Protocol #: MCC 18684

TITLE: A Phase II Investigator Sponsored Study of Nivolumab in Patients with Advanced Refractory Biliary Tract Cancers

Sponsor/IND Holder: H. Lee Moffitt Cancer Center

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Supplied Agent: Nivolumab

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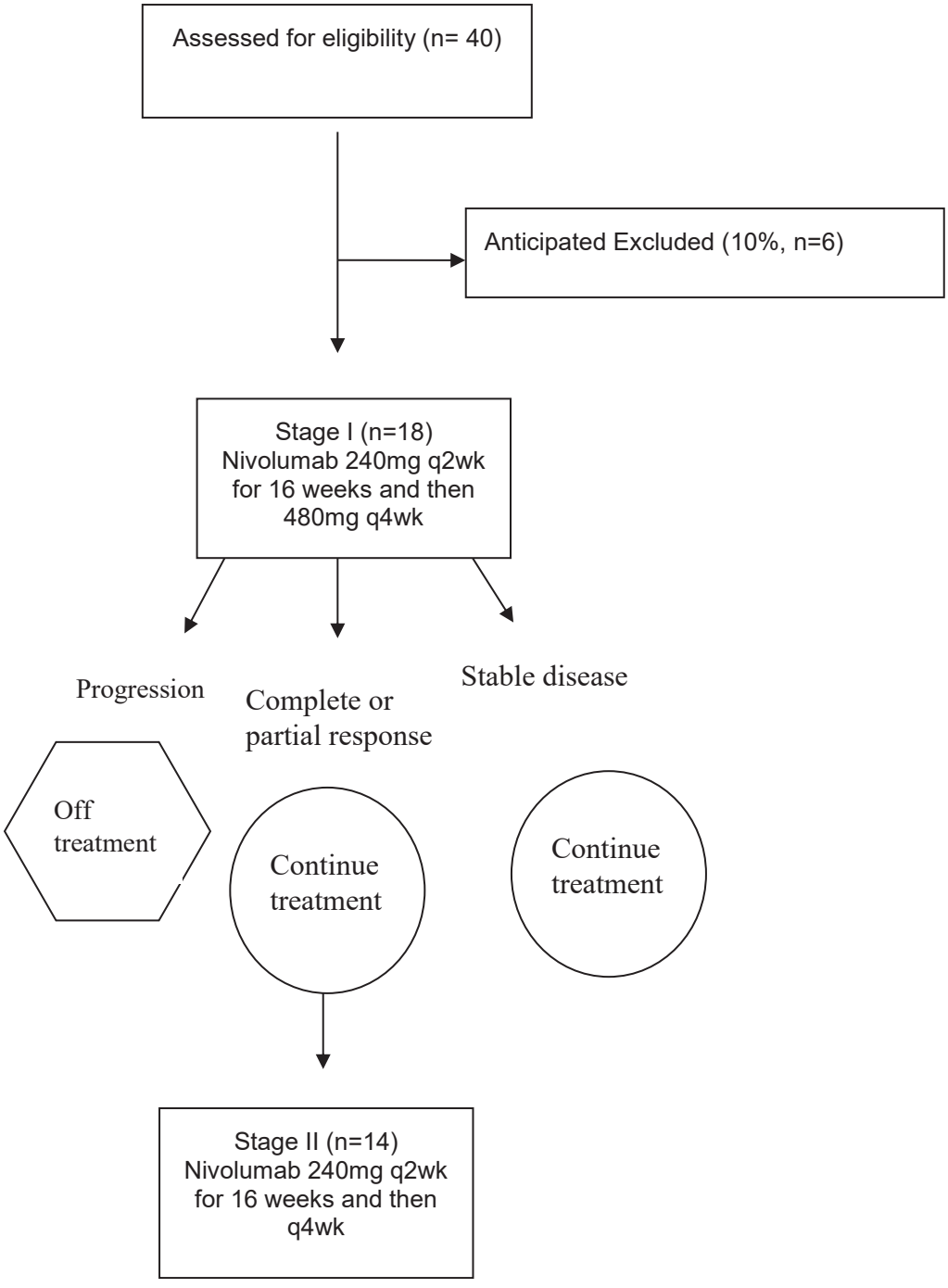
Study Synopsis

Title	A Phase II Investigator Sponsored Study of Nivolumab in Patients with Advanced Refractory Biliary Tract Cancers
Clinical study phase	Phase II
Study objective(s)	**Primary Objective** The primary endpoint will be overall response rate (ORR). ORR is defined as complete responses (CR) plus partial responses (PR). **Secondary Objectives** • To determine the frequency and severity of adverse events and tolerability of the regimen in patients with advanced refractory BC receiving nivolumab • To determine the progression-free survival (PFS) in patients with advanced refractory BC receiving nivolumab. PFS is defined as the duration of time from start of treatment to time of progression or death, whichever comes first. • To determine the overall survival in patients with advanced refractory BC receiving nivolumab • To determine the overall response rate by the immune response criteria **Exploratory Objectives** The CancerPlex® testing will be performed to assess the neoantigen burden of the tumor. The resulting "immune signature" will be correlated with outcome in a descriptive analysis. This analysis will include assessment of microsatellite instability.

