CTLA-4 in non-human primates including cynomolgus monkeys.

Ipilimumab was originally produced and purified from a hybridoma clone. Subsequently, a transfectoma (CHO cell) has been generated that is capable of producing more ipilimumab on a per cell basis than the hybridoma. Material from the transfectoma will be utilized in this and future ipilimumab clinical studies. Biochemical, immunologic and in vivo preclinical primate assessments demonstrated similarity between hybridoma and transfectoma-derived ipilimumab.

5.1.4. Pre-clinical Toxicology:

Complete information on the pre-clinical toxicology studies can be found in the ipilimumab Investigator Brochure (IB). Non-clinical toxicity assessments included in-vitro evaluation for the potential of ipilimumab to mediate complement-dependent cellular cytotoxicity (CDCC) or antibody-dependent cellular cytotoxicity (ADCC), and toxicology assessments in cynomolgus monkeys alone and in the presence of vaccines.

The *in vitro* studies demonstrated that ipilimumab did not mediate CDCC of PHA- or (CD)3-activated human T cells. However, low to moderate ADCC activity was noted at concentrations up to 50 ug/mL. These data are consistent with the requirement of high levels of antigen expression on the surface of target cells for efficient ADCC or CDCC. Since ipilimumab is a human IgG1, an isotype generally capable of mediating CDCC and ADCC, the lack of these activities is likely due to a very low expression of CTLA-4 on activated T cells. Therefore, these data suggest that ipilimumab treatment would not result in depletion of activated T cells in-vivo. Indeed, no depletion of T cells or T cell subsets were noted in toxicology studies in cynomolgus monkeys.

No mortality or signs of toxicity were observed in three independent 14-day intravenous toxicology studies in cynomolgus monkeys at multiple doses up to 30 mg/kg/dose. Furthermore, ipilimumab was evaluated in sub chronic and chronic toxicology studies in cynomolgus monkeys with and without hepatitis B (HepB) and melanoma vaccine. Ipilimumab was well tolerated alone or in combination in all studies. There were no significant changes in clinical signs, body weight values, clinical pathology values or T-cell activation markers. In addition, there were no significant histopathology changes in the stomach or colon.

5.1.5. Pharmacokinetics of Ipilimumab in Patients:

Pharmacokinetic (PK) profiles for ipilimumab have been analyzed. The primary objective of Protocol MDX-010-015 was to determine the safety and PK profile of single and multiple doses of ipilimumab derived from a transfectoma or hybridoma cell line. This study is still ongoing and data is preliminary. Mean plasma concentrations of ipilimumab administered at dosages of 2.8 mg/kg (transfectoma-derived drug product), 3 mg/kg (hybridoma-derived drug product,), 5 mg/kg and 7.5 mg/kg (transfectoma) appear to be dose-proportional over time. Preliminary PK analyses reveal that the volume variables were approximately that of plasma volume (range of mean apparent volume of distribution at steady state [Vss] across cohorts 2.8, 3, 5, 7.5, 10, 15 and 20 mg/kg was 57.3 to 82.6 mL/kg), indicating drug distribution was mostly limited to the intravascular space. The clearance (Cl) was low (range 0.11 to 0.29 mL/h/kg) and reflective of the half-life (range 297 to 414 h). Mean residence time (MRT) was long (range 435 to 538 h), consistent with the long terminal disposition phase of ipilimumab. In general, there was moderate variability in the PK parameters among patients, with coefficient of variation (CV) of 11% to 48% in AUC (0-21d), 20% to 59% in Cl and 17% to 46% in ss. Future clinical studies, including this study, will utilize the transfectoma derived product.

5.1.6. Clinical Safety:

The safety profile of ipilimumab has been consistent across trials with a) the majority of adverse events being inflammatory in nature and consistent with the proposed mechanism of action of ipilimumab (immune-related adverse events, IRAEs), b) the same types of such immune-mediated events in the GI tract, skin, liver, and endocrine system being reported and c) most of these events being manageable with immune suppressive therapies. Overall, nearly all subjects in clinical studies with ipilimumab reported AEs of any grade and most reported at least 1 AE that was considered treatment related.

5.1.7. Drug-Related Adverse Events (AEs) and Severe Adverse Events (SAEs):

Details of Drug-Related AEs and SAEs:

Drug-related adverse events (AEs) have been reported in studies with ipilimumab as monotherapy as well as in combination studies with vaccines, cytokines, chemotherapy, and other checkpoint inhibitors.

The AE profile of ipilimumab is relatively well characterized with drug-related AEs mostly being immune-related adverse events (IRAEs), which are considered to be associated with the mechanism of action of ipilimumab. The most common IRAEs are colitis and diarrhea, rash, pruritus, deficiencies of endocrine organs (pituitary, adrenal, or thyroid), hepatitis, or uveitis. Rare complications (all <1%) are ocular inflammation, arthritis/arthralgias, autoimmune meningitis, autoimmune nephritis, pure red cell aplasia, polymyositis, infusion reaction, myasthenia gravis, and bowel perforations resulting from underlying severe colitis, which have required surgical intervention.

Drug-related Grade 3 or 4 serious AEs (SAEs) consist mostly of immune-related SAEs and include: rash/desquamation, pruritus, uveitis, speech impairment, abdominal pain,

diarrhea/colitis, nausea/vomiting, transaminase elevation, adrenal insufficiency, myocarditis and panhypopituitarism Please refer to the most recent version of Investigator's Brochure (IB) for the latest update on SAEs.

5.1.8. Immune-Related Adverse Events (IRAEs):

Many of the adverse events considered related to ipilimumab appear to be immune in nature and presumably a consequence of the intrinsic biological activity of ipilimumab. An immune-related adverse event (IRAE) is defined as any adverse event associated with drug exposure and consistent with an immune-mediated phenomenon. Disease progression, infections and other etiologic causes are ruled out or deemed unlikely as contributing to the event. Supportive data, such as autoimmune serology tests or biopsies, are helpful but not necessary to deem an event an IRAE. Events of unclear etiology which were plausibly "immune mediated" have been conservatively categorized as IRAEs even if serologic or histopathology data are absent. These IRAEs likely reflect a loss of tolerance to some self-antigens or an unchecked immune response to gut or skin flora. Some breakthrough of immunity may be inseparably linked to the clinical antitumor activity of ipilimumab.

Pooled analysis of phase II and III trials of ipilimumab in patients with advanced melanoma showed the following: Of 622 subjects treated with 3mg/kg ipilimumab, 56.8-61.3% reported any IRAEs, 6.3-13% reported Grade 3/4 IRAEs and 0.8-1.1% reported Grade 5 IRAEs. Of 325 patients treated with 10mg/kg ipilimumab, 84.3% reported any drug related AE, and 30.5% reported Grade 3/4 IRAEs (IB v 16.

1. **Immune-related gastrointestinal events:** GI IRAEs occurred in 28.2-31.1% (Grade3/4 4.5-7.6%, Grade 5 0-0.9%) of subjects treated with 3mg/kg of ipilimumab and in 36.3% (Grade 3/4: 11.7%; Grade 5: 0%) of subjects treated with 10mg/kg of ipilimumab. The clinical presentation of GI IRAEs included diarrhea, increase in the frequency of bowel movements, abdominal pain or hematochezia, with or without fever. Among approximately 10,000 subjects in the BMS internal safety database, 0.5% (51/10,000) reported colitis that was unresponsive to medical management and necessitated colectomy, or had bowel wall perforations associated with ipilimumab-induced colitis. Fourteen of the 51 subjects died of bowel wall perforation complications. Patients should be carefully monitored for GI symptoms that may be indicative of immune-related colitis, diarrhea or GI perforation. Diarrhea or colitis occurring after initiation of ipilimumab therapy should be evaluated to exclude infectious or alternate etiologies. In clinical trials, immune-related colitis was associated with evidence of mucosal inflammation, with or without ulcerations, and lymphocytic infiltration. GI IRAEs should be monitored until resolution.

2. **Inflammatory hepatotoxicities**: Hepatic IRAEs were reported in 2.1-3.8% (Grade 3/4: 0-2.3%; Grade 5: 0-0.8%) subjects treated with 3mg/kg of ipilimumab and in 8% (Grade 3/4: 6.8%, Grade 5: 0%) of patients treated with 10mg/kg of ipilimumab. Hepatic IRAEs were mostly clinically silent and manifested as transaminase or bilirubin laboratory abnormalities. Fatal hepatic failure has been reported in clinical trials of ipilimumab. Serum transaminase and bilirubin levels must be evaluated before each dose of ipilimumab as early laboratory changes may be indicative of emerging immune-related hepatitis. Evaluations to exclude other causes of hepatic injury, such as infections, disease progression or medications should be undertaken, Liver function abnormalities should be monitored until resolution. Liver biopsies from subjects who had IR hepatotoxicity showed evidence of acute inflammation (neutrophils, lymphocytes, and macrophages).

3. **Endocrine toxicities**: Endocrine IRAEs were reported in 3.4-7.6% (Grade 3/4: 0.9-3.8%,

Grade 5: 0%) of subjects receiving 3mg/kg of ipilimumab and in 6.2% (Grade 3/4: 2.5%; Grade 5: 0%) of subjects receiving 10mg/kg of ipilimumab. Ipilimumab can cause inflammation of the endocrine system organs, specifically hypophysitis, hypopituitarism, and adrenal insufficiency and patients may present with nonspecific symptoms, which may resemble other causes such as brain metastasis or underlying disease. The most common presentation includes headache and fatigue. Symptoms may also include visual field defects, behavioral changes, electrolyte disturbances and hypotension. Adrenal crisis as a cause of the patient's symptoms should be excluded. Based on the available data with known outcome, most of the subjects symptomatically improved with hormone replacement therapy. It is possible that long-term hormone replacement therapy will be required for subjects developing hypophysitis/hypopituitarism after treatment with ipilimumab.

4. **Dermatologic toxicities**: Skin IRAEs were reported in 38.9-42.3% (Grade 3/4 0.8-2.4%, Grade 5 0) of subjects receiving 3mg/kg of ipilimumab and in 51.4% (Grade 3/4: 2.5%; Grade 5:0%) of subjects receiving 10mg/kg of ipilimumab. Skin IRAEs presented mostly as a rash and/or pruritus. Some subjects reported vitiligo associated with ipilimumab administration. Fatal toxic epidermal necrolysis has been reported in clinical trials of ipilimumab.

5. **Neurological toxicities**: Neurological IRAEs were reported in 0-0.5% (Grade 3/4: 0-0.3%, Grade 5: 0-0.3%) of subjects receiving 3mg/kg of ipilimumab and in 0.3% (Grade 3/4: 0%; Grade 5: 0%) of subjects receiving 10mg/kg of ipilimumab. Neurological manifestations included muscle weakness and sensory neuropathy. Among approximately 10,000 subjects treated in the ipilimumab program as of 24-Jun-2011, 11 (0.1%) cases of Guillain-Barre syndrome and 5 (0.05%) cases of myasthenia gravis considered related to study drug were reported, and 2 of the Guillain-Barre syndromes had a fatal outcome. Patients may present with muscle weakness. Sensory neuropathy may also occur. Unexplained motor neuropathy, muscle weakness, or sensory neuropathy lasting more than 4 days should be evaluated and non-inflammatory causes such as disease progression, infections, metabolic syndromes and medications should be excluded.

6. **Other toxicities**: Other IRAEs were reported in 2.3-3.8% (Grade 3/4: 0.8-1.5%, Grade 5: 0-0.3%) of subjects receiving 3mg/kg of ipilimumab and in 5.2% (Grade 3/4: 2.2%; Grade 5: 0.6%) of subjects receiving 10mg/kg of ipilimumab. Ocular inflammation, manifested as Grade 2 or Grade 3 epislcleritis or uveitis, was associated with concomitant diarrhea in a few subjects (<1%) and occasionally occurred in the absence of clinically apparent GI symptoms. Other presumed IRAEs reported include, but were not limited to, arthiritis/arthralgias, pneumonitis, pancreatitits, autoimmune (aseptic) meningitis, autoimmune nephritis, pure red cell aplasia, noninfective myocarditis, polymyositis, and myasthenia gravis, of which were individually reported for <1% of subjects.

5.1.9. Onset and Resolution of IRAEs:

The median time to onset of Grade 3-5 IRAEs in MDX010-20 and Phase 2 studies was 7 to 9 weeks. The time to onset of IRAEs was comparable between the 3- and 10-mg/kg doses. With the recommended treatment guidelines, the median times to resolution of Grades 3-4 IRAEs was 4 to 8 weeks. The time to resolution of IRAEs was comparable between the 3 and 10-mg/kg doses.

5.1.10. Ipilimumab Dose-dependent Safety Profile:

In MDX010-20, immune-related adverse events (irAEs) occurred in 60% of subjects treated with ipilimumab (3mg/kg) and ≥ Grade 3 events occurred in 12-16%. Treatment related Aes leading to discontinuation of therapy were reported in 9.9% of the ipilimumab monotherapy arm

vs 3.0% of the gp100 monotherapy arm. The most common (>1%) treatment related Aes leading to discontinuation in the ipilimumab monotherapy arm were colitis (2.3%), diarrhea (1.5%), and uveitis (1.5%). In a pooled 3mg/kg group from the Phase 2 studies, 8.1% of subjects reported treatment-related Aes leading to discontinuation. The most common were hypopituitarism (2.7%), colitis (1.8%), and decreased appetite (1.8%). In MDX010-20, treatment-related deaths (defined as a treatment-related AE with an outcome of death, reported at any time during the study) were reported in 4 subjects (3.1%) in the ipilimumab monotherapy group, 8 subjects (2.1%) in the ipilimumab plus gp100 group and 2 (1.5%) subjects in the gp100 monotherapy group.

In CA184024, any irAEs occurred in 76% of subjects treated with ipilimumab (10mg/kg) + DTIC, Grade 3 events were reported in 31.6% and Grade 4 events in 10.1%. Treatment-related SAEs were reported for 47% and 6.8% in the ipilimumab plus DTIC and DTIC monotherapy groups respectively. The most common events in the ipilimumab plus DTIC group were increased ALT and AST (19% each). Other SAEs reported in ≥5% of subjects in the ipilimumab plus DTIC group included diarrhea (6.5%) and pyrexia (5.7%). There were no treatment-related Aes with an outcome of death in the ipilimumab plus DTIC group and 1 (0.4%) in the DTIC group (GI hemorrhage). In a pooled analysis of 325 patients receiving 10mg/kg ipilimumab therapy, Aes (any grade) were reported in 96.9%, Grade 3-4 Aes in 37.5%, related Aes in 84.3%, Grade 3-4 related Aes in 30.5%, SAEs in 51.7%, related SAEs in 29.2%.

In CA184022, 3 dose levels of ipilimumab were studied, including 0.3 (n=72) vs 3 (n=71) vs 10mg/kg (n=71). Overall irAEs were reported in 64.8% and 70.4% of patients treated at 3mg/kg and 10mg/kg respectively, Grade 3-4 irAEs were reported in 7% and 25.4% respectively, GI irAEs in 32.4% and 39.4% respectively, Grade 3-4 GI irAEs in 2.8% and 15.5% respectively, hepatic grade 3-4 irAEs in 0% and 2.8% respectively, endocrine Grade 3-4 irAEs in 2.8% and 1.4% respectively and skin Grade 3-4 irAEs in 1.4% and 4.2% respectively.

In summary, the safety profile of ipilimumab 10mg/kg remains consistent with the low-dose safety profile in that most of the treatment-related SAEs are characteristic of immune-related toxicity, and most of the IRAEs are reported in the GI, hepatic and endocrine systems. However, the frequency of IRAEs, particularly of high grade events, is higher with 10mg/kg of ipilimumab at multiple doses compared with the IRAE frequency reported for lower doses.

5.1.11. Drug Related Deaths:

Based on the data available in the BMS internal safety database as of 24-June-2011, study-drug related deaths based on the investigator's assessment were reported in 82 subjects. Therefore, the reported rate of treatment-related deaths from the program-wide studies was approximately 0.8% (82/10,000). While a causal role of ipilimumab in these 82 deaths could not be ruled out, confounding factors could be identified in most of these cases.

5.1.12. Clinical Efficacy:

Ipilimumab prolonged survival in subjects with pre-treated and previously untreated advanced melanoma, based on results from 2 large, multinational, double-blind, Phase 3 studies (MDX010-20 and CA184024), supported by data from Phase 2 studies.

In prostate cancer, ipilimumab is being evaluated in Phase 1 and 2 studies, as well as in a randomized Phase 3 trial. Although sample sizes were small, response as measured by ≥50% decline in PSA have been reported. Responses were durable, ranging between 2 and 24 months.

5.1.13. Association between Safety (IRAEs) and Efficacy (OS)

Results from MDX010-20 suggested a tendency for improved OS in subjects with any IRAEs. In CA184024, analyses using the Cox proportional hazards model were conducted to assess the association of IRAEs and OS. Overall, the results showed a significant improvement in OS in subjects with Grade 3/4 IRAEs (any Grade 3/4: HR 0.23 [95% CI: 0.10, 0.54]; liver Grade 3/4: HR 0.25 [95% CI: 0.10, 0.65])(27). These results should be interpreted with caution, as the analysis was not adjusted for other prognostic factors.

Based on the current clinical experience with the use of corticosteroids for the management of treatment-emergent IRAEs, corticosteroids do not adversely affect the antitumor response in subjects with objective responses and concomitant serious IRAEs(28)

5.1.14. Formulation

The Ipilimumab injection, 200 mg/40 mL (5 mg/mL), is formulated as a clear to slightly opalescent, colorless to pale yellow, sterile, nonpyrogenic, single-use, isotonic aqueous solution that may contain particles. The ipilimumab injection, 200 mg/40 mL, is supplied in 50-cc type I flint glass vials, respectively, stoppered with gray butyl stoppers and sealed with aluminum seals. The drug product is formulated at a concentration of 5 mg/mL at a pH of 7.0. The quantitative composition for the 50- and 200-mg/vial products is provided in Table 1.

Table 1. Quantitative Composition of Ipilimumab Injection

	Process B		Process C/C.1	
Component	**50 mg/vial[a]**	**200 mg/vial[b]**	**50 mg/vial[a]**	**200 mg/vial[b]**
Ipilimumab	53.5 mg	213.0 mg	53.5 mg	213.0 mg
Sodium Chloride	62.6 mg	249.0 mg	62.6 mg	249.0 mg
TRIS Hydrochloride	33.7 mg	134.3 mg	33.7 mg	134.3 mg
Pentacetic Acid[c]	0.42 mg	1.67 mg	0.42 mg	1.67 mg
Mannitol	107 mg	426 mg	107 mg	426 mg
Polysorbate 80	1.07 mg	4.26 mg	1.18 mg	4.69 mg
Sodium Hydroxide	QS to pH 7.0			
Hydrochloric Acid	QS to pH 7.0			
Water for Injection	QS to10.7 mL	QS to 42.6 mL	QS to10.7 mL	QS to 42.6 mL
Nitrogen[d]	Processing Agent			

a Includes a 0.7-mL overfill for vial-needle-syringe withdrawal losses.
b Includes a 2.6-mL overfill for vial-needle-syringe withdrawal losses.
c Diethylenetriaminepentaacetic acid.
d Nitrogen is used to transfer the bulk solution through the prefilter and sterilizing filters into the aseptic area.
Abbreviations: QS = quantity sufficient

5.1.15. Packaging and labeling

Ipilimumab available at a concentration of 5 mg/mL, in single use vials, containing 40 mL (NDC 0003-2328-22) solution.