Background	The outcome of patients with advanced biliary cancer remains dismal with the current standard of care options. There is currently an unmet medical need for patients with advanced BC who have failed systemic therapy. BC includes a heterogeneous group of cancers but data has suggested that there is an immune component to the development of these tumors and high PD-1 protein expression has been found. The second line setting therefore offers a unique opportunity to evaluate the activity of anti-PD1 immunotherapy agents like nivolumab.
Indication	Patients with advanced biliary tumor who have failed at least one prior line of systemic therapy.
Diagnosis and main criteria for inclusion	Patients must have histologically or cytologically documented carcinoma primary to the intra- or extra-hepatic biliary system or gall bladder with clinical and/or radiologic evidence of unresectable locally advanced or metastatic disease. Patients with ampullary carcinoma are not eligible. Patients must have failed one but no more than 3 prior lines of systemic chemotherapy for advanced biliary cancer. Patients who are intolerant to first line therapy will be allowed. Patients who had disease recurrence after first line therapy will be allowed. Patients who received adjuvant chemotherapy and had evidence of disease recurrence within 6 months of completion of the adjuvant treatment are also eligible. If patient received adjuvant treatment and had disease recurrence after 6 months, patients will only be eligible after failing one line of systemic chemotherapy used to treat the disease recurrence. Patients must have measurable disease, as defined by RECIST 1.1 criteria. Patients must not have been treated with any prior anti-PD1, anti-PDL1, or anti-CTLA4 agents
Study design	This is a multi-institutional phase II single arm two-stage design trial using nivolumab as a single agent.

Type of control	Patients will receive nivolumab at a dose of 240 mg IV every 2 weeks for 16 weeks and then 480 mg IV every 4 weeks until disease progression or unacceptable toxicity. After 2 cycles (1 cycle= 28 days), tumor response will be evaluated using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) as well as immune response criteria. Treatment beyond progressive disease (PD) will be allowed for pseudo progression as determined by clinical benefit or immune response criteria.
Number of subjects	32 evaluable
Plan for statistical analysis	The primary endpoint for this study will be response rate (CR + PR) at 4 months. We will use a Simon's Two-Stage Design in which the power is 0.9 and the type 2 error is 10%. The study will be expanded to the second stage if there is a 20% probability of response. At least 1 patient of the first 18 enrolled will need to have a complete or partial response for study continuation. Alternatively, if there are at least 4 patients with stable disease for 16 weeks (2 restaging assessments), the principal investigator will discuss proceeding to the second stage of the study with the BMS medical team. The second stage of this study will involve an additional 14 patients. The study will have met its primary endpoint of response rate if there are at least four patients in the nivolumab only arm who achieve a response. We anticipate an attrition rate of 10%, so about 40 patients will be recruited. Based on previous trials, we expect to enroll about 12 patients per year at our center and so will involve 2 other centers to complete enrollment within 18 months.

Schema


Assessed for eligibility (n= 40)
Anticipated Excluded (10%, n=6)
Stage I (n=18)
Nivolumab 240mg q2wk
for 16 weeks and then
480mg q4wk
Progression
Complete or
partial response
Stable disease
Off
treatment
Continue
treatment
Continue
treatment
Stage II (n=14)
Nivolumab 240mg q2wk
for 16 weeks and then
q4wk

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1. Introduction

1.1 Background

Biliary tract cancers (BTC) typically include intra and extrahepatic cholangiocarcinoma and cancers of the gallbladder. In the US in 2015, an estimated 2,600 intrahepatic cholangiocarcinomas and 10,000 cases of extrahepatic bile duct cancer. Of the latter, two thirds were gallbladder cancers.[1] This is a rare but aggressive group of malignancies with many patients presenting with advanced disease and overall dismal outcomes.[2]

The only cure for patients who present with local disease is surgical resection or liver transplantation. However, the rate of disease recurrence remains high even in resectable patients and there is no compelling data regarding the role for adjuvant therapy in this setting. Though meta-analyses have shown a nonsignificant overall survival benefit to adjuvant therapy,[3] there is limited prospective data on which agents are active in this disease.

However, the majority of patients present with unresectable disease and treatment options are very limited. Systemic chemotherapy has historically been disappointing in advanced BTC, though new combination regimens have shown activity. ABC-02, a randomized phase III study, enrolled 410 patients and compared gemcitabine plus cisplatin with gemcitabine alone.[4] The median overall survival (OS) and progression-free survival (PFS) were greater for gemcitabine plus cisplatin than for gemcitabine alone without significantly increased toxicity (OS: 11.7 *v* 8.1 months; log-rank *P* = .002; PFS: 8.0 *v* 5.0 months; *P* = .003). This drug combination set a new international standard of care for the first line treatment of advanced BTC. Based on phase II data, the combination of gemcitabine and oxaliplatin is also used in the first line setting after efficacy and tolerability were shown.[5]

Several phase II trials have evaluated various chemotherapy regimens in the second line setting, including FOLFOX (oxaliplatin, 5-fluorouracil, and leucovorin), oxaliplatin with capecitabine, and 5-fluorouracil and cisplatin.[6,7] However, there is no established regimen for treatment in patients with progression on first line therapy or refractory disease. The survival in this setting remains dismal at a median of less than 6 months.[8-10] Advances have been slow in part because of the tumor heterogeneity of BTCs.[11] There remains a significant need to identify novel agents and to treat this deadly disease.

Outcomes can perhaps be improved with greater understanding of the underlying disease biology. The development of BTC appears to be related to the immune system, and carcinogenesis has been linked to chronic parasitic infections as well as autoimmune conditions like primary sclerosing cholangitis.[12,13] In addition, patients with evidence of immune system activation, measured by higher levels of lymphocytes, have been shown to have improved prognosis.[14] Recent data suggests that the immune regulatory protein PD-1 is upregulated in intrahepatic cholangiocarcinoma tissues compared to cancer adjacent tumors.[15] It has also been shown that hilar cholangiocarcinomas may evade immunologic surveillance through the apoptosis of lymphocytes.[16]

In pre-clinical work at Moffitt Cancer Center, we found that cholangiocarcinoma tumors which stained positive for CD45R0 (lymph node like structure) were associated with improved median OS (63 months vs 18 months, P = 0.003).[17] These immune active tumors are likely to have escaped the inhibitory effects of programmed death ligand complex.

Immunotherapy has been evaluated in a few patients with BTCs. In one case report, a patient with a locally advanced intrahepatic cholangiocarcinoma was treated initially with surgical resection followed by adjuvant treatment with immunotherapy (CD3 activated T cells as well as dendritic

cells). She had no disease recurrence for over 3 years.[18] More recently, an anti-PD1 agent was recently evaluated in tumors with microsatellite instability in a phase II study.[19] Included in this cohort was one patient with mismatch repair deficient bile duct cancer who had a partial response with a 41% decrease in tumor size and a 93% decrease in tumor marker at 20 weeks.

1.2 Nivolumab

Human tumors have a myriad of genetic alterations leading to neoantigens which should be recognized by the host immune system. However, cancer can dysregulate immune checkpoint proteins as a way of evading the host immune system and ensuring survival.[20] Immunotherapy in oncology has been evaluated as a means of upregulating the host immune system so that tumors can be recognized as foreign and endogenous anti-tumor immunity can attack tumor cells. Immune checkpoint pathway inhibitors such as anti-CTLA4 and anti-PD-1 antibodies have been evaluated in the treatment of a variety of tumors.

Preclinical Studies

Programmed death 1 is a protein which limits T-cell activity in an effort to minimize autoimmunity.[21] When activated by ligands, PD-1 along with its costimulatory protein B7, decrease T cell activity which can allow tumors to escape immune recognition. Antibodies against PD-1 have been developed in an effort to increase T cell activity.

Nivolumab is a human monoclonal antibody that targets the programmed death-1 (PD-1) CD279 cell surface membrane receptor and inhibits PD-1 interaction with its ligands PD-L1 and PD-L2. PD-1 knockout mice develop autoimmune conditions from excessive T cell activity including glomerulonephritis and autoimmune cardiomyopathy.[22,23] In vitro, nivolumab has resulted in increased T-cell proliferation and interferon gamma release in mixed lymphocyte reaction.[24] In vivo, PD-1 blockade by a nivolumab analog resulted in enhanced anti-tumor response and tumor rejection in several murine models (BMS investigator's brochure). Nivolumab has been generally well tolerated in the preclinical setting. In toxicity studies of cynomolgus monkeys, nivolumab was tolerated at doses of 50mg/kg every 2 weeks. There was increased neonatal mortality in pregnant monkeys, in keeping with the role of PD-L1 in maintaining murine fetomaternal tolerance.[25]

Clinical Studies

Clinical Pharmacokinetics
Nivolumab has been tested in over 8600 human subjects with doses ranging from 0.1 to 10 mg/kg as both a single dose as well as multiple doses every few weeks. Steady state drug concentration was achieved by 12 weeks when nivolumab was administered at 3mg/kg every 2 weeks. Drug clearance has not been affected by age, gender, race, or tumor type. Though glomerular filtration rate and mild hepatic impairment have had an effect on clearance, it has not been clinically meaningful.