5.1.16. Storage, handling and dispensing of Ipilimumab

Ipilimumab injection, 50 mg/10 mL (5 mg/mL) or 200 mg/40 mL (5 mg/mL), must be stored refrigerated (2°C to 8°C) and protected from light. Ipilimumab injection must not be frozen.
Partially used vials or empty vials of ipilimumab injection should be discarded at the site according to appropriate drug disposal procedures.
Ipilimumab injection may be stored undiluted (5 mg/mL) or following dilution in 0.9% Sodium

Chloride Injection, USP or 5% Dextrose Injection, USP in PVC, non-PVC/non-DEHP, or glass containers for up to 24 hours at 2°C to 8°C or room temperature/room light.
Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.
Ipilimumab injection (5 mg/mL) can be used for intravenous (IV) administration without dilution after transferring to a polyvinyl chloride (PVC), non PVC/non di (2 ethylhexyl)phthalate (DEHP), or glass container and is stable for 24 hours at 2°C to 8°C or room temperature/room light. Ipilimumab injection may be diluted in 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) or 5% Dextrose Injection, USP to concentrations between 1 mg/mL and 4 mg/mL and stored in PVC, non PVC/non DEHP, or glass containers for up to 24 hours at 2°C to 8°C or room temperature/room light. The product may be infused using a volumetric pump at the protocol-specific dose(s) and rate(s) through a PVC IV solution infusion set with an in-line, sterile, nonpyrogenic, low protein binding filter (pore size of 0.2 μm to 1.2 μm). Ipilimumab injection must not be administered as an IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents.

5.1.17. Dose Calculations

- Total dose should be calculated as follows:
- Subject body weight in kg x 3 mg = total dose, mg Total infusion volume should be calculated as follows:

Total dose in mg ÷ 5 mg/mL = infusion volume, mL

- Rate of infusion should be calculated as follows:

Infusion volume in mL ÷ 90 minutes = rate of infusion, mL/min

For example, a patient weighing 114 kg (250 lb) planned to receive 3 mg/kg of the study drug would be administered 342 mg of ipilimumab (114 kg x 3 mg/kg = 342 mg) with an infusion volume of 68.4 mL (342 mg ÷ 5 mg/mL = 68.4 mL) at a rate of approximately 0.8 mL/min (68.4 mL ÷ 90 minutes) in 90 minutes.

5.1.18. Withholding dose due to toxicities likely attributable to Ipilimumab:

Doses may be "withheld" for 21 days from the date when the dose was scheduled after which time the decision must be made by the principle investigator whether to withhold for an additional 21 days (see criteria below), withdraw the patient from the study, or to continue with the next cycle: *Example: it may be necessary to withhold (maximum 21 days) an ipilimumab dose for the following adverse event(s) considered related to ipilimumab:*

Any Grade 2 non-skin related adverse event except for laboratory abnormalities
Any ≥ Grade 3 laboratory abnormality.

It is necessary to withhold (maximum 21 days) ipilimumab dosing for the following adverse events:

Any ≥ Grade 3 skin-related adverse event regardless of causality;
Any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, warrants withholding the dose of study medication.
A dose withholding longer than 21 days after the scheduled dose will lead to permanent discontinuation.

5.1.19. Criteria to resume Ipilimumab therapy addressed:

When the adverse event(s) resolve(s) to Grade 1 or baseline value, and for endocrinopathies which are controlled with chronic therapy:

Restart dosing at the next scheduled time point per protocol.

If the adverse event has not resolved in the protocol-specified dosing window (ie, 3 weeks from last dose ± 2 days), the next scheduled dose will be withheld.

5.1.20. Drug ordering

Please see Appendix A for information on provisions for ordering ipilimumab from BMS

It is possible that sites may have more than one ipilimumab clinical study ongoing at the same time. It is imperative that only product designated for this protocol be used for this study.

5.2. Anti-GITR agonist monoclonal antibody (BMS-986156): manufactured by Bristol-Myers Squibb Co (BMS)

5.2.1 Physical/Chemical Properties:

BMS-986156 is a fully human anti-GITR mAb, which is a soluble protein consisting of 4 polypeptide chains that include 2 heavy chains and 2 light chains. BMS-986156 is produced from cell culture using a Chinese hamster ovary (CHO) cell line. It has a projected relative mass (Mr) of 145,861 daltons (d) based on amino acid sequence.

GITR is expressed not only in T cells but was also found in a subset of lung tumor cells as determined by IHC. No consequence of GITR engagement by BMS-986156 on proliferation of many GITR+ lung tumor cell lines was observed.

5.2.2 Mechanism of Action:

BMS-986156 is a fully human agonist antibody of the immunoglobulin G subclass 1 (IgG1) isotype that binds to the human glucocorticoid-induced tumor necrosis factor receptor-related (GITR) protein. GITR is a costimulatory molecule on T cells and potentiates T-cell activation when engaged. BMS-986156, a partial ligand-blocking antibody, binds with high affinity to GITR expressed on activated human T cells (half-maximal effective concentration [EC50] 0.42 to 0.44 nM) as well as activated cynomolgus T cells (EC50 0.86 to 0.96 nM). In vitro, BMS-986156 promoted enhanced interleukin (IL)-2 secretion from a mouse T-cell hybridoma expressing human GITR compared to isotype control. BMS-986156 also promoted positive costimulation of anti- CD3 antibody-activated human CD4+ T cells, manifested as an increase in interferon (IFN)-γ secretion.

5.2.3 Nonclinical Pharmacology:

When BMS-986156 binds to GITR and also to Fc gamma receptor (FcγR)-bearing cells via the Fc region of IgG1, GITR is effectively cross-linked, leading to enhanced activity over that of soluble antibody. IgG1 antibodies can also mediate antibody-dependent cellular cytotoxicity (ADCC) or antibody dependent cellular phagocytosis (ADCP) and such activities were observed in vitro using GITR+ target cells. GITR expression is found on multiple lymphoid cell subtypes but is highest on regulatory T cells (Tregs), especially in the tumor microenvironment, and thus, Tregs are the most likely lymphoid cell lineage to be depleted by anti-GITR antibody therapy.

The importance of GITR as an immunotherapy target was validated in murine syngeneic tumor models using a surrogate antibody administered to tumor-bearing mice specific for mouse GITR

(EC50 ≤ 0.22 nM). GITR antibody resulted in both overall tumor growth inhibition and an increase in the number of tumor-free (TF) mice compared to controls. Anti-GITR antibody administered in combination with anti-programmed death-1 (PD-1) antibody provided enhanced antitumor activity above the activity of either agent alone in agreement with previous observations by Lu et al.

As BMS-986156 does not recognize mouse GITR, transgenic mice were derived where the murine ectodomain of GITR was replaced with the human ectodomain. Treatment of these mice bearing MC38 tumors with BMS-986156 promoted antitumor activity compared to isotype control-treated mice. This demonstrates that BMS-986156 has in vivo antitumor activity as a human IgG1 antibody. As such, BMS-986156 has the potential to reduce tumor growth of multiple malignancies when administered as a single agent or in combination with other immuno-oncology (IO) therapeutics.

5.2.4. Clinical Pharmacokinetics:

The pharmacokinetics (PK) of BMS-986156 was evaluated in cynomolgus monkeys and mice. In cynomolgus monkeys, following a single intravenous (IV) dose of 0.4 or 4 mg/kg of BMS-986156, total serum clearance (CLTs) was low, and the apparent elimination half-life (T-HALF) was 6 to 8 days. After a single 2 mg/kg IV dose of the surrogate monoclonal antibody (mAb) anti-GITR mIGg2a to C57BL/6 mice, the T-HALF was 1.2 days and CLTs was 1.5 mL/h/kg. The steady-state volume of distribution (Vss) of BMS-986156 or anti-GITR mIgG2a indicated that anti-GITR mIgG2a largely resides in the extracellular space in mice, while BMS-986156 has limited extravascular distribution in monkeys.

The human PK of BMS-986156 was projected by allometric scaling of the PK in cynomolgus monkeys. The human efficacious dose was projected to achieve an average concentration at steady state of 13 µg/mL, equivalent to the concentration of DTA-1-mIgG2a in the CT26 mouse syngeneic tumor model that rendered 70% of mice TF.3 Based on the projected human PK parameters, the human efficacious dose was estimated to be 0.7 mg/kg following a once-every- 2-week (Q2W) dosing regimen.

5.2.5. Non-clinical Studies

The nonclinical safety of BMS-986156 was evaluated in in vitro tissue cross-reactivity studies in addition to cytokine release assays and lymphocyte assessment in human tissues and cells. In normal human tissues, BMS-986156 binds to the plasma membrane of mononuclear leukocytes in numerous tissues, the epithelium of the parathyroid (peripheral cytoplasm), skin (epidermis and hair follicles; peripheral cytoplasm), and uterus (cervix; cytoplasm and cytoplasmic granules).

In vitro BMS-986156 did not induce cytokine release or increase the expression of activation markers on human T or B cells at concentrations up to approximately 33 µg/mL. A BMS-986156-related dose-dependent increase in natural killer (NK) cell activation marker expression (CD25 and CD69) was observed and considered pharmacologically mediated since GITR is expressed on NK cells. However, these findings were considered of no risk to human safety due to the lack of effects on cytokine release, cell death, or on T- or B-cell activation markers.

The cynomolgus monkey was selected as the toxicology species because BMS-986156 binds to cynomolgus GITR with similar affinity as human GITR, is pharmacologically active in monkeys, and does not bind rodent GITR.5 As part of an exploratory 1-month pharmacodynamic (PD), toxicokinetic (TK), and toxicity study in cynomolgus monkeys (with dosing at 4 or 40 mg/kg, every 10 [Q10] days, x4), BMS-986156 was clinically well tolerated with no adverse findings at either dose. BMS-986156-related findings were considered pharmacologically mediated and were limited to an increase in the level of keyhole limpet hemocyanin (KLH)-specific antibodies from Days 8 to 43 at 40 mg/kg (KLH challenge administered on Day 1). In the pivotal 1-month IV toxicity study in monkeys (0, 10, 40, or 154 mg/kg, once a week [QW], x5), BMS-986156 was clinically well tolerated with no adverse effects at any dose.7 BMS-986156-related findings were again considered pharmacologically mediated and were limited to increases in ex vivo recall response to KLH (as measured by CD4+ T-cell activation)

and an increase in anti-KLH antibodies (immunoglobulin M [IgM] and IgG; mean up to 2.4 x control) at all doses. The high dose of 154 mg/kg (mean sex-combined area under the concentration-time curve [AUC] 495,000 µg·h/mL) was considered the no-observed-adverse-effect level (NOAEL). In addition, an exploratory 2-week toxicity study in mice using an engineered anti-mouse GITR mAb (as an IgG2a), dosed 4 times at 0, 1, or 30 mg/kg, twice weekly (2QW) demonstrated that GITR agonism was also clinically tolerated in mice when administered intraperitoneally (IP), with no evidence of hepatotoxicity.

No significant irritation or local tolerance issues were observed at the injection sites following repeated IV administration of BMS-986156 as a slow bolus injection (3.1 mL/kg; 0.1 to 0.2 mL/sec) at ≤ 154 mg/kg in cynomolgus monkeys.7 There were no BMS-986156-related cardiovascular, respiratory, ophthalmologic, or neurological effects at ≤ 154 mg/kg in monkeys (mean maximum observed concentration [Cmax] ≤ 5,430 µg/mL).

Overall, the nonclinical toxicology assessment of BMS-986156 has demonstrated an acceptable safety profile, supporting clinical use in oncology patients, with AUC and Cmax safety margins relative to projected human exposures at the proposed clinical doses (10 to 800 mg; AUC during the dosing interval [AUC(TAU)] 833.33 to 66,666.7 µg·h/mL; Cmax 4.3 to 342.8 µg/mL) of 1,188 to 15x and 1,263 to 16x, respectively.

5.2.6. Clinical Studies

As of the data lock point for this Investigator Brochure (IB) (15-Jun-2017), 34 subjects have received at least 1 dose of BMS-986156 as monotherapy. All 34 subjects experienced adverse events (AEs). AEs were mostly Grade 1 and Grade 2. The most frequently reported AEs (>10% of subjects) were fatigue, nausea, malignant neoplasm progression, constipation, abdominal pain, decreased appetite, pyrexia, back pain, diarrhea, vomiting, dyspnea, headache, peripheral edema, and pain. AEs reported for 20 subjects were considered related to study drug because no other potential cause for the events could be identified. There were no dose-limiting toxicities (DLTs). The 5 most frequent drug-related AEs included pyrexia, nausea, fatigue, chills, and diarrhea. Nineteen subjects experienced serious adverse events (SAEs), and 1 SAE of Grade 2 pneumonitis was considered related to study drug. There was 1 event of disease progression that led to discontinuation from the study. There were no related AEs that led to discontinuation from study drug during monotherapy. Twenty-two subjects died due to disease progression. Two additional subjects died from other causes. There were no deaths related to study drug reported during monotherapy.

Detailed information about safety, use, and storage of BMS-986156 can be found in the current version of the BMS-986156 IB.

5.2.7 Formulation

BMS-986156 injection is available as 100 mg/vial (10 mg/mL) and is formulated as a colorless to pale yellow liquid, clear to slightly opalescent. It may contain few white or translucent particles. Each 100 mg vial contains BMS-986156, L -histidine, L -histidine hydrochloride monohydrate, sucrose, pentetic acid, hydrochloric acid for pH adjustment, polysorbate 80, water for injection. The fill volume is 10.7 mL and it is provided in a 10-cc type I flint glass vial stoppered with fluoropolymer film-laminated rubber stopper and sealed with aluminum seal. Includes the 0.7-mL overfill for vial, needle, and syringe (VNS) holdup

5.2.8 Packaging and Labeling

BMS-986156 is available as 100 mg/vial (10 mg/mL), in a single use vials, containing 10mL solution.

5.2.9 Storage, handling and dispensing of BMS-986156

Vials of BMS-986156 injection must be stored at 2°C to 8°C (36°F to 46°F), protected from light,

and must not be frozen.BMS-986156 injection is to be administered as an IV infusion through a 0.2 μm pore size, low-protein-binding polyethersulfone membrane in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. BMS-986156 injection can be infused undiluted (10 mg/mL) or diluted with 0.9% sodium chloride injection, or 5% dextrose injection, to protein concentrations as low as 0.1 mg/mL. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Detailed instructions for drug product dilution and administration are provided in the pharmacy manual for the clinical study. Care must be taken to ensure sterility of the prepared solution because the product does not contain any antimicrobial preservative or bacteriostatic agent. No incompatibilities between BMS-986156 injection and polyvinyl chloride (PVC) or non-PVC/non-di(2 ethylhexyl)phthalate (DEHP) containers with non-DEHP infusion sets have been observed. Partially used vials or empty vials of BMS-986156 injection should be discarded at the site according to appropriate drug disposal procedures.

5.2.10 Dose Calculations

BMS-986156 dose as determined in group 1.

- If dose was determined to be 100 mg, then it will be infused undiluted at a concentration of 10mg/mL using 10 mL as infusion volume.
- If dose was determined to be 30 mg, then, 3mL should be extracted from the vial containing BMS-986156 at a 10mg/mL concentration and transferred to a sterile and compatible container (vial #2). Then, 7 mL of 0.9% sodium chloride injection or 5% dextrose injection will be added to vial #2 as diluent to achieve a volume of 10mL.

A volume of 10mL, independent of dose determined in group 1, will be infused over 60 min at a rate of 0.167mL/min.

5.3. Nivolumab (Opdivo™): manufactured by Bristol-Myers Squibb Co (BMS)

5.3.1 Physical/Chemical Properties:

Nivolumab, also referred to as BMS-936558-01 or BMS-936558, is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains with a molecular weight of 146,221 daltons. nivolumab is a clear to opalescent, colorless to pale yellow liquid, with few particulates maybe present and a pH of 5.5 to 6.5.

5.3.2 Mechanism of action:

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.1 Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

OPDIVO™ (nivolumab) is approved for use in multiple countries including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

5.3.3. Nonclinical Studies

Nivolumab has been shown to bind specifically to the human PD-1 receptor and not to related members of the CD28 family. Nivolumab inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and interferon-gamma (IFN-γ) release in vitro. Nivolumab binds with high affinity to activated human T-cells expressing cell surface PD-1 and to cynomolgus monkey PD-1.2 In a mixed lymphocyte reaction (MLR), nivolumab promoted a reproducible concentration-dependent enhancement of IFN-γ release.

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab was well tolerated at doses up to 50 mg/kg, administered weekly for 5 weeks, and at doses up to 50 mg/kg, administered twice weekly for 27 doses. While nivolumab alone was well tolerated in cynomolgus monkeys, combination studies have highlighted the potential for enhanced toxicity when combined with other immunostimulatory agents.

In addition, an enhanced pre- and postnatal development (ePPND) study in pregnant cynomolgus monkeys with nivolumab was conducted. Administration of nivolumab at up to 50 mg/kg 2QW was well tolerated by pregnant monkeys; however, nivolumab was determined to be a selective developmental toxicant when administered from the period of organogenesis to parturition at ≥ 10 mg/kg (area under the concentration-time curve [AUC] from time zero to 168 hours [AUC(0-168 h)] 117,000 µg·h/mL). Specifically, increased developmental mortality (including late gestational fetal losses and extreme prematurity with associated neonatal mortality) was noted in the absence of overt maternal toxicity. There were no nivolumab-related changes in surviving infants tested throughout the 6-month postnatal period. Although the cause of these pregnancy failures was undetermined, nivolumab-related effects on pregnancy maintenance are consistent with the established role of PD-L1 in maintaining fetomaternal tolerance in mice

5.3.4. Clinical Pharmacokinetics

The pharmacokinetics (PK) of nivolumab was studied in subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. The geometric mean (% CV%) clearance (CL) was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) was 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) was 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. Additionally, nivolumab has a low potential for drug-drug interactions. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1. A PPK analysis suggested no difference in CL of nivolumab based on age, gender, race, solid tumor type, baseline tumor size, and hepatic impairment.

Although ECOG status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment had an effect on nivolumab CL, the effect was not clinically meaningful. PPK analysis suggest that nivolumab CL in subjects with cHL was approximately 32% lower relative to subjects with NSCLC; however, the lower CL in cHL subjects was not considered to be clinically relevant as nivolumab exposure was not a significant predictor for safety risks for these patients. When nivolumab is administered in combination with ipilimumab, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab. Additionally, PPK and exposure response analyses have been performed to support use of 240 mg Q2W dosing in addition

to the 3 mg/kg Q2W regimen. A flat dose of nivolumab 240 mg Q2W was selected since it is identical to a dose of 3 mg/kg for subjects weighing 80 kg, the observed median body weight in nivolumab-treated cancer patients. Using a PPK model, the overall distributions of nivolumab exposures (Cavgss, Cminss, Cmaxss, and Cmin1) are comparable after treatment with either 3 mg/kg or 240 mg nivolumab. The predicted range of nivolumab exposures (median and 90% prediction intervals) resulting from a 240 mg flat dose across the 35 to 160 kg weight range is maintained well below the corresponding exposures observed with the well tolerated 10 mg/kg nivolumab Q2W dosage.

5.3.5. Clinical Efficacy

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy and in combination with ipilimumab in several tumor types, including NSCLC, melanoma, RCC, cHL, SCLC, gastric cancer, urothelial cancer, HCC, and CRC. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in subjects with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or SCCHN. Nivolumab in combination with ipilimumab improved PFS and ORR over ipilimumab alone in subjects with unresectable or metastatic melanoma.

5.3.6. Clinical Safety

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 12,300 subjects treated to date. For monotherapy, the safety profile is similar across tumor types. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. In Phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using established safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care.

In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. The most advanced combination under development is nivolumab/ipilimumab, which is approved in subjects with unresectable or metastatic melanoma, and being studied in multiple tumor types. Results to date suggest that the safety profile of nivolumab/ipilimumab combination therapy is consistent with the mechanisms of action of nivolumab and ipilimumab. The nature of the AEs is similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs are increased with the combination.

Additional details regarding use, warnings and precautions, storage and administration, safety and efficacy are provided in the current version of the nivolumab Investigator Brochure (IB) v16.

5.3.7. Formulation

Nivolumab injection are available in 100 mg/10 mL (10 mg/mL). The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80 (Tween™ 80), at pH 6.0 and includes an overfill to account for vial, needle, and syringe holdup. It is supplied in 10-cc type I flint glass vials, stoppered with butyl rubber stopper and sealed with aluminum seals.

5.3.8. Packaging and labeling

Nivolumab is available 100 mg/10 mL (10 mg/mL), in single use vials (NDC 0003-3774-12).

5.3.9. Storage, handling and dispensing of Nivolumab

Vials of nivolumab injection must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing. The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20°C to 25°C, 68°F to 77°F) and room light. The maximum of 8 hours under room temperature and room light conditions includes the product administration period. During drug product preparation and handling, vigorous mixing or shaking is to be avoided.
Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, pharmacy manual, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride(PVC) or polyolefin containers and infusion sets, and glass bottles.
Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. When the dose is based on patient weight (ie, mg/kg), nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (eg, 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL.

5.3.10 Dose Calculations

A total dose of 480 mg will be infused in a diluted form by mixing four 100 mg vials (10mL) plus 8 mL of a fifth vial into a sterile and compatible container, followed by the addition of 102 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. The total infusion volume will be 150 mL, which is within the acceptable range stated in the Nivolumab investigational brochure version 17. The infusion will take place over a 30 minute span resulting in an infusion rate of 5 mL/min.

6. Radiation Information

For the radiation in this trial we allow multiple tumor sites to be treated at the same time, for example physician can treat 3-4 lung lesions at the same time on this trial. Additionally palliate radiation needed for patient symptoms is allowed as standard of care and is allowed prior to the trial and during the trial as per the treating physician discretion.

6.1. Dosimetry

All patients will receive stereotactic body radiation therapy (SBRT) for a total dose of 50 Gy with 12.5 Gy/fraction in 4 fractions or 60 Gy in 10 fractions prescribed to the planning target volume (PTV). It is recommended that prescribed isodose line cover more than 95% of the PTV if normal tissue dose is within threshold (as defined in 6.5). In the event that normal tissue dose is considered unacceptably high when treated with 50 Gy in 4 fractions, then patients can be alternatively treated with 60 Gy in 10 fractions. For lesion close to critical structures, compromised PTV coverage is allowed in order to meet normal tissue dose constraints. In this case, treating physician should make clinical judgments regarding optimal target coverage and normal tissues sparing.

There is no or little aperture margin recommended. The external border of the PTV will be covered by a lower isodose surface than usually used in conventional radiotherapy planning, which typically ranges from 70-95%. However, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. Heterogeneity correction should be applied for planning. The recommended radiation dose and fraction will be either at the initial XRT dose (50 Gy in 4 fractions or 60 Gy in 10 fractions) lower dose may be used if felt to be clinically indicated by the treating physician. Other tumor sites may be treated for palliation concurrently or sequentially if needed at the discretion of the treating radiation oncologist.

6.2. Radiation Technique

Patients will be evaluated for regularity of breathing, responsiveness to feedback guidance, breath-hold capability. Based on this evaluation, a treatment delivery technique will be selected among the following:

1. Breath-hold (with or without feedback guidance).

2. Gated treatment.

3. Free-breathing (with or without feedback guidance).

4. Abdominal compression.

5. A combination of the above techniques.

A CT scan obtained using the same method of respiratory management as intended for treatment will be required for treatment planning purposes. This CT simulation may include a 4-dimensional CT (4DCT) for free-breathing, gated or abdominal compression techniques or repeated breath-hold CTs for breath hold techniques. Feedback guidance, including visual and/or audio techniques, will be used for all patients who would both benefit from and respond to training with such devices.

4DCT is a fast CT scan that capable of imaging tumor position during the entire breath cycle. A CT scan is obtained with the patient in each couch position for a whole breath cycle (usually lasting 5 to 6 seconds in each position) followed by repositioning to the next couch position. Following a scan, the computer resorts all images and reconstructs the tumor positions for an entire breath cycle, i.e., a movie file is created which captures organ movement throughout the breath cycle. Radiotherapy will be designed based on the path of organ motion captured by 4DCT.

6.3. Target Volumes

1. Gross Target Volume (GTV): Gross tumor as observed on a non-contrast CT should be delineated on lung (for lung tumors) or abdominal (for liver tumors) windows from either 4DCT or repeated breath-hold CTs (see IGTV below).

2. Internal Gross Target Volume (IGTV): IGTV is the volume containing the GTV throughout its motion during respiration or positional variability during repeated breath holds. The motion during free breathing (with or without abdominal compression) will be determined from 4DCT, the variability of tumor location during breath hold will be determined by repeated breath hold CTs obtained on the same day. One method to combine the data from the multiple CT datasets is to create a maximal intensity projection (MIP) that is used as an aid to contour the IGTV. All CT datasets will be transferred to the treatment planning system for reference.

3. Clinical Target Volume (CTV) + Planning Target Volume (PTV): GTV plus 5-10 mm margin (based on physician discretion). Due to tight PTV margin, CTV margin is not recommended to be edited except when normal tissue toxicity is concerning based on treating physician's judgment. The prescribed dose of radiation (either 50 Gy or 60 Gy) will be dosed to the PTV, we recommend 95% coverage if possible, lower coverage is allowed if clinically indicated.

6.4. Daily treatment setup:

The appropriate immobilization will be chosen for each patient. Most patients will be immobilized with arms up using a commercially available vacuum immobilization bag that extends from the patient's head to their pelvis combined with a wing board.

On-board imaging: Daily on-board imaging such as CT on-rails, cone beam CT, or 4-D cone beam CT will be conducted prior to each radiation fraction. Position adjustment and target coverage confirmation will be performed daily based on imaging study. The setup uncertainty will be kept to less than a 3 mm (2 s) variation. This value is based on the uncertainties of the couch readouts added in quadrature with ½ the voxel size of the CT. Adjustment of patient position is needed if target coverage is judged by the treating physician to be inadequate and/or critical normal tissues toxicity is concerning. Repeated on-board CT after position adjustment is recommended if more than 5 mm shift is conducted.

6.5. Dose Volume Constraints

Maximum doses allowed in radiation planning are as outlined below. In the event that a treatment plan cannot reasonably meet dose constraints for 50 Gy in 4 fractions (or the corresponding dose de-escalation), then a separate plan will be generated for 60 Gy in 10 fractions. In the event that the subsequent treatment plan cannot reasonably meet dose constraints for 60 Gy in 10 fractions (or the corresponding dose de-escalation), then this patient is ineligible for this study, pending treating physician judgement.

50 Gy in 4 fractions dose constraints:

- Spinal Cord: 25 Gy ≤1 cc
- Lung: V20 ≤20%, V10<30%, V5<40%
- Esophagus: 40 Gy ≤1 cc, 36 Gy ≤10 cc
- Trachea: 40 Gy ≤1 cc, 36 Gy ≤10 cc
- Main bronchus and bronchial tree: 48 Gy ≤1 cc, 40 Gy ≤10 cc
- Heart: 48 Gy ≤1 cc, 40 Gy ≤10 cc
- Brachial plexus: 40 Gy ≤1 cc, 35 Gy ≤10 cc
- Major vessels: 48 Gy ≤1 cc, 40 Gy ≤10 cc
- Skin (defined as outer 0.5 cm of body surface): 40 Gy ≤1 cc, 35 Gy ≤10 cc
- Kidney: 8.4Gy to 200cc

60 Gy in 10 fractions dose constraints:

- Spinal Cord: 40 Gy ≤1 cc
- Lung: V20 ≤20%, V10<30%, V5<50%
- Esophagus: 60 Gy ≤1 cc, 40 Gy ≤10 cc
- Trachea: 70 Gy ≤1 cc, 60 Gy ≤10 cc
- Main bronchus: 70 Gy ≤1 cc, 60 Gy ≤10 cc
- Heart: 70 Gy ≤5 cc, 50 Gy ≤10 cc
- Brachial plexus: 50 Gy ≤1 cc, 40 Gy ≤10 cc
- Major vessels: 70 Gy ≤5 cc, 60 Gy ≤10 cc

- Skin (defined as outer 0.5 cm of body surface): 60 Gy ≤1 cc, 50 Gy ≤10 cc
- Kidney: V50 ≤33%

For patients who have received previous radiotherapy, the attending radiation oncologist is required to evaluate the previous treatment plan, particularly the dose delivered to critical structures and make a clinical judgment based on BED, previous radiation therapy, and current SBRT doses using above dose volume constrains as a guide.

7. Treatment Plan

Notice: Treatment schedules shall have a standing window of allowance of +/- 3 days unless patient/logistical/medical reasons intervene. Any treatment day that falls on a weekend or holiday will be scheduled on the next business day. Patients will undergo a therapy wash out period of 5 drug half-lives or 4-weeks whichever is shorter. We will allow prior radiation to other sites with no washout period prior to study entry as long as the high dose regions of the prior and proposed radiation fields do not overlap. If patient had prior radiation with an overlap in the intended radiation field and prior there must be a washout period of three months.

Any treatment day that falls on a weekend or holiday will be scheduled on the next business day. For treatment or dose modification questions, please contact Joe Chang, MD by phone (713-563-2337) or email (jychang@mdanderson.org), Thoracic Radiation Oncology, or David Hong, MD by phone (713-563-5844) or e-mail (dshong@mdanderson.org), Clinic Center for Targeted Therapy (CCTT). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Initially, patients that are enrolled on study will be placed in either treatment group 1 or in treatment group 3. After BMS-986156 dose determination in group 1, enrollment of patients in group 2 will be initiated.

7.1. Agent Administration (BMS-986156 dose escalation / de-escalation) and SBRT

Following enrollment, patients will be categorized into appropriate treatment groups.

Treatment group 1) Ipilimumab + BMS-986156 (30 or 100 mg) x 4 for safety assessment (No SBRT) → Nivolumab x 26.
Ipilimumab dose will be modified based on the outcome of DLT assessment, as described below.

Treatment group 2) Sequential (late SBRT) Ipilimumab + BMS-986156 x 2 → SBRT → Ipilimumab + BMS-986156 x 2 → Nivolumab x 26.
BMS-986156 dose as determined in group 1.
Ipilimumab dose will be modified based on the outcome of DLT assessment, as described below.

Treatment group 3) Concurrent (early SBRT) Nivolumab (480mg) + BMS-986156 (30 mg) + SBRT→ Nivolumab + BMS-986156 x 3 → Nivolumab x 22.
BMS-986156 dose will be modified based on the outcome of DLT assessment, as described below.

In the event that patients meet criteria for multiple groups (i.e. exhibit treatable liver and lung metastasis), patient will be assigned to one group based treating physician preference guided by

SBRT dosimetric considerations. Assignment may include evaluation of competing treatment plans with attention to normal tissue toxicities.

In the event that a treatment plan cannot reasonably meet dose constraints for 50 Gy in 4 fractions, then a separate plan will be generated for 60 Gy in 10 fractions. In the event that the subsequent treatment plan cannot reasonably meet dose constraints for 60 Gy in 10 fractions, then % PTV coverage can be reduced to make it safe.

All studies will be conducted with the following treatment scheme: Patients will be simulated up to 3 weeks prior to the anticipated SBRT start date. The first SBRT fraction will optimally be administered on a Monday. Patients receiving sequential SBRT will start SBRT about 1 week after the second dose of ipilimumab and BMS-986156. Patients receiving concurrent SBRT will start SBRT on day 1 of cycle 1 (with nivolumab and BMS-986156). If scheduling does not permit infusions and radiation to fall on the same day then SBRT of 50 Gy in 4 fractions may be administered starting day 2 of cycle 1.

Prior to starting each treatment cycle, patients will arrive at the Clinical Center for Targeted Therapy or Thoracic Medical Oncology Clinic and undergo safety assessments. In all groups, safety will be assessed by physical examination, observation and adverse experiences, and monitoring clinical chemistry and hematology. Disease progression will be based upon the irRC Criteria. All patients will be evaluated for toxicity upon their first receipt of the trial drug(s) and for therapy response after receiving at least 2 doses of drugs and at least half the scheduled radiation doses.

7.1.1 Dose escalation / de-escalation of BMS-986156 when combined with ipilimumab based on a (3+3) design to determine MTD

Ipilimumab (Yervoy™)
Ipilimumab (3 mg/kg) will be administered as a single 90 minute (+/- 15 minutes) intravenous infusion on the first day of each cycle, every 21 days (± 3d).

BMS-986156
BMS-986156 (30 mg or 100 mg) will be given as a single 60 min (+/- 15 minutes) intravenous infusion on the first day of each cycle (± 3d). When given in combination with Ipilimumab, BMS-986156 will be given every 21 days (± 3d).

7.1.1.1 Group 1: Dose Escalation of BMS-986156 when combined with ipilimumab

Treatment group 1: A modified 3+3 dose escalation then expansion to a total of 10 patients per arm (escalation + expansion, if applicable) will be performed on two dose levels of this combination therapy.

- The first 3 subjects will be enrolled at dose level 1 (3 mg/kg ipilimumab + 30 mg BMS-986156).
    - If 0 out of these 3 patients have a DLT, 3 patients will then be enrolled on dose level 2 (3 mg/kg ipilimumab + 100 mg BMS-986156).
    - If 1 of 3 subjects have a DLT in dose level 1 (30 mg), 3 more patients will then be enrolled at this dose level. If only 1 of the 6 total subjects at dose level 1 has a DLT, then 3 patients will then be enrolled on dose level 2, 100 mg BMS-986156.
    - Additionally, 4 patients will be enrolled on dose level 1 to a total of 10 patients at 30 mg BMS-986156.
    - If 2 of 3 subjects have a DLT at dose level 1, then dose escalation is stopped and the MTD is reached (dose level 1).
- Subjects will be receiving 3 mg/kg ipilimumab + 100 mg BMS-986156 at dose level 2.

- At this dose level, if 0 of the 3 subjects have a DLT, then both dose level 1 and dose level 2 will be expanded to more patients so that each arm has a total of 10 patients enrolled.
- If 1 of the 3 subjects at dose level 2 have a DLT, 3 more subjects will then be enrolled at this dose level. If only 1 of the 6 total subjects at dose level 2 have a DLT, both dose level 1 and dose level 2 will be expanded to more patients so that each arm has a total of 10 patients enrolled. If 2 of the 6 total subjects at dose level 2 have a DLT, then dose escalation is stopped and the MTD is reached (dose level 1). Only dose level 1 will be expanded to a total of 10 patients enrolled.
- If 2 of 3 subjects at dose level 2 have a DLT, then dose escalation is stopped and the MTD is reached (dose level 2).
- The expansion phase dose will be selected based on safety and response readouts. For example, the dose exhibiting the best therapeutic response or pharmacodynamic profile with the best safety profile.

Dose Escalation of BMS-986156 when combining with Ipilimumab.

Dose Level 1	3 mg/kg Ipilimumab + 30 mg BMS-986156
Dose Level 2	3 mg/kg Ipilimumab + 100 mg BMS-986156

7.1.1.2 Group 2: Dose De-Escalation of BMS-986156 when combined with ipilimumab plus SBRT

BMS-986156 dose as determined in group 1, for combination treatment with ipilimumab, before adding SBRT to the treatment regimen.

Treatment group 2: A modified 3+3 dose de-escalation then expansion to a total of 20 patients will occur at the MTD.

The first 3 subjects will be enrolled at dose level 1 (3 mg/kg ipilimumab + BMS-986156).

- If 0 out of these 3 patients have a DLT, 3 additional patients will then be enrolled on this same dose level.
- If 1 of 3 subjects have a DLT, 3 more patients will then be enrolled at this dose level. If only 1 of the 6 total subjects at dose level has a DLT, then this dose level will be considered safe and all other patient in this arm will be treated at this dose level.
- If 2 of 6 subject have DLT at dose level 1, then the dose will be de-escalated as per table below.
- If 2 of 3 subjects have a DLT at dose level 1, then the dose will be de-escalated as per table below

Dose De-Escalation of Ipilimumab when combining with BMS-986156 plus SBRT.

If MTD from group 1 finds the 30mg BMS-986156 then:

Dose Level 1	3 mg/kg Ipilimumab + 30 mg BMS-986156
Dose Level -1	1 mg/kg Ipilimumab + 30 mg BMS-986156

If MTD from group 1 finds the 100mg BMS-986156 then:

Dose Level 1	3 mg/kg Ipilimumab + 100 mg BMS-986156
Dose Level -1	1 mg/kg Ipilimumab + 100 mg BMS-986156
Dose Level -2	1 mg/kg Ipilimumab + 30 mg BMS-986156

7.1.1.3 Group 3: Dose De-Escalation of BMS-986156 when combined with Nivolumab plus SBRT

For group 3 of this trial, BMS-986156 at 30 mg will be co-administered with nivolumab at a flat dose of 480mg on days 1, 29, 57, 85, followed by 22 cycles of Nivolumab monotherapy starting on day 113.