Clinical Efficacy
Nivolumab has been FDA approved for the treatment of metastatic melanoma, metastatic non-small cell lung cancer, and clear cell renal cancer based on the results of phase III studies.[26-29] The majority of responses have been durable and have exceeded 6 months. In melanoma, nivolumab has been approved in metastatic disease in the first line setting. In non-squamous lung cancer, it has been approved in advanced disease after progression on one prior treatment. Similarly, nivolumab is approved for the treatment of renal cell carcinoma patients who have progressed on previous therapy.

Clinical Safety
No maximum tolerated dose of nivolumab has been established at doses tested up to 10mg/kg. The safety profile is similar across tumor types and there has been no pattern of adverse effects with regards to incidence or severity based on dose level. Common drug related adverse effects have included pulmonary toxicity, GI toxicity, liver toxicity, and dermatologic toxicity, the majority of which have been manageable with supportive care, dose delay, or steroid treatments.

The overall safety experience with nivolumab is based on clinical experience in approximately 8,600 subjects. In general, for monotherapy, the safety profile is similar across tumor types. The most frequently reported treatment-related AE is fatigue, which is almost always of low grade.

Rationale:

The outcome of patients with advanced biliary cancer remains dismal with the current standard of care options. There is no established second line option for patients with advanced BC who have failed one prior systemic therapy.

Given that immune modulatory agents are known to have activity in BTCs,[30] we propose to evaluate the anti-PD1 agent nivolumab in advanced, refractory BTC, a rare malignancy in which there is a critical unmet clinical need.

2. Study Objectives

Primary Objective
To determine the disease response rate (Complete Response + Partial Response) in patients with advanced biliary tract cancers (BTC) receiving nivolumab as a single agent

Secondary Objectives
1. To determine the median progression free survival (PFS) and overall survival (OS) and response rate by immune response criteria in patients with advanced BTC receiving nivolumab

2. To determine the safety and tolerability of nivolumab in BTC

Exploratory Objectives

1. To explore potential correlations between mismatch repair status and outcome

2. To explore potential correlation of mutational burden and outcome, as evaluated by the Kew CancerPlex immune signature panel.

3. Study Design

This is a multi-institutional single arm study with two stage design using nivolumab in advanced BTC, who have failed or are intolerant to at least one line of therapy and no more than 3 lines of therapy. In the first stage, 18 patients will be accrued. If there is at least one response (or several patients with stable disease based on the study team's discretion), an additional 14 patients will be accrued for a total of 32 patients. Patients will receive nivolumab at a flat dose of 240mg every 2 weeks for 16 weeks (4 cycles). Response and progression will be evaluated using the new

international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1). The primary endpoint is disease response after 2 cycles of treatment (8 weeks). Patients with stable disease or disease response will continue on therapy until progression. Patients can continue on therapy if there is pseudo-progression which is defined by the immune response criteria or if they are having clinical benefit as determined by the investigator after discussion with the principal investigator.

4. Eligibility

4.1 Inclusion Criteria

- Patients must have histologically or cytologically documented carcinoma primary to the intra- or extra-hepatic biliary system or gall bladder with clinical and/or radiologic evidence of unresectable, locally advanced or metastatic disease. Patients with ampullary carcinoma are not eligible.

- Patients must have failed or are intolerant to one line of systemic treatment but no more than 3 prior lines of systemic chemotherapy for advanced BTC. Patients who received adjuvant chemotherapy and had evidence of disease recurrence within 6 months of completion of the adjuvant treatment are also eligible. If the patient received adjuvant treatment and had disease recurrence after 6 months, patients will only be eligible after failing or having intolerance to one line of systemic chemotherapy used to treat the disease recurrence.

- Age ≥ 18 years.

- Eastern Cooperative Oncology Group (ECOG) Performance Status Assessment of 0 or 1.

- The patient must have radiographic measurable disease per RECIST 1.1 criteria
  - Life expectancy of at least 12 weeks (3 months).
  - For patients who have received prior radiation, cryotherapy, radiofrequency ablation, therasphere, ethanol injection, transarterial chemoembolization (TACE) or photodynamic therapy, the following criteria must be met:
    - 28 days have elapsed since that therapy
    - Lesions that have not been treated with local therapy must be present and measureable
  - Subjects must be able to understand and be willing to sign the written informed consent form. A signed informed consent form must be appropriately obtained prior to the conduct of any trial-specific procedure. Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other study requirements.
  - All acute toxic effects of any prior treatment have resolved to NCI-CTCAE v4.0 Grade 1 or less at the time of signing the Informed