The combination of nivolumab plus anti-GITR was well-tolerated in a clinical study, CA009002A, "Phase 1/2a Dose Escalation and Cohort Expansion Study for Safety, Tolerability, and Efficacy of BMS-986156 Administered Alone and in Combination with Nivolumab (BMS-936558, anti PD-1 Monoclonal Antibody) in Advanced Solid Tumors." To date, 225 subjects (100 male and 125 female) have been treated with the combination of BMS-986156 and nivolumab. BMS-986156/nivolumab has been tested in a dose escalation phase. During dose escalation, there was no pattern in the incidence, severity, or causality of AEs to BMS-986156 across these dose levels. Overall, the safety profile of BMS-986156 combination therapy is manageable with no MTD reached. One of the doses chosen for expansion was a flat dose of 240 mg nivolumab Q2W administered in combination with BMS-986156, based on clinical data and modeling and simulation approaches using population PK and exposure-response analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) where body weight-normalized dosing (mg/kg) has been used. The safety and efficacy of 240 mg Q2W is expected to be similar to the approved dose of 3 mg/kg Q2W. Additionally, BMS-986156 in combination with nivolumab was evaluated in a more convenient schedule of Q4W, with a dose of 480 mg BMS-986156/480 mg nivolumab; 12 subjects were treated as of the data cut-off date. The majority of the subjects treated with BMS-986156 in combination with nivolumab were Caucasian (91.1%), with a median age of 60.0 years.

Treatment group 3: A modified 3+3 dose de-escalation then expansion to a total of 20 patients (de-escalation + expansion, if applicable) will be performed on one dose level of this combination therapy.

- The first 3 subjects will be enrolled at dose level 1 (480mg Nivolumab + 30mg BMS-986156).
    - If 0 out of these 3 patients have a DLT, 3 additional patients will then be enrolled on this same dose level.
    - If 1 of 3 subjects have a DLT in dose level, 3 more patients will then be enrolled at this dose level. If only 1 of the 6 total subjects at dose level has a DLT, then this dose level will be considered safe and all other patient in this arm will be treated at this dose level.
    - If 2 of 6 subject has DLT then the dose will be de-escalated as per table below.
    - If 2 of 3 subjects have a DLT at dose level 1, then the dose will be de-escalated as per table below

Dose De-Escalation of BMS-986156 when combining with Nivolumab plus SBRT.

Dose Level 1	480mg Nivolumab + 30 mg BMS-986156

Dose Level -1 480mg Nivolumab + 10 mg BMS-986156

7.1.2. Reinduction for all arms

Reinduction will be allowed for patients in which the treating physician feels there was benefit from the trial treatment. It will consist of repeating the original treatment using the same schedule for each arm. Radiation may be given during reinduction, but is not required. Pending the treating radiation oncologist judgment, additional radiation therapy to a previously non-irradiated lesion can be administered during re-induction. Timing of radiation during reinduction will be at the discretion of treating Radiation Oncologist.

The target lesion for radiation will be chosen by the treating radiation oncologist. The target lesion must not have been previously irradiated. The target lesion does not have to be within the same organ that was initially treated during the initial treatment (e.g. patients who received initial lung lesion irradiation can have liver or a bone lesion irradiated during re-induction). Radiation dose and fraction will be either at the initial dose (50 Gy in 4 fractions or 60 Gy in 10 fractions) or at a lower palliation dose (30 Gy in 10 fractions) and may also be combined with low dose radiation ranging from 200cGy-1000cGy in multiple fractions, at the discretion of the treating radiation oncologist.

Other tumor sites may be treated for palliation concurrently or sequentially if needed at the discretion of the treating radiation oncologist.

Reinduction will be allowed after the 4th cycle of systemic imaging (CT, MRI, Ultrasound, or x-ray) to assess the global disease burden will be conducted. If disease control is once again observed (SD or PR by ir-RC, compared to the original pretreatment baseline imaging) without severe (Grade >3) toxicity then patients will be eligible for a second round of reinduction therapy to given in the same manner as the first round of treatment. Patients may continue to have additional rounds of reinduction therapy until PD is observed at their post cycle 4 imaging or severe toxicity (Grade >3) occurs.

7.2. Definition of Dose-Limiting Toxicity:

DLT time frames:

- Group 1: The time frame for DLT assessment will be within 29 days of therapy initiation in the ipilimumab/BMS-986156 group

Group 2: within 43 days of therapy initiation in the sequential arm (ipilimumab/BMS-986156/radiation)

- Group 3: within 29 days of therapy initiation in the nivolumab/BMS-986156 concurrent group

- Groups 1 (ipilimumab + BMS-986156) and 2 (ipilimumab + BMS-986156 + radiation): Patients will get DLT assessments done every other week (14 ± 3 days after the drug infusion) during the DLT period. When patient is unable to make a clinic visit, a visit to a local healthcare provider must be done for DLT assessment. A report and lab test results must be provided to the trial treating physician or to the trial PI. This will be done case by case in association with the local physician of the patient.

7.2.1. Dose Limiting Toxicity (DLT):

DLT is defined as any:

Group 1 DLT definition:

- Any ≥ Grade 3 bronchospasm or other hypersensitivity reactions lasting for >6h;
- Any other ≥ Grade 3 non-skin related adverse event with the exception of laboratory abnormalities that is asymptomatic, not requiring hospitalization, responsive to supplementation within 24 hours).
- Any Grade 4 laboratory abnormalities, except AST, ALT, or total bilirubin;
    - AST or ALT > 8 x ULN,
    - Total bilirubin > 5 x ULN;
    - AST or ALT > 3 x ULN AND Total Bilirubin > 2 X ULN (Potential drug-induced liver injury as defined by Hy's Law)
- Grade 3/4 rash if no improvement (i.e. resolution to ≤Grade 1) after a 1-2 week infusion delay. Use of topical steroids is permitted.
- Any other Grade 4 adverse event;
- 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 study drug dosing;
- Any motor neurologic toxicity ≥ Grade 3 regardless of causality;
- Any ≥ Grade 3 treatment-related sensory neurologic toxicity.
- Combination related toxicity, such as infusion reactions, diarrhea, colitis, etc., that prevents administration of ipilimumab/BMS-986156 for > 21 days and/or nivolumab/BMS-986156 for > 28 days from the scheduled dose.

- Any clinically ≥ grade 3 non-hematologic toxicity as defined in the NCI CTC v4.0, expected and believed to be related to the combination of study drug and radiation (except nausea and vomiting, diarrhea and electrolyte imbalances responsive to appropriate regimens, alopecia or fatigue lasting less than 7 days).

- Grade 3 Febrile neutropenia

- Any grade 4 neutropenia (with or without fever and/or sepsis) or thrombocytopenia (without bleeding) lasting at least 1 week or longer (as defined by the NCI-CTC v4.0).

- Any of the Grade 4 hematologic adverse events for >7 days.

- Any ≥ grade 3 nausea or vomiting lasting > 5 days despite anti-emetics regimens or ≥ grade 3 diarrhea refractory to anti-diarrhea medications, >48 h.

- 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 ≤2 weeks OR requires systemic treatment. Any other grade 3 non-hematologic toxicity including symptoms/signs of vascular leak or cytokine release syndrome; or any severe or life-threatening complication or abnormality not defined in the NCI-CTCAE v4.0 that is attributable to the therapy, with the following EXCEPTIONS:
    - Grade 3 or grade 4 electrolyte abnormalities that are not complicated by associated clinical adverse experiences, last ≤48 hours and either resolve spontaneously or respond to conventional medical intervention
    - Isolated Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
    - Isolated Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical or laboratory evidence of impaired end-organ perfusion)

- Grade 3 endocrinopathy that is well controlled by hormone replacement
- Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor)
- Grade 3 fatigue for ≤7 days.
-

Group 2 and Group 3 definition of DLTs:

- DLTs used to define the MTD in combination with radiation section 7.1.1.2 and 7.1.1.3 will only use DLTs associated with organ toxicity for the organ irradiated.

- SBRT related adverse events: Any grade ≥3 events occurring in radiation volume field will be considered as DLT.

- Any ≥ Grade 3 bronchospasm or other hypersensitivity reactions lasting for >6h;
- Any other ≥ Grade 3 non-skin related adverse event with the exception of laboratory abnormalities that is asymptomatic, not requiring hospitalization, responsive to supplementation within 24 hours).
- Any Grade 4 laboratory abnormalities, except AST, ALT, or total bilirubin;
    - AST or ALT > 8 x ULN,
    - Total bilirubin > 5 x ULN;
    - AST or ALT > 3 x ULN AND Total Bilirubin > 2 X ULN (Potential drug-induced liver injury as defined by Hy's Law)
- Grade 3/4 rash if no improvement (i.e. resolution to ≤Grade 1) after a 1-2 week infusion delay. Use of topical steroids is permitted.
- Any other Grade 4 adverse event;
- 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 study drug dosing;
- Any motor neurologic toxicity ≥ Grade 3 regardless of causality;
- Any ≥ Grade 3 treatment-related sensory neurologic toxicity.
- Combination related toxicity, such as infusion reactions, diarrhea, colitis, etc., that prevents administration of ipilimumab/BMS-986156 for > 21 days and/or nivolumab/BMS-986156 for > 28 days from the scheduled dose.

- Any clinically ≥ grade 3 non-hematologic toxicity as defined in the NCI CTC v4.0, expected and believed to be related to the combination of study drug and radiation (except nausea and vomiting, diarrhea and electrolyte imbalances responsive to appropriate regimens, alopecia or fatigue lasting less than 7 days).

- Grade 3 Febrile neutropenia

- Any grade 4 neutropenia (with or without fever and/or sepsis) or thrombocytopenia (without bleeding) lasting at least 1 week or longer (as defined by the NCI-CTC v4.0).

- Any of the Grade 4 hematologic adverse events for >7 days.

- Any ≥ grade 3 nausea or vomiting lasting > 5 days despite anti-emetics regimens or ≥ grade 3 diarrhea refractory to anti-diarrhea medications, >48 h.

- 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 ≤2 weeks OR requires systemic treatment. Any other grade 3 non-hematologic toxicity including symptoms/signs of vascular leak or cytokine release syndrome; or any severe or life-threatening complication or abnormality not defined in the NCI-CTCAE v4.0 that is attributable to the therapy, with the following EXCEPTIONS:
  - Grade 3 or grade 4 electrolyte abnormalities that are not complicated by associated clinical adverse experiences, last ≤48 hours and either resolve spontaneously or respond to conventional medical intervention
  - Isolated Grade 3 elevation of amylase or lipase not associated with clinical or radiographic evidence of pancreatitis
  - Isolated Grade 3 fever not associated with hemodynamic compromise (eg, hypotension, clinical or laboratory evidence of impaired end-organ perfusion)
  - Grade 3 endocrinopathy that is well controlled by hormone replacement
  - Grade 3 tumor flare (defined as pain, irritation, or rash that localizes to sites of known or suspected tumor)
  - Grade 3 fatigue for ≤7 days.
-

7.3. Duration of Therapy and Criteria for Treatment Delay

7.3.1. Duration of Therapy:

In the absence withholding treatment cycles due to adverse events, study treatment will be continued for the full 4 Ipilimumab/BMS-986156 cycles, followed by 26 cycles of Nivolumab (group 1 and 2). Nivolumab/BMS-986156 will be given for 4 cycles, followed by 22 cycles of Nivolumab (group3). Nivolumab will be given for a total of 26 cycles on all groups.

7.3.2. Criteria for Treatment Delay:

Patients will delay treatment with ipilimumab/BMS-986156 or nivolumab/BMS-986156 if they experience at least one of the following adverse events considered by the Investigator to be "possibly", probably" or "certainly" related to trial drug treatment with or without SBRT treatment:

- Any Grade 3 non-skin related adverse event (excluding alopecia, and Grade 3 nausea, vomiting, and diarrhea for which adequate supportive therapy has been instituted)
- Any Grade 3 skin-related adverse event (including irAEs)
- Any of the Grade 4 hematologic adverse events for >7 days
- Grade 3 fatigue only if ≥ 7 days
- SBRT scheduling conflicts or machine maintenance issues

7.3.3. Criteria for Restart of Ipilimumab/BMS-986156 or nivolumab/BMS-986156 Treatments:

Patients requiring delay or cessation of treatments of trial drugs based on the judgment of the attending physician can be restarted as long as:

- The adverse event is not listed in 7.2.1, and:

- If the adverse event has resolved to ≤ Grade 1 severity or returns to baseline within 4 weeks (28 days) of dose administration, treatment will be restarted ≥4 weeks from the last dose administration, to complete dosing regimen outlined above.
- If the adverse event has not resolved to ≤ Grade 1 severity or returned to baseline in the protocol-specified dosing window (3 weeks, for ipilimumab/BMS-986156; 4 weeks for nivolumab/BMS-986156), the next scheduled dose will be omitted and remaining doses will be administered if approved by the Principal Investigator.
- For ipilimumab/BMS-986156: Treatment delays for reasons other than adverse events (e.g. for scheduling conflicts or SBRT machine maintenance issues) are allowed as long as all four 3 week cycle ipilimumab/BMS-986156 doses are given within 8 months. In this scenario, all 4 doses should be administered separated by a minimum interval of 3 weeks.
- For nivolumab/BMS-986156: Extensions to the period of dose delays may be granted for individual subjects on a case by case basis decided by the Investigator in settings where benefit/risk may justify continued study therapy (e.g., subject deriving clinical benefit who requires prolonged steroid taper for management of non-DLT drug-related AEs, or experiences delays for management of a non-drug related AE).
- The end of cycle tumor assessments (i.e., CT/MRI, positron emission tomography, etc) will continue on an every 8 weeks schedule relative to the subject's 1st dose regardless of any treatment delay incurred.

7.3.4. Criteria for Permanent Discontinuation of Ipilimumab/BMS-986156 or nivolumab/BMS-986156

Patients who demonstrate signs of progression of disease prior to completion of Ipilimumab/BMS-986156 or Nivolumab/BMS-986156 may continue on trial if determined to provide clinical benefit per the treating physicians and/or PI's discretion.

- Patients will continued to be monitored with visits or phone calls (if patient is unable to arrive) as discussed in section 9.1.3 but will no longer receive further treatment if:

- Patients suffer any of the following adverse events with at least a possible, probable or definite attribution to study treatments:*Adverse event(s) considered related to study treatments as described below:*
  - *Any ≥ Grade 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of starting therapy OR requires systemic treatment;*
  - *Any ≥ Grade 3 bronchospasm or other hypersensitivity reaction;*
  - *Any other ≥ Grade 3 non-skin related adverse event with the exception of laboratory abnormalities;*
  - *Any Grade 4 laboratory abnormalities, except AST, ALT, or total bilirubin;*
    - *AST or ALT ≥ 8 x ULN,*
    - *Total bilirubin ≥ 5 x ULN;*
  - *Any other Grade 4 adverse event;*
  - *Drug related toxicity that prevents administration of ipilimumab/BMS-986156 for ≥ 21 days or nivolumab/BMS-986156 for 14 days from the scheduled dose*
- *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 study drug dosing;*
- *Subject experiences an allergic/infusion reaction while receiving study drug at a slower infusion rate due to a prior allergic/infusion reaction;*
- *Any motor neurologic toxicity ≥ Grade 3 regardless of causality;*

- *Any ≥ Grade 3 treatment-related sensory neurologic toxicity.*
- *Drug related toxicity that prevents administration of ipilimumab for ≥ 21 days from the scheduled dose*

Exceptions to Permanent Discontinuation of ipilimumab dosing:

- Hospitalization for ≤ Grade 2 adverse events where the primary reason for hospitalization is to expedite the clinical work-up;

7.3.5 Criteria for Removal from Study

Subjects MUST be discontinued from study therapy AND withdrawn from the study for the following reasons:

- The development of unacceptable toxicity
- Pregnancy (Note: pregnancy on study should be reported to BMS within 24 h)
- Any other situation where, in the opinion of the treating physician, continued treatment per protocol, would not be in the best interest of the patient.
- The patient withdraws consent (subject's decision to withdraw for any reason).
- Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
- Patient refusal or non-compliance with SBRT (only applicable to groups 2 and 3).
- Study completion

7.4. Immune Related Adverse Events (IRAEs): Definition, Monitoring and Treatment

Blocking CTLA-4/PD-1/GITR function may permit the emergence of auto-reactive T cells and resultant clinical autoimmunity. Rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis and hypopituitarism were drug-related, presumptive autoimmune events, now termed IRAEs.

For the purposes of this study, an IRAE is defined as an AE of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE an IRAE. Serological, immunological, and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity. Suspected IRAEs must be documented on an AE or SAE form.

Patients should be informed of and carefully monitored for evidence of clinically significant systemic IRAE (e.g., systemic lupus erythematosus-like diseases) or organ specific IRAE (e.g., rash, colitis, uveitis, hepatitis or thyroid disease). If an IRAE is noted, appropriate work-up (including biopsy if possible) should be performed, and steroid therapy may be considered if clinically necessary.

It has been reported that systemic corticosteroid therapy does not seem to have an attenuating effect on ipilimumab activity (28). However, administration of a prophylactic corticosteroid, budesonide, did not impart any clinical benefit in patients treated with ipilimumab (29). If utilized, corticosteroid therapy should be individualized for each patient. Prior experience suggests that colitis manifested as Grade ≥ 3 diarrhea requires corticosteroid treatment.

7.4.1 Management Algorithms for Immuno-oncology Agents

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Ipilimumab, Nivolumab and BMS-986156 are considered I-O agents in this protocol. Early recognition and management of AEs associated with I-O agents may mitigate severe toxicity. Management algorithms that have been developed from

extensive experience with nivolumab to assist Investigators in assessing and managing the following groups of AEs:

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

The algorithms recommended for utilization in this protocol are included in Appendix B.

7.4.2. Treatment of Drug-related Infusion Reactions

If BMS-986156 and nivolumab found to be immunogenic and induce infusion or hypersensitivity reactions, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE v4.03 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 acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional study drug administrations.

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

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); monitor subject until resolution of symptoms.
- Bronchodilator or corticosteroid therapy may also be administered as appropriate.
- The infusion may be restarted 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.
- The amount of study drug infused must be recorded on the CRF.
- If symptoms recur, then no further nivolumab, as the case may be, will be administered at that visit.
- The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If

necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

Late-occurring symptoms: In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

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

Immediately discontinue study drug infusion. 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. Study drug will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

7.5. Radiation Related Adverse Events: Definition, Monitoring and Treatment

Acute radiation reactions occurring in the radiation volume field including esophagitis, pneumonitis, gastritis, soft tissue toxicity and other adverse events will be evaluated during the period of treatment and during subsequent visits. The adverse events will be graded according to National Cancer Institute (NCI) CTCAE v4.0.

Toxicity following SBRT treatment for liver and lung lesions appears to elicit minimal toxicity. With regard to liver SBRT, the actuarial rate of any Grade ≥ 3 toxicities have been reported to be 2% with only one instance of grade 3 soft tissue toxicity (13). Toxicity rates in patients receiving lung SBRT have been reported to 7.9% which included 1 instance of grade 3 dyspnea, chest wall fraction and skin reaction. Dosimetric considerations are important as centrally located lung lesions have been associated with significantly higher incidence of grade ≥ 3 toxicities (17%) compared with peripheral lesions (46%)(30).

7.6. Infusion Reactions and Fever Associated with Ipilimumab

7.6.1. Infusion Reactions

Since ipilimumab contains only human protein sequences, it is less likely that any allergic reaction will be seen in patients. However, it is possible that infusion of ipilimumab will induce a cytokine release syndrome that could be evidenced by fever, chills, rigors, rash, pruritus, hypo- or hypertension, bronchospasm or other symptoms. No prophylactic pre-medication will be given unless indicated by previous experience in an individual patient.

The following treatment guidelines are suggested:

Severe infusion reactions require the immediate interruption of ipilimumab and permanent discontinuation from further treatment.

Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms. In each case of an infusion reaction, the investigator should institute treatment measures according to the best available medical practice and institutional norms.

The following treatment guidelines are suggested:

CTCAE Grade 1 Allergic reaction/hypersensitivity (transient flushing or rash, drug fever < 38°C)

Treatment: Decrease the ipilimumab infusion rate by 50% and monitor closely for any worsening.

CTCAE Grade 1 or Grade 2 Allergic reaction/hypersensitivity manifesting only as delayed drug fever (starting after the completion of ipilimumab infusion)

Treatment: Maintain ipilimumab dose and infusion rate for future infusions. Consideration could be given to administration of acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) prior to the subsequent ipilimumab infusion, if not otherwise contraindicated in subjects. Dose and schedule of these agents is entirely at the investigator's discretion.

CTCAE Grade 2 Allergic reaction/hypersensitivity (Rash, flushing urticaria, dyspnea, drug fever ≥ 38°C)

Treatment: Interrupt ipilimumab infusion. Administer bronchodilators, oxygen, etc as medically indicated. Resume infusion at 50% of previous rate once infusion reaction has resolved or decreased to Grade 1 in severity, and monitor closely for any worsening.

CTCAE Grade 3 or Grade 4 Allergic Reaction/Hypersensitivity: A CTCAE Grade 3 hypersensitivity reaction (symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/ angioedema; hypotension) or a Grade 4 hypersensitivity reaction (anaphylaxis).

Treatment: Stop ipilimumab infusion immediately and disconnect infusion tubing from the subject. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc, as medically indicated. Contact the PI and document as a serious adverse event. No further ipilimumab treatment to be administered.

Once an ipilimumab infusion rate has been decreased due to an infusion reaction, it should remain decreased for all subsequent infusions. If the subject has a second allergic/infusion reaction at the slower infusion rate, then the infusion should be stopped and the subject should be discontinued from ipilimumab. If a subject experiences a Grade 3 or 4 allergic/infusion reaction at any time, the subject should be discontinued from ipilimumab.

7.7. Treatment of Ipilimumab Related Isolated Drug Fever

In the event of isolated drug fever, the Investigator must use clinical judgment to determine if the fever is related to the ipilimumab or to an infectious etiology.

If a patient experiences isolated drug fever, for the next dose, pre-treatment with acetaminophen or non-steroidal anti-inflammatory agent (Investigator discretion) should be instituted and a repeated antipyretic dose at 6 and 12 hours after ipilimumab infusion should be administered. The infusion rate will remain unchanged for future doses.

If a patient experiences recurrent isolated drug fever following pre-medication and post dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be decreased to 50% of

the previous rate. If fever recurs following infusion rate change, the Investigator should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further ipilimumab.

7.8. Concomitant, Prohibited and Restricted Therapies During the Study

7.8.1. Concomitant Therapies

- All patients should have antiemetic medications available once discharged from the clinic. Oral antiemetic medications should be prescribed and administered as needed, and adjusted during the cycle at the discretion of the treating investigator.
- If patients experience nausea and vomiting despite the premedication, the patient may take PRN antiemetics per treating physician's discretion.
- All patients may have emollient or lubricating creams to be placed on the corresponding SBRT field for symptomatic skin irritation after SBRT treatment completion at the discretion of the treating investigator.

Radiation outside of the SBRT treatment fields will also be allowed based on the treating physician discretion.

7.8.2. Prohibited Therapies

Patients in this study may not use vaccines for the treatment of cancer or prevention of disease for up to one month pre and post dosing with ipilimumab.

Concomitant systemic or local anti-cancer medications or treatments are prohibited in this study while receiving ipilimumab treatments, other than palliative (pain controlling) radiation therapy (RT) in situations that are not clearly indicative for PD.

Patients may not use any of the following therapies during the study:

- Any non-study anti-cancer agent (investigational or non-investigational);
- Any other investigational agents;
- Any other (non-CA184024 related) CTLA-4 / PD-1 / PDL-1 inhibitors or agonists;
- Immunosuppressive agents;
- Chronic systemic corticosteroids while receiving ipilimumab (as long as steroid replacement is significantly greater than what is required for physiologic replacement, i.e. in hypothyroidism);
- Any non-oncology vaccine therapies used for the prevention of infectious diseases (for up to 30 days prior to or after any dose of study drug).

8. Criteria for Evaluation

8.1. Evaluations at Baseline

Notice: On-study tests/visits that must occur within a defined time frame shall have a standing window of allowance that is equal to +/- 3 days for any laboratory testing unless patient/logistical/medical reasons intervene**.** Overlapping baseline tests can be combined with tests required for cycle 1 of drug administration as long as these baseline tests occur within 3 days before cycle 1.

8.1.1. Four weeks prior to study initiation

The following appropriate imaging studies for tumor assessment should be obtained within 4 weeks

prior to study initiation to provide diagnosis and measurement of target lesions.

- CT scans of the chest, abdomen and/or pelvis (contrast-enhanced preferred); or
- MRI of the abdomen or pelvis; or
- PET/CT scan (preferred)

The following imaging modalities are to be used in the event that above imaging modalities cannot be obtained

- Ultrasound (US) (special circumstances only, as described below in 9.4); or
  Chest radiograph (least preferred)

8.1.2. Within 3 weeks prior to radiation initiation.

- CT simulation for purposes of SBRT planning (as described in 6.2).

8.1.3. Within 2 weeks prior to study initiation.

The following studies should be obtained within 14 days prior to study initiation. All abnormal and normal results must be noted in the case report forms (CRF).

- Medical history to include determination of tumor-related symptoms.
- ECG
- Physical examination to include height, weight, vital signs, and performance status.
- CBC with differential and platelet count.
- Serum chemistry studies to include sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, magnesium, calcium, phosphorus, albumin, total protein, SGOT or SGPT, total bilirubin, alkaline phosphatase, and uric acid.
- Routine urinalysis.
- Serum evaluation for presence of Hepatitis B, C, and HIV. This will include (but not limited to) hepatitis C virus Ab, hepatitis B total Ig core Ab, hepatitis surface B Ag, and HIV 1/2 Antigen and Antibodies.
- Serum pregnancy test for females of childbearing potential within 7 days of registration.
- Mandatory tumor biopsy from any lesion at the discretion of PI and treating physician for tumor marker studies.
- Mandatory tumor biopsy from a lesion any time after SBRT for additional tumor marker studies.
- Tumor mutation biomarker analysis (whole exome sequencing) using left over tissue from a prior biopsy (optional procedure #1) and/or from the mandatory tumor biopsy samples.
- Initial serum samples for biomarker testing.

8.1.4. Monitoring following study completion.

Patients will return every 2-4 months for up to a year following completion of the last cycle of ipilimumab/BMS-986156/nivolumab with the following evaluations: CBC with differential and platelet count, serum chemistries, laboratory evaluation, and body imaging to assess for toxicity and disease response.

At the end of the study period, Bristol-Myers Squibb Company will not continue to supply study drug to subjects/investigators unless the Sponsor-Investigator chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the investigator to treat the condition under study.

8.2. Evaluations During Study

8.2.1. Before each drug administration

Every patient needs to be evaluated by the treating physician before each drug administration with the following laboratory tests. Overlapping baseline tests can be combined with tests required for cycle 1 of drug administration as long as these baseline tests occur within 3 days before cycle 1:

- CBC with differential/platelets
- Serum chemistry studies to include sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, magnesium, calcium, phosphorus, albumin, total protein, SGOT (AST) or SGPT (AGT), total bilirubin, alkaline phosphatase and uric acid.
- TSH measurement
- Patient weight for dose calculation purposes

8.2.2 DLT assessment (Concurrent- group 1 & 3: Cycle 2, Day 1/Day 8 (Day 29); Sequential-group 2: Cycle 3, Day1 (Day 43).

- Physical examination to include weight and vital signs.
- Physical examination, interim history pertaining to any change from baseline, current medications and treatment-related toxicities. Adverse events will be monitored using the NCI CTCAE Version 4.0.
- Laboratory testing CBC with differential/platelets
- Serum chemistry studies to include sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, magnesium, calcium, phosphorus, albumin, total protein, SGOT (AST) or SGPT (AGT), total bilirubin, alkaline phosphatase and uric acid.

8.2.3. Follow up - every 2 to 4 months

- Physical examination to include weight and vital signs.
- Physical examination, interim history pertaining to any change from baseline, current medications and treatment-related toxicities. Adverse events will be monitored using the NCI CTCAE Version 4.0.
- Laboratory testing CBC with differential/platelets
- Serum chemistry studies to include sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, magnesium, calcium, phosphorus, albumin, total protein, SGOT (AST) or SGPT (AGT), total bilirubin, alkaline phosphatase and uric acid.
- All appointments after the last cycle of BMS-986156 will allow a window of ±1 months.
- Radiation oncology follow up appointments will be at the discretion of the treating radiation oncologist. We recommend follow up at 3 and 6 months after the completion of the last cycle of BMS-986156 followed by appointments as per standard of care.

8.2.4. Re-induction follow up

Follow up with radiation oncology will be scheduled at the end of every 3rd study cycle and every 2-4 months from completion of last cycle of drug .

- Imaging studies: Response assessment during and post treatment should be performed using the same modality as the pretreatment assessment whenever feasible, and all lesions assessed pretreatment must be included in the post-treatment evaluation:
  - CT scans of the chest, abdomen and/or pelvis (preferred); or
  - MRI of abdomen and pelvis; or
  - PET/CT (preferred)

- All appointments after the last cycle of BMS-986156 will allow a window of ±1 months.

8.2.5. Tumor biopsies and serum biomarker evaluation

All patients with accessible tumor will undergo a baseline biopsy of a non-irradiated tumor and a post SBRT biopsy of an irradiated tumor, with low dose radiation, or non-irradiated tumor, as well as a biopsy at the point of progression as determined by the treating physician or PIs of the study. Blood will be drawn with baseline labs, during week 1 of cycle 2 (group 1) or on the last day of radiation treatment (groups 2 and 3), and at progression of disease decided by the discretion of the treating physician and/or study PIs. Blood and tissue biopsies will be mandatory. A tentative calendar is shown in Section 12 in Study Calendar group 1, group 2, group 3.

8.3. Measurement of Effect

1. Response and progression will be evaluated in this study using guidelines proposed by the Immune Related Response Criteria (irRC).
2. The best achieved objective response per irRC criteria (as described below) will consider all imaging conducted after week 1 of cycle 5 for group 1 and 2, or week 2 cycle 3 for group 3 of drug administration. After initial response imaging is obtained, additional imaging will be obtained every 12 weeks (±4 weeks, or sooner if clinically indicated by treating physician's or PIs discretion) for re-evaluation of treatment response. If in the event that patient receives re-induction, imaging will be obtained after the 4th cycle of re-induction and every 2-3 months thereafter. All imaging obtained during and after re-induction will be considered when obtaining the best achieved objective response for patients who got re-induction treatments.

irRC: Measurable Disease Prior to Therapy (day <1)

Index lesions: Up to 15 index lesions per patient (5 per organ, up to 10 visceral and 5 cutaneous) with minimum size 5 x 5 mm will be accurately measured in two dimensions (two largest perpendicular diameters) on CT or MRI scan (slice thickness no greater than 5 mm) prior to therapy initiation. Lesions measured with calipers by clinical exam may be conducted on lesions no smaller than 10 mm in the smallest dimension. Lesions that cannot be accurately measured with calipers should be recorded as non-measurable.

SBRT-treated index lesions: Defined as all index liver and lung lesions treated by SBRT as part of this protocol.

Non-SBRT-treated index lesions: Defined as all index lesions not treated by SBRT as part of this protocol.

irRC: Index and non-Index Lesions:

For the irRC, index and measurable new lesions are taken into account (in contrast to conventional WHO treatment response criteria, which do not require the measurement of new lesions, nor are new lesion measurements included in the assessment of evolving tumor burden). At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥5 x 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 new visceral lesions) are added together to provide the total tumor burden. In addition to a global irRC

which will encompass all lesions under the previous definition, the irRC of lesions included within the SBRT PTV and outside the SBRT PTV will also be assessed as follows:

1. **Global irRC:** irRC that factors all lesions including both index and non-index as outlined in 9.5.

2. **In-Field irRC:** irRC in which only index within the SBRT PTV will be considered and any non-index lesions arising inside the SBRT PTV

3. **Out-Field irRC**: irRC in which only index lesions outside the SBRT PTV will be considered and any non-index lesions arising outside the SBRT PTV

8.4. Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or physical calipers. All baseline evaluation studies should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, cross sectional imaging is preferable.

Multidetector CT, PET/CT and MRI. These techniques should be performed with contiguous slices of 5 mm or less in thickness. This applies to tumors of the neck, chest, abdomen and pelvis. Head and neck tumors and those of extremities may require specific imaging protocols or evaluation with ultrasound. When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, Laparoscopy. These will not be used to assess response on this study.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) if clinically indicated.

8.5. Response Criteria

8.5.1. *Immune Related Response Criteria (irRC)*

Evaluation of Target Lesions

Response in new patients will be conducted using the Immune Related Response Criteria (irRC), as described by (12). “For irRC, only index and measurable new lesions are taken into account. At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥5 x 5mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden:”

For the purposes of this study, 3 separate tumor burdens will be calculated for each patient and used to define 3 separate irRCs as discussed in 8.3. All criteria will be considered separately for all 3 irRCs: global, in-field, and out-field.

Global Tumor Burden = SPD(all index lesions) + SPD(new, measurable lesions)

In-Field Tumor Burden = SPD(all index lesions targeted by SBRT in this protocol) + SPD(new, measurable lesions inside the SBRT PTV)

Out-Field Tumor Burden = SPD(all index lesions NOT targeted by SBRT in this protocol) + SPD(new, measurable lesions outside the SBRT PTV)

Complete Response (irCR): irCR, complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented.

Partial Response (irPR): irPR, decrease in tumor burden ≥50% relative to baseline confirmed by a consecutive assessment at least 4 wk after first documentation.

Progressive Disease (irPD): irPD, increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden) confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented.

3. If a patient is classified as having irPD at a post-baseline tumor assessment, then confirmation of irPD by a second scan in the absence of rapid clinical deterioration is required. The definition of confirmation of progression represents an increase in tumor burden ≥25% compared with the nadir at two consecutive time points at least 4 wk apart. It is recommended that this be done at the discretion of the investigator because follow-up with observation alone may not be appropriate for patients with a rapid decline in performance status.

Stable Disease (irSD): irSD, not meeting criteria for irCR or irPR, in absence of irPD. In contrast to other response criteria, this criteria does not require repeat confirmation. Clinical benefit will be established as having irSD for up to 6 months for irSD.

The following two tables are adapted from (12) and describe irRC criteria and compare/contrast irRC criteria with standard WHO criteria.

Table 2. Derivation of irRC overall responses

Measurable response	Nonmeasurable response		Overall response
Index and new, measurable lesions (tumor burden),* %	Non-index lesions	New, nonmeasurable lesions	Using irRC
↓100	Absent	Absent	irCR†
↓100	Stable	Any	irPR†
↓100	Unequivocal progression	Any	irPR†
↓≥50	Absent/Stable	Any	irPR†
↓≥50	Unequivocal progression	Any	irPR†
↓<50 to <25↑	Absent/Stable	Any	irSD
↓<50 to <25↑	Unequivocal progression	Any	irSD
≥25?	Any	Any	irPD†

*Decreases assessed relative to baseline, including measurable lesions only (>5 × 5 mm).
†Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 wk apart.

8.6 Systemic Biomarkers

The objective of this portion of the study is to correlate systemic serum markers, obtainable by peripheral venous access to patient responses and observed toxicities. Participation in this portion of the protocol is mandatory for all study participants.

Systemic lymphocyte counts obtained from routine CBC with differential will be analyzed and associated with clinical outcomes and toxicities from the lab draws obtained throughout this protocol.

8.7. Biopsies

The objective of this portion of the study is to correlate histologic/immunohistologic analyses of biopsy samples to patient responses and observed toxicities. Voluntary participation in this portion of the protocol is mandatory for all study participants. All patients will have a tumor assessment on the initial tumor sample via a standard mutation biomarker panel (MD Anderson 46 gene panel, foundation one panel). Assessment can be conducted from any prior biopsy or from the mandatory tumor biopsy sample, if available. When it is feasible (sufficient biopsy material and blood sample), we will examine, tumor mutational burden by whole exome sequencing and TIL profiling by flow cytometry. We will evaluate whether tumor mutational burden and/or TILs correlates with improved clinical outcomes and response criteria. Additionally, we will determine if radiation enhances the tumor DNA availability in blood compared to baseline.

This study will be done in collaboration with Interventional Radiology Investigators. Biopsies can be obtained 1-2 weeks prior to therapy initialization, at week 1 of cycle 2 (± 1 week) for groups 1 and 3 or at week 3 of cycle 2 for group 2 OR at any time at the discretion of the treating physician and the PI for research and / or due to medical necessity. See study calendars for tentative schedules (Section 12 Study Calendars).

9. Adverse Event Reporting

An Adverse Event (AE) is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is considered not to be related to the study drug. Medical conditions/diseases present before starting the study drug are only considered adverse events if they worse after starting the study drug. Abnormal laboratory values or test results constitute adverse events only if they include clinical signs or symptoms, are considered clinically significant, or require therapy.

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual 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.)

Non-serious Adverse Event

- Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [eg, IND US trial] as part of an annual reporting requirement.
- Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

A ***non-serious adverse event*** is an AE not classified as serious.

Non-serious Adverse Event Collection and Reporting

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

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

Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported to BMS as such.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- any laboratory 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).

Potential Drug Induced Liver Injury (DILI)

Standard medical practice in identifying and monitoring hepatic issues should be followed.

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

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

AND

3) 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.

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.

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state 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 > 40 mIU/mL to confirm menopause.

Note: 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.

- 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. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

Contraception Guidance for Female Participants of Child Bearing Potential

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure. For BMS-986156 monotherapy or in combination therapy treatment with nivolumab is defined as BMS-986156 plus 5 half-lives plus 30 days (duration of ovulatory cycle), for a total of **160 days** post treatment completion. Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must have a pregnancy test. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of >1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

Contraception Guidance for Male Participants with Partner(s) of Child Bearing Potential

- Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.
- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- **Male** participants are required to use a condom for study duration and until the end of relevant systemic exposure defined as **220 days** after the end of treatment.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as **160 days** after the end of treatment of the male participant.

- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until **220 days** after the end of treatment.
- Refrain from donating sperm for the duration of the study treatment and for **220 days**.

Collection of Pregnancy Information

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form.

Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 months after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant).

The investigator must immediately notify Worldwide.Safety@bms.com of this event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the CIOMS, MedWatch, BMS Pregnancy Surveillance Form, **or** approved site SAE form. A BMS Pregnancy Surveillance Form may be provided upon request.

Any pregnancy that occurs in a female partner of a male study participant must be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

Overdose

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

Other Safety Considerations

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

9.1. Serious Adverse Event Reporting (SAE) (Appendix B)

It is the responsibility of the PI and the research teams to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

A serious adverse event (SAE) is any untoward medical occurrence that at any dose, may result in any of the following outcomes:

- Death

- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity – a substantial disruption of a person's ability to conduct normal life functions.
- 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 or the development of drug dependency or drug abuse (21 CFR 312.32).

- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

- Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

- An important medical event is 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.)

  Important medical events as defined may also be considered serious adverse events. Any important medical event can and should be reported as an SAE.

The following hospitalizations are not considered SAEs in BMS clinical studies:

- 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 (applies to oncology protocols).

NOTE: Immune-mediated adverse reactions are expected and well described in the package insert for ipilimumab. Hospitalizations required for intravenous administration of high dose steroids will be considered adverse events and will not be considered SAEs. If the adverse event has not improved within 7 days of intravenous high dose steroids, it will be deemed serious and reported in an expedited manner to the appropriate groups.

Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigators.

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to IND Office, regardless of attribution (within 5 working days of knowledge of the event).

Serious adverse events will be captured from the time the patient signs consent until **100 days** after the last dose of drug, whether related or not related to the study drug or any protocol related procedure. Serious adverse events must be followed until clinical recovery is complete and laboratory test have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

Additionally, any serious adverse events that occur after the 100 day time period that are related to the study treatment must be reported to the IRB as per MDACC policy. This may include the development of a secondary malignancy.

All life-threatening or fatal events, that are unexpected, and related to the study drug, must have written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

Reporting to the FDA:

- Serious adverse events will be forwarded to the FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

9.2. Reporting of Adverse Events

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

Adverse Events that are routinely collected according to GCP shall be submitted to BMS every three (3) months by the last working day of the third month.

The Adverse Event information required to be sent to BMS is noted in an attached 'Bristol-Myers Squibb Early Asset Investigator Sponsored Research (ISR) Import Plan' which describes the method of collection and submission to BMS via the mailbox:

MG-RD-GPVE-PHARMACOVIGILANCE@bms.com

When the file is submitted to BMS, it must be noted whether the file contains all Non Serious Adverse Events (only adverse events not previously submitted to BMS within the 3 months).

All Serious Adverse Events must be reported to BMS Worldwide Safety

It is the responsibility of the PI and the research teams to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).
- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these aforementioned time periods, which 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.

An appropriate SAE form (e.g. ex-US = CIOMS form or USA = Medwatch form) should be used to report SAEs to BMS. If you prefer to use your own Institutional form, it must be reviewed by the BMS Protocol Manager prior to study initiation to ensure that at a minimum all of the data elements on the CIOMS form are present. Note: Please include the BMS Protocol number on the SAE form or on the cover sheet with the SAE form transmission.

  - The CIOMS form is available at: http://www.cioms.ch/index.php/cioms-form-i
  - The MedWatch form is available at: MedWatch 3500 Form

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  - The Sponsor will reconcile the clinical database AE cases (**case level only**) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com).
    - The Investigator will request from BMS GPV&E, aepbusinessprocess@bms.com the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary
    - GPV&E will send the investigator the report to verify and confirm all SAEs have been transmitted to BMS GPV&E.
    - The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS (Worldwide.Safety@bms.com).
  - In addition to the Sponsor Investigator's responsibility to report events to their local HA, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the

relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

- In accordance with local regulations, BMS will notify sponsor investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Sponsor investigator notification of these events will be in the form of either a SUSAR Report or a Semi-Annual SUSAR Report.
    - Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor or BMS decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event. SAEs must be recorded on either CIOMS, MedWatch, or approved site SAE form.

Pregnancies must be reported and submitted to BMS. BMS will perform due diligence follow-up using the BMS Pregnancy Form which the investigator must complete.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual 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.)

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

10. Statistical Considerations

Data Collection
All patients who meet eligibility criteria and are enrolled in this trial will be registered in Clinical Oncology Research (CORe) Database at the University of Texas M D Anderson Cancer Center at Houston. This study will utilize CORe and Moclia as its case report forms (CRF) for data collection.

Data Protection and Confidentiality

All patients who meet eligibility criteria and are enrolled in this trial will be registered in Clinical Oncology Research Database (CORe) at the University of Texas M D Anderson Cancer Center at Houston. All protocol participants must be registered in the CORE. The date in the current informed consent document is displayed to ensure only the most current IRB approved version is used. Consent date, registration date, off study date, and evaluability data are required for all registrants.

The principal investigator agrees to keep all information and results concerning the study confidential. The confidentiality obligation applies to all personnel involved with this clinical trial. The Investigator must ensure that each participant's anonymity will be maintained in accordance with applicable laws. The principal investigator should keep a separate log of ID numbers, names and addresses. Documents that contain the names associated with these ID numbers (e.g., written consent/assent forms), should be

maintained by the Investigator in strict confidence except to the extent necessary to allow auditing by regulatory authorities, auditing or monitoring by the IRB.

The Principal Investigator shall obtain all such permissions and authorizations as may be necessary or desirable to allow the collection and use of information protected under federal privacy laws and state privacy laws, including permission/authorization for monitoring and analysis (including re-analysis in combination with results of other studies), for regulatory submission purposes and for applicable reporting (if any).

Tumor response will be determined using the Immune Related Response Criteria (irRC) as described in section 8.3.

The Investigator is responsible for completing an efficacy/safety summary report, and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval. This should be submitted after the first 3 evaluable patients in groups 1 and 3 complete 29 days of study treatment, and after the first 3 evaluable patients in group 2 complete 43 days of therapy initiation, and every 3 evaluable patients per group thereafter. IND Office approval must be obtained prior to advancing/changing dose levels.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder.

10.1. Data Set Descriptions

For group 1, after BMS-986156, dose as determined in group 1, an additional 4 patient expansion per dose level (10 patients total for each dose level) will be enrolled in that group, at the determined dose from group 1, to help determine biological endpoints. Should DLTs occur in more than 33% of patients enrolled into this expanded group, dosing at that level will be stopped. The next lower dose level will be considered the safe dose. A review of all DLTs observed will be conducted, and the need to lower the dose will be based on the discussion and agreement between the IRB and the Investigator.

All patients who receive any ipilimumab, BMS-986156, or nivolumab will be considered evaluable for toxicity.

For toxicity and response: all patients receiving at least 1 (concurrent group) or 2 (sequential group) treatment with trial drugs and completed half of the planned radiation treatment (except for group 1 where no radiation is given) will be considered evaluable for toxicity and response and included in the efficacy data set.
Group 1: (Total of 20 patients: 10 patients with 30 mg and 10 patients with 100 mg of BMS-986156, when combined with ipilimumab at 3mg/kg). Nivolumab (480mg) Q4W monotherapy will be administer for 26 cycles.
Group 2: 20 patients: trial drugs, two doses of ipilimumab (3mg/kg) combined with BMS-986156 (dose as determined in group 1) are given before SBRT. SBRT is given sequentially; followed by 2 more doses of ipilimumab + BMS-986156. Nivolumab (480mg) Q4W monotherapy will be administer for 26 cycles.
Group 3: 20 patients: First dose of trial drugs nivolumab (480 mg) and BMS-986156 (30 mg) are given concurrently with SBRT; followed by 3 doses of nivolumab (480 mg) and BMS-986156 (30 mg). Finally, Nivolumab as monotherapy for 22 cycles. Nivolumab will be administered for a total of 26 cycles in this group.

10.1.1. Safety Evaluation

The incidence of clinical and laboratory adverse events will be reported and graded according to the NCI-CTCAE version 4.0 (available at http://ctep.cancer.gov/reporting/ctc.html). Adverse events will be reported in frequency tables overall, by intensity, and by relationship. Laboratory values will be reported in shift tables and with summary statistics.

10.1.2. Efficacy Evaluation

Information on the anti-tumor activity of study drug(s) and SBRT combination therapies will be collected throughout this study. Tumor response will be determined using the Immune Related Response Criteria (irRC) as described in section 8.3.

10.2. Analysis

10.2.1. Statistical Analysis

Descriptive statistics will be computed for all relevant outcomes, including tumor response, and biomarker response. Descriptive analysis will include a global assessment of patient outcomes among all three groups. Group analysis will be conducted between groups. All patients receiving at least 1 (concurrent group) or 2 (sequential group) treatment with ipilimumab/Nivolumab/BMS-986156 and completed half of the planned radiation treatment (except for group 1 where no radiation is given) will be considered evaluable for toxicity and response and included in the analysis. Patients receiving any portion of the study drugs or interventions will be evaluable for toxicity.

Demographics, safety, and treatment efficacy will be compared in two separate analyses: (these tests are not for formal hypothesis testing, but for exploratory/descriptive purposes)

1. Among different treatment regimens: treatment group 1 vs. treatment group 2.

2. Among different treatment regimens: treatment group 2 vs. treatment group 3.

3. Among different SBRT targets liver vs lung: treatment group 2 vs. treatment group 3.

10.2.2. Demographics and Baseline Characteristics

Frequency distributions of gender and race will be tabulated by dose/group. Summary statistics for age, body weight, height, and Body Mass Index (BMI) will be tabulated by dose/group. Comparisons by Chi-Squared or Fisher Exact Test will be conducted, for categorical variables, to assess for baseline differences between groups.

10.2.3. Safety Analyses

All recorded adverse events will be recorded per MDACC guidelines using CTCAE Version 4.0. Frequency of grade ≥3 adverse events will be compared via Chi-Squared or Fisher Exact Test.

10.2.4. Efficacy Analyses

Treatment success and clinical benefit will be defined as irCR or irPR or irSD, assessed using irRC (e.g. the best response obtained by a patient). Clinical benefit will be established as having irCR or irPR or irSD > 6 months. Measurements from all imaging, including those obtained during and after re-induction, will be considered in this analysis. Patients will be continuously evaluated for disease response via imaging until they are removed from the study. For secondary objectives a), b), and c), success probabilities will be estimated for each target separately (liver, lung) along with appropriate 95% confidence intervals. Safety comparisons among the groups will be assessed (primary end points) and efficacy comparisons between groups will be assessed with regard to the irRC outcomes while global, in-field irRC will be used for

hypothesis generating using Pearson chi-squared or Fisher exact tests. For secondary objective d) comparisons will be performed between group 2 and 3 as well as per treatment site (liver, or lung).

1. **Global irRC:** irRC that factors all lesions both index and non-index as outlined in 8.3.

2. **In-Field irRC:** irRC in which only SBRT-treated lesions will be considered and non-index lesions arising inside the SBRT PTV

3. **Out-Field irRC**: irRC in which only non SBRT-treated lesions will be considered and non-index lesions arising outside the SBRT PTV

For the secondary objective comparing the response between the arms. With 20 patients per arm, we would have 80% power using a two-sided 10% alpha with a chi-squared test to detect the following differences in response rates between treatment groups 44% vs 10%, 57% vs 20%, 68% vs 30% and 78% vs 40%. To increase statistical power, we may also combine the patients into a single dataset and fit a logistic regression model with response (CR+PR) as the outcome and SBRT dose, target (liver or lung) among other factors (including but not limited to: number of metastatic disease sites, number of prior treatments, primary cancer histology, age, pre-treatment KPS and Royal Marsden Score) as the predictors.

Time-to-event analyses will be conducted via Kaplan-Meier analysis, with comparisons via the log-rank test made with regards to **overall survival**, with analysis beginning at receipt of the first SBRT fraction. At the discretion of the investigators, and if appropriate, a multivariate Cox regression will be done to adjust for (among other factors): number of metastatic disease sites, number of prior treatments, primary cancer histology, age, pre-treatment KPS and Royal Marsden Score.

10.2.5. Sample Size/Accrual Rate

The maximum planned number of evaluable patients will be 60, with 20 patients being treated in each group (groups: 1, 2 and 3). It is estimated that approximately 3 patients per month will be accrued and an approximate 4 week interval will be allowed between dose levels.

10.2.6. Treatment Group Stratification

In the event that a patient presents with both a liver and a lung lesion that are both amenable to stereotactic radiation, the treatment of either the liver or lung site will be at the discretion of the treating physician.

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12. Study Calendars

Study Calendars

Group 1: Ipilimumab + BMS-986156 x4 → Nivolumab x 26

Assessment Tool (Study related visit range ± 2 days)	Baseline[3]	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5 to 30				PD	Follow Up Period (1 year)
		Week			Week			Week			Week			Week					Every 2-4 months +1 month[9,10]
		1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	4		
Ipilimumab		X[4]			X			X			X								X[10]
BMS-986156		X[4]			X			X			X								X[10]
Nivolumab														X[5]					
DLT Assessment						X[7]		X			X								
History & Physical Exam (including weight measurement)[1]	X[3]	X			X	X		X			X			X					X[9]
CBC & differential[1]	X[3]	X			X	X		X			X			X					X[9]
ECG[6]	X[3,6]																		
Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, phosphorus, albumin, total protein, alkaline phosphatase, total bilirubin, uric acid, SGOT (AST), SGPT[ALT], TSH[1]	X[3]	X			X	X		X			X			X					X[9]
Urinalysis[1]	X[3]																		
Hepatitis B/C & HIV Screening[1]	X[3]																		

Serum pregnancy test (women of childbearing potential) [1]	**X**[3]																		
irRC imaging and tumor assessment	**X**[2]													**X**[11]					**X**[11]
Biomarker studies	**X**[8]				**X**[8]													**X**[8]	
Biopsies[8]	**X**[8]				**X**[8]													**X**[8]	

1. Physical exams and lab test measurements will be given a window of ± 3 days unless patient/logistical/medical reasons intervene. Every patient requires physician evaluation within 7 days before start of study and ± 3 days before each subsequent ipilimumab/BMS-986156 administration. Physical examination to include weight, vital signs, and performance status.
2. Initial tumor assessment should occur within 4-weeks before start of study and should be obtained via CT scans of the chest, abdomen and/or pelvis (contrast-enhanced preferred); MRI of the abdomen and pelvis; PET/CT scan (Preferred).If the aforementioned imaging modalities cannot be obtained an Ultrasound (US); or chest radiograph (least preferred) may be obtained.
3. Baseline visit within 2 weeks prior to initiation of therapy. Overlapping baseline tests can be combined with tests required for cycle 1 of ipilimumab/BMS-986156 administration as long as these baseline tests occur within 3 days before cycle 1.
4. First ipilimumab/BMS-986156 treatment will begin on day 1 (± 3) and start a 21 day/cycle combination therapy.
5. Nivolumab treatment will begin on day 85 (± 3) and start a 28 day/cycle combination therapy.
6. A baseline ECG will be recorded within 1-2-weeks (± 3 days) prior to therapy initiation
7. DLT assessment will include both evaluation by the phase I research nurse with optional input from the radiation oncology research nurses.
8. Mandatory blood and tissue biopsies samples will be obtained at baseline prior to the first cycle of ipilimumab/BMS-986156, at week 1 of cycle 2 (±7 days) and at time of progression of disease.
9. Follow up appointments after last cycle of ipilimumab/BMS-986156 will occur in the Clinical Center for Targeted Therapy. Radiation oncology follow up visits will occur at the discretion of the treating radiation oncologist, recommended at 3 and 6 months.
10. Patients will be offered 4 cycles of reinduction ipilimumab/BMS-986156 if disease control (SD or PR) is observed at the first imaging after cycle 4 of ipilimumab. Reinduction can occur 8 weeks or later after the last cycle of ipilimumab/BMS-986156 induction. Patients can be offered repeat reinduction if disease control is observed and severe (grade >3 toxicity) is not observed.
11. Patients will receive routine scans to evaluate response by receiving either CT scans of the chest, abdomen, and/or pelvis (preferred); MRI of abdomen and pelvis; or PET/CT (preferred). After imaging performed for cycle 5, repeat imaging will be collected every 12 weeks (± 4 weeks) or sooner if clinically indicated by the discretion of PIs or treating physician.

Group 2: Ipilimumab + BMS-986156 x2→ SBRT→ Ipilimumab + BMS-986156 x2 → Nivolumab x 26

Assessment Tool (Study related visit range ± 3 days)	Baseline [3]	Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5 to 30				PD	Follow Up Period (1 year)
		Week			Week			Week			Week			Week					Every 2-4 months +1 month[10,11]
		1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	4		
SBRT simulation (4DCT performed within 3 weeks prior to SBRT treatment)					X														
SBRT treatment						X[4]													X[11]
Ipilimumab		X[5]			X			X			X								X[11]
BMS-986156		X[5]			X			X			X								X[11]
Nivolumab														X[6]					
DLT Assessment[8]								X[8]											
History & Physical Exam (includingweight measurement)[1]	X[3]	X			X	X		X			X			X					X[10]
CBC & differential[1]	X[3]	X			X	X		X			X			X					X[10]
ECG[7]	X[3,7]																		
Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, phosphorus, albumin, total protein, alkaline phosphatase, total bilirubin, uric acid, SGOT (AST), SGPT[ALT], TSH[1]	X[3]	X			X	X		X			X			X					X[10]
Urinalysis[1]	X[3]																		
Hepatitis B/C & HIV Screening[1]	X[3]																		

Serum pregnancy test (women of childbearing potential) [1]	**X**[3]																		
irRC imaging and tumor assessment	**X**[2]													**X**[12]					**X**[12]
Biomarker studies	**X**[13]						**X**[13]											**X**[13]	
Biopsies[9]	**X**[9]						**X**[9]											**X**[9]	

1. Physical exams and lab test measurements will be given a window of ± 3 days unless patient/logistical/medical reasons intervene. Every patient requires physician evaluation within 7 days before start of study and ± 3 days before each subsequent ipilimumab/BMS0986156 administration. Physical examination to include weight, vital signs, and performance status.
2. Initial tumor assessment should occur within 4-weeks before start of study and should be obtained via CT scans of the chest, abdomen and/or pelvis (contrast-enhanced preferred); MRI of the abdomen and pelvis; PET/CT scan (Preferred).If the aforementioned imaging modalities cannot be obtained an Ultrasound (US); or chest radiograph (least preferred) may be obtained.
3. Baseline visit within 2 weeks prior to initiation of therapy. Overlapping baseline tests can be combined with tests required for cycle 1 of ipilimumab/BMS-986156 administration as long as these baseline tests occur within 3 days before cycle 1.
4. SBRT will be given on days 29-32 (50Gy in 4 fractions) or day 29-40 (60Gy in 10 fractions).
5. First ipilimumab/BMS-986156 treatment will begin on day 1 (± 3) and start a 21 day/cycle combination therapy.
6. Nivolumab treatment will begin on day 85 (± 3) and start a 28 day/cycle combination therapy.
7. A baseline ECG will be recorded within 1-2-weeks (± 3 days) prior to therapy initiation
8. DLT assessment will include both evaluation by the phase I research nurse with optional input from the radiation oncology
9. Mandatory tissue biopsies will be obtained prior to the first cycle of ipilimumab/BMS-986156,at the end of the cycle 2, and at progression of disease as determined per the discretion of the treating physician and/or study PIs.
10. Follow up appointments after last cycle of ipilimumab/BMS-986156 will occur in the Clinical Center for Targeted Therapy. Radiation oncology follow up visits will occur at the discretion of the treating radiation oncologist, we recommend at 3 and 6 months.
11. Patients will be offered 4 cycles of reinduction ipilimumab/BMS-986156 +/- radiation if disease control (SD or PR) is observed at the first imaging after cycle 4 of ipilimumab/BMS-986156. Reinduction can occur 8 weeks or later after the last cycle of ipilimumab/BMS-986156 induction. Patients can be offered repeat reinduction if disease control is observed and severe (grade >3 toxicity) is not observed.
12. Patients will receive routine scans to evaluate response by receiving either CT scans of the chest, abdomen, and/or pelvis (preferred); MRI of abdomen and pelvis; or PET/CT (preferred).
13. Mandatory blood will be obtained prior to the first cycle of ipilimumab/BMS-986156, on the last day of radiation treatment (Day 32/33 for patients receiving 50 Gy in 4 fractions or on day 40 for patients receiving 60 Gy in 10 fractions), and at progression of disease determined by the discretion of the treating physician and/or study PIs.

Group 3: Concurrent Nivolumab + BMS-986156 + SBRT → Nivolumab + BMS-986156 x3 → Nivolumab x 22

Assessment Tool (Study related visit range ± 3 days)	Baseline[3]	Cycle 1		Cycle 2		Cycle 3		Cycles 4		Cycles 5-26			Follow Up Period (1 year)
		Week		Week		Week		Week		Week		PD	Every 2-4 months +1 month[10,]
		1	2	1	4	1	4	1	4	1	4		
SBRT simulation (4DCT performed within 3 weeks prior to SBRT treatment)	X												
SBRT		X[4]											X[13]
Nivolumab		X[5]		X[5]		X[5]		X[5]		X[5]			X[13]
BMS-986156		X[5]		X[5]		X[5]		X[5]					X[13]
DLT Assessment[8]				X[8]									
History & Physical Exam (including weight measurement)[1]	X[1,3]	X		X		X		X		X			X[10]
CBC & differential[1]	X[1,3]	X		X		X		X					X[10]
ECG[7]	X[3,7]												
Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, phosphorus, albumin, total protein, alkaline phosphatase, total bilirubin, uric acid, SGOT (AST), SGPT[ALT], TSH[1]	X[1,3]	X[1]		X[1]		X[1]		X[1]		X[1]			X[10]
Urinalysis[1]	X[1,3]												
Hepatitis B/C & HIV screening	X[1,3]												
Serum pregnancy test (women of childbearing potential) [1]	X[1,3]												
irRC imaging and tumor assessment[2]	X[2]					X[11]				X[11]			X[10,11]
Biomarker studies	X[12]		X[1] [2]									X[12]	

Biopsies[9]	**X[9]**			**X[9]**								**X[9]**	

1. Physical exams and lab test measurements will be given a window of ± 3 days unless patient/logistical/medical reasons intervene. Every patient requires physician evaluation within 7 days before start of study and ± 3 days before each subsequent nivolumab/BMS-986156 administration. Physical examination to include weight, vital signs, and performance status.
2. Initial tumor assessment should occur within 4-weeks before start of study and should be obtained via CT scans of the chest, abdomen and/or pelvis (contrast-enhanced preferred); MRI of the abdomen and pelvis; PET/CT scan (Preferred).If the aforementioned imaging modalities cannot be obtained an Ultrasound (US); or chest radiograph (least preferred) may be obtained.
3. Baseline visit within 2 weeks prior to initiation of therapy. Overlapping baseline tests can be combined with tests required for cycle 1 of nivolumab/BMS-986156 administration as long as these baseline tests occur within 3 days before cycle 1.
4. SBRT will be given on days 1-4 or 2-5 (50Gy in 4 fractions) or 1-12 (60Gy in 10 fractions) of treatment protocol.
5. First nivolumab/BMS-986156 treatment will begin on day 1 (± 3) and start a 28 day/cycle combination therapy for 4 cycles total.
6. Nivolumab monotherapy will start on cycle 5 and end cycle 26. Nivolumab will be administered for 22 cycles as monotherapy for a total of up to 26 cycles.
7. A baseline ECG will be recorded within 1-2-weeks (± 3 days) prior to therapy initiation
8. DLT assessment will include both evaluation by the phase I research nurse with optional input from the radiation oncology research nurses.
9. Mandatory tissue biopsies samples will be obtained at baseline prior to the first cycle of nivolumab/BMS-986156, after cycle 2 infusion (week 1 of cycle 2), and at time of progression of disease.
10. Follow up appointments after last cycle of nivolumab will occur in the Clinical Center for Targeted Therapy. Radiation oncology follow up visits will occur at the discretion of the treating radiation oncologist, recommended at 3 and 6 months.
11. Patients will receive routine scans to evaluate response by receiving either CT scans of the chest, abdomen, and/or pelvis (preferred); MRI of abdomen and pelvis; or PET/CT (preferred). Routine scans will be performed every 12 weeks (±4 weeks or sooner if clinically indicated per the discretion of the treating physician or study PIs.
12. Mandatory blood samples will be obtained at baseline prior to the first cycle of nivolumab/BMS-986156, on the last day of radiation treatment (day 4/5 of cycle 1 for patients receiving 50 Gy in 4 fractions or day 12 of cycle 1 for patients receiving 60 Gy in 10 fractions), and at progression of disease determined by the discretion of treating physician and/or study PIs.
13. Patients will be offered 4 cycles of reinduction nivolumab/BMS-986156 +/- radiation if disease control (SD or PR) is observed at the first imaging after cycle 4 of ipilimumab/BMS-986156. Reinduction can occur 8 weeks or later after the last cycle of nivolumab/BMS-986156 induction. Patients can be offered repeat reinduction if disease control is observed and severe (grade >3 toxicity) is not observed

13. APPENDIX A: DRUG INFORMATION

IPILIMUMAB:

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	IP	Open label	Clear to slightly opalescent, colorless to pale yellow, sterile, nonpyrogenic, single-use, isotonic aqueous solution that may contain particles. Carton containing 5 vials of 200mg	2-8° C. Protect from light and freezing.

BMS-986156:

Product Description Class and Dosage Form	Potency	IP/Non-IP	Blinded or Open Label	Packaging/Appearance	Storage Conditions (per label)
BMS-986156 Injection	100 mg/vial (10 mg/ml)	IP	Open	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light

NIVOLUMAB

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection	100mg (10mg/ml)	IP	Open label	Clear to opalescent colorless to pale yellow liquid. May contain particles. Carton containing 5 vials of 100mg	2-8° C. Protect from light and freezing.

14. APPENDIX B: MANAGEMENT ALGORITHMS FOR IMMUNO-ONCOLOGY AGENTS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

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

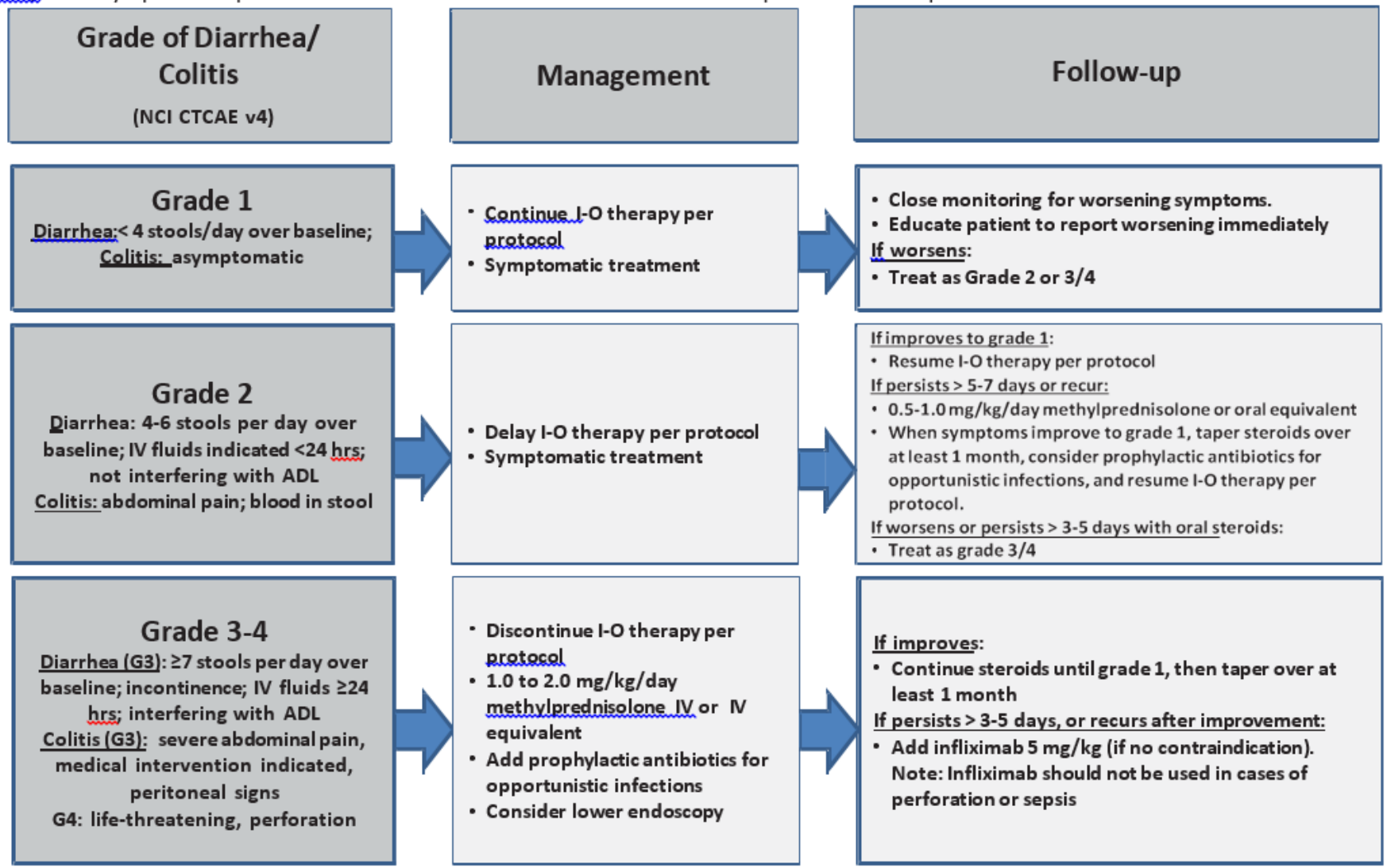
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

GI Adverse Event Management Algorithm

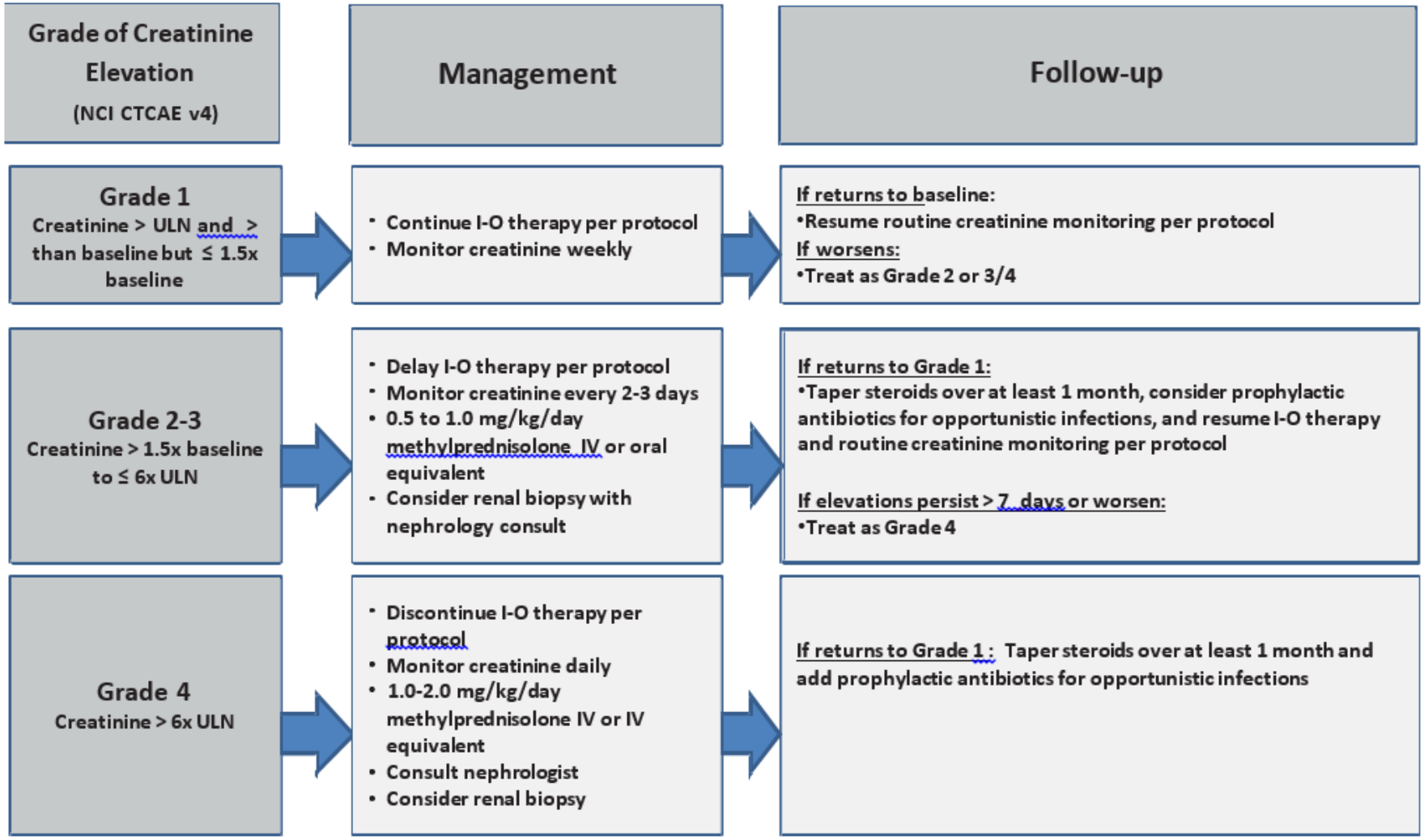
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

Renal Adverse Event Management Algorithm

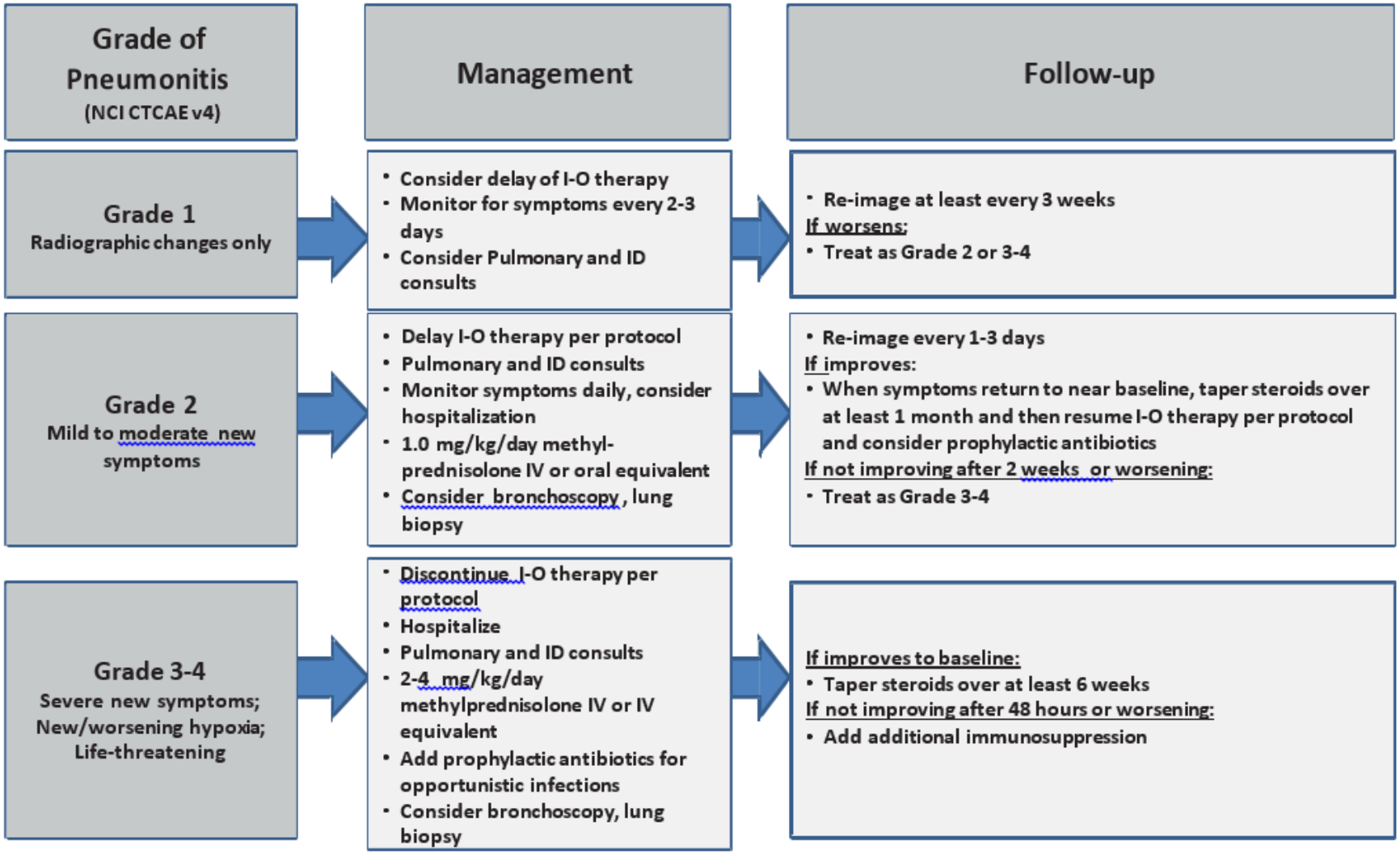
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

Pulmonary Adverse Event Management Algorithm

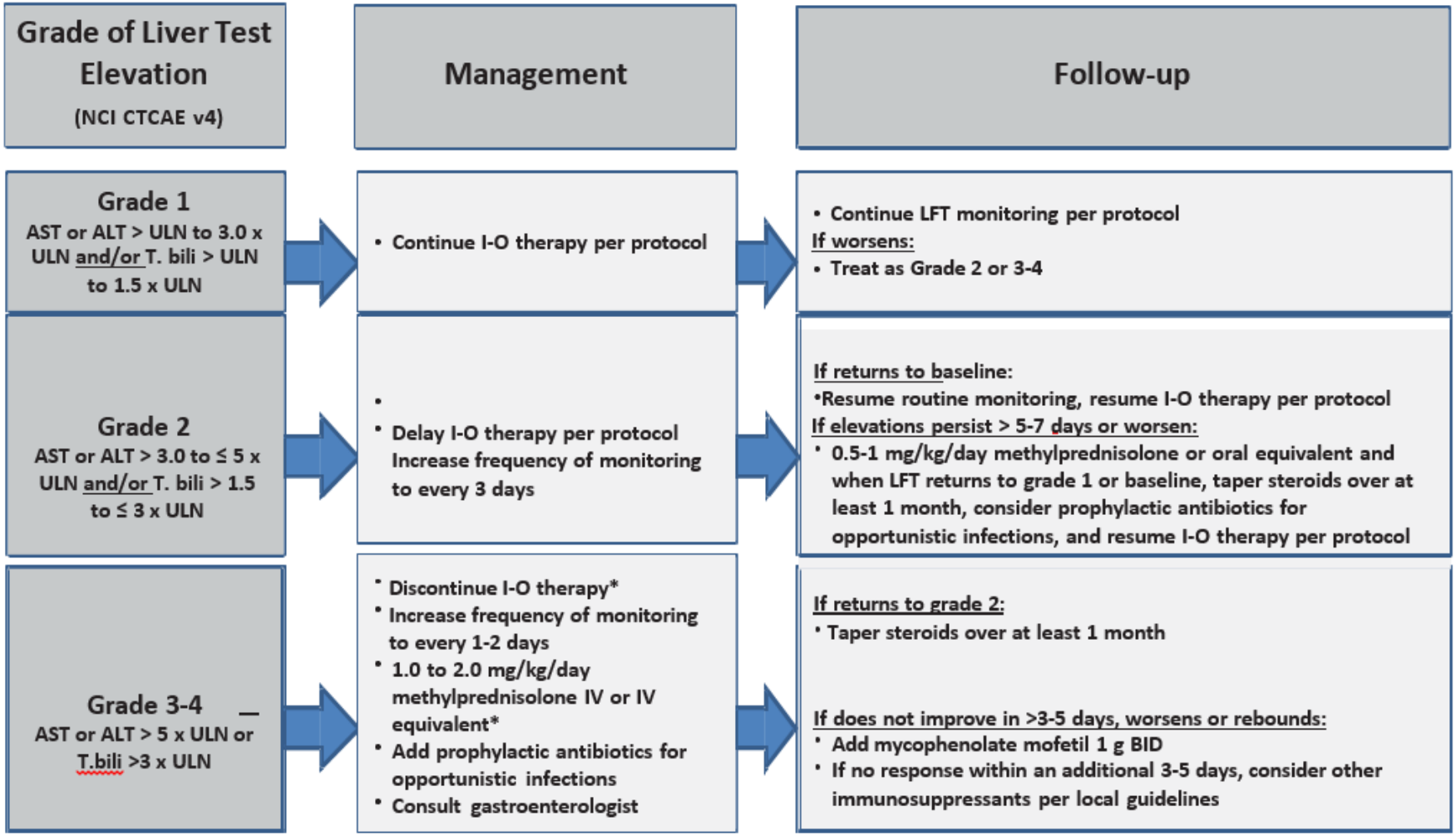
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

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.

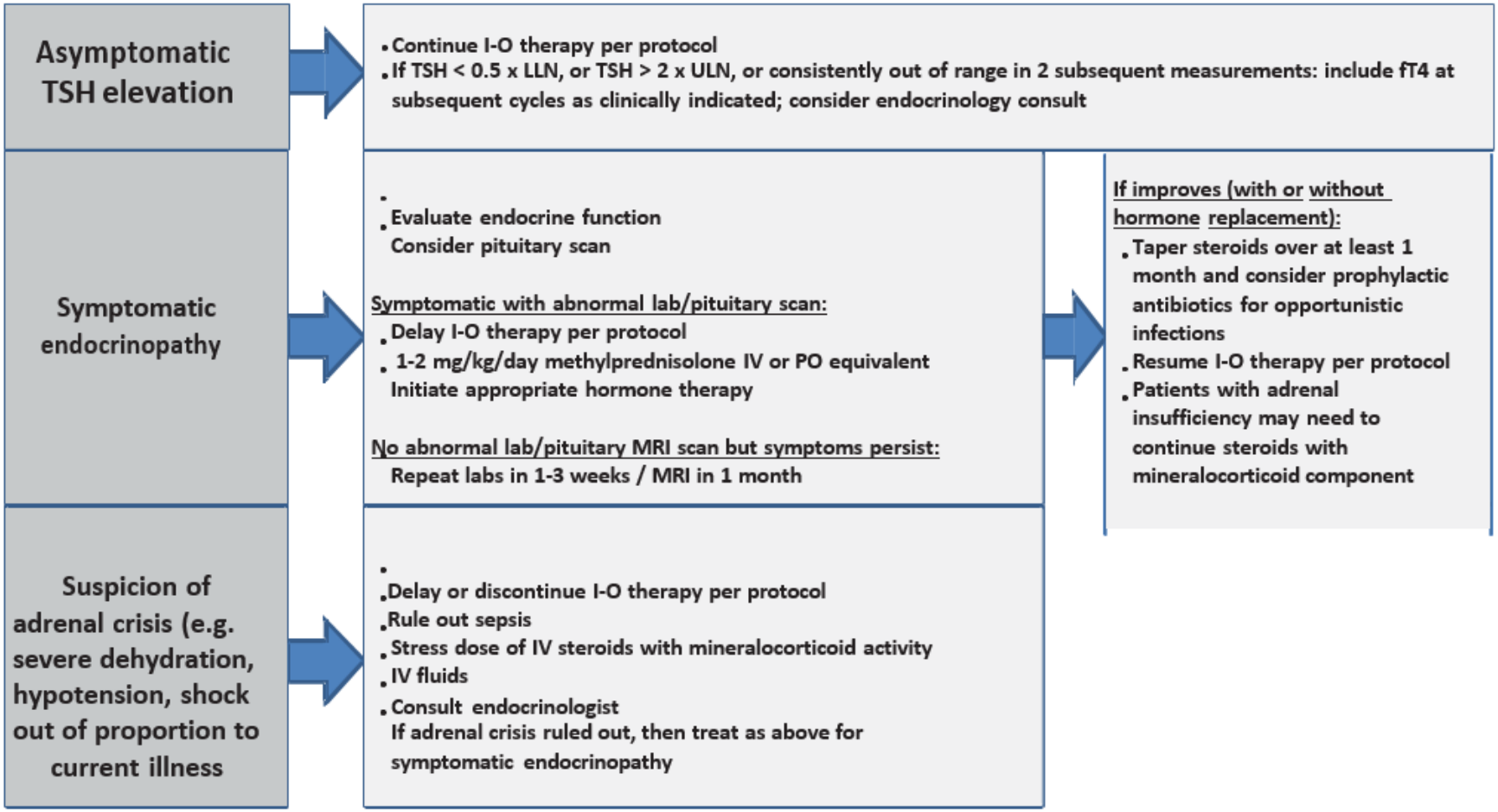


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

Endocrinopathy Adverse Event Management Algorithm

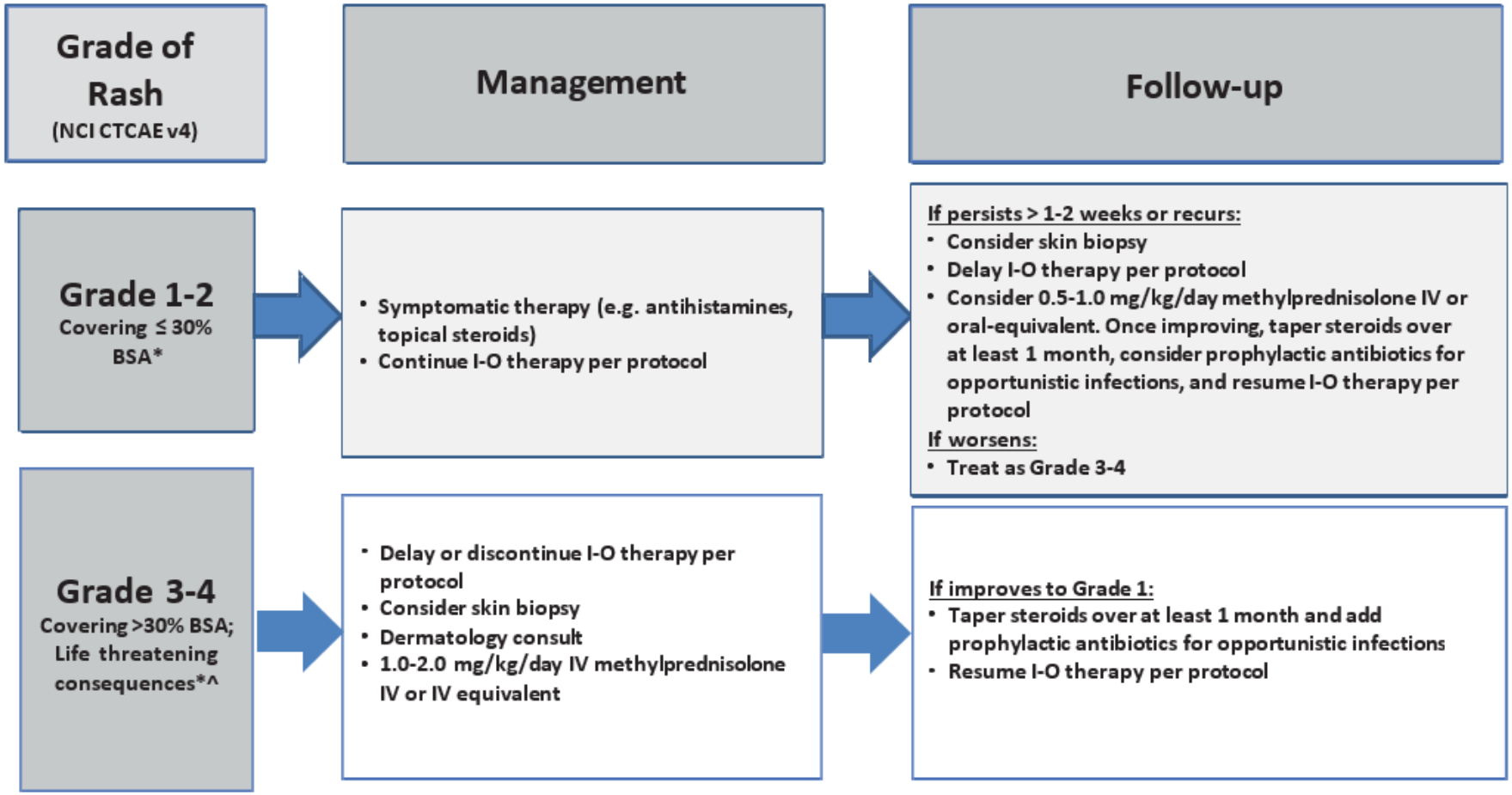
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



- 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.



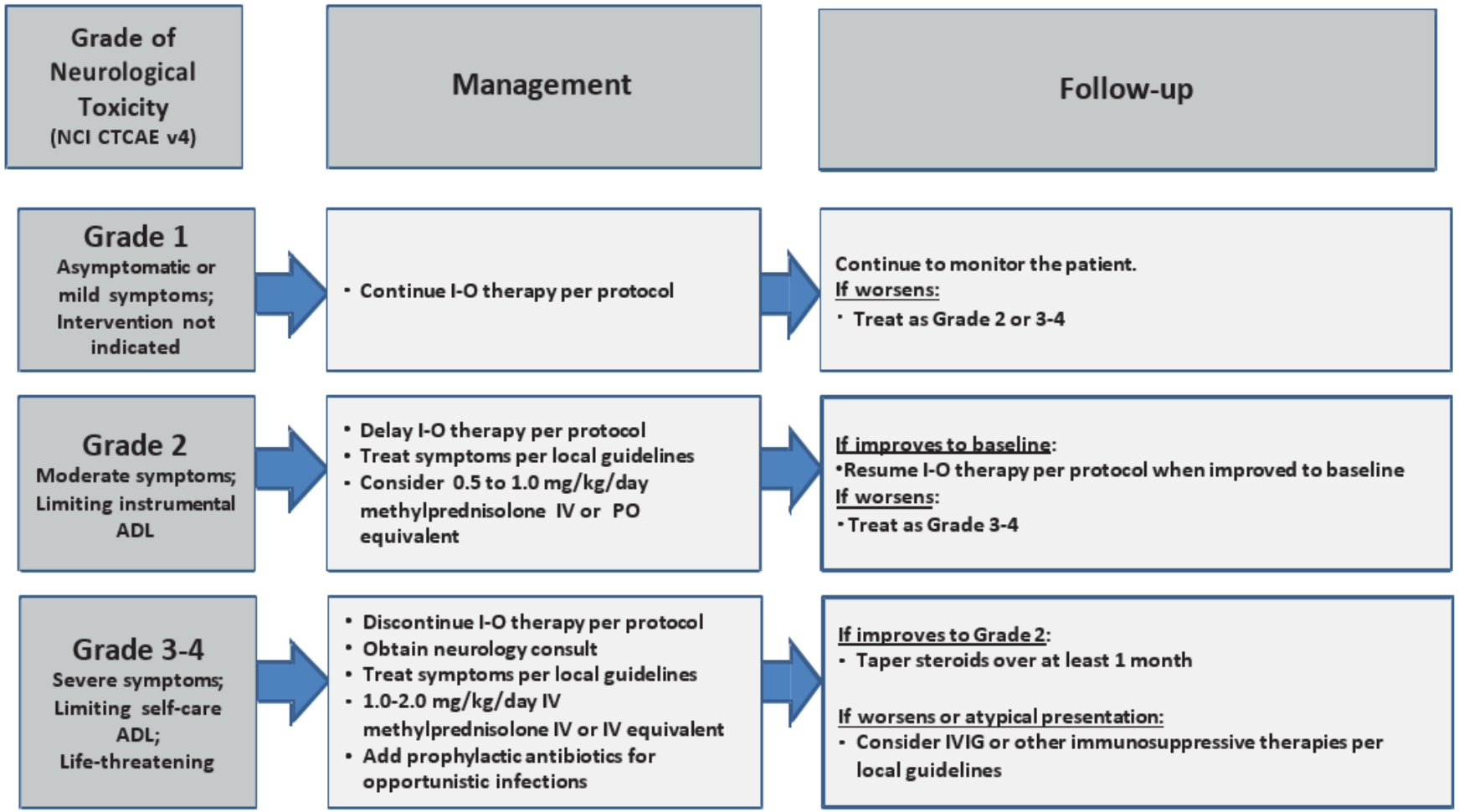
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

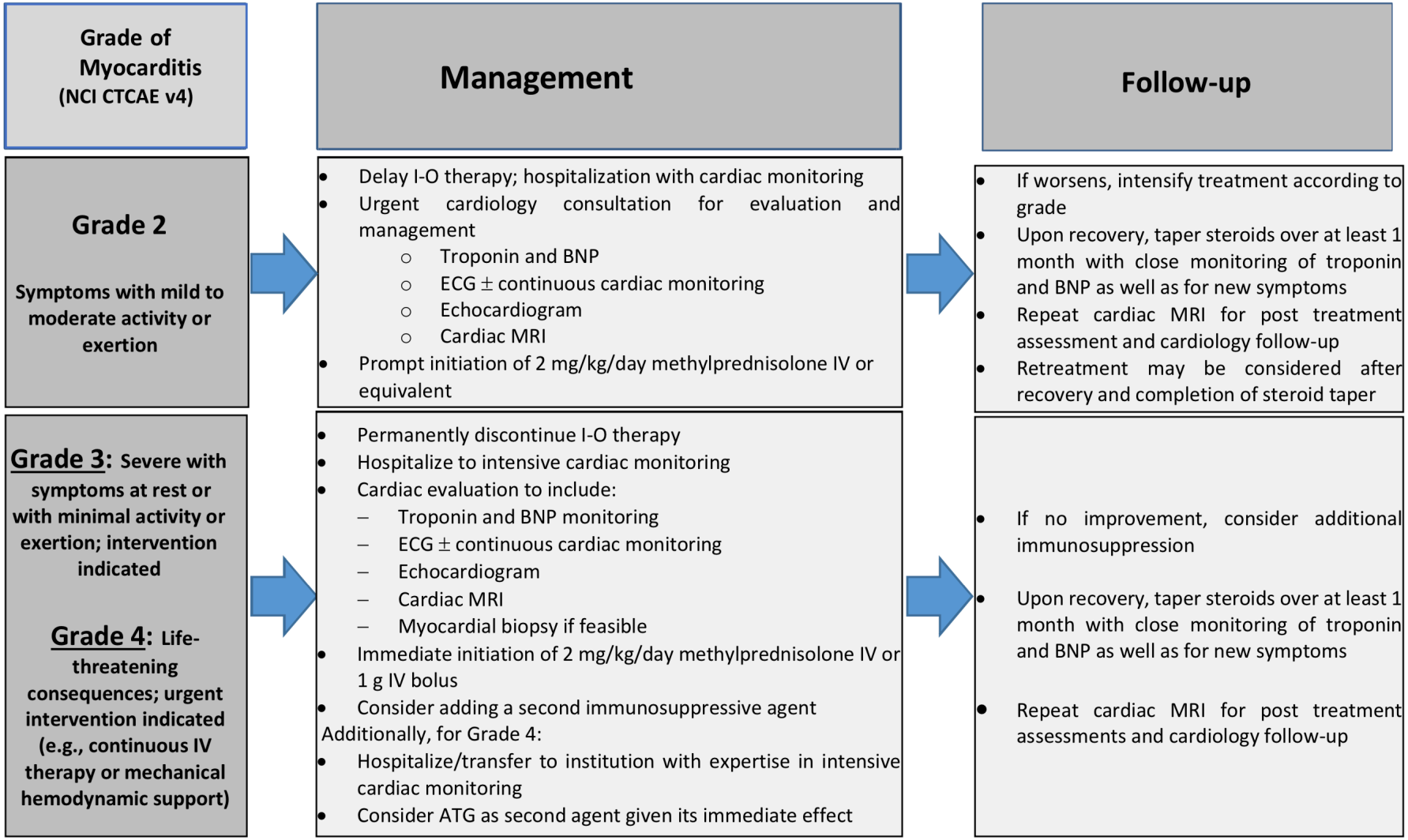
Neurological Adverse Event Management Algorithm

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.

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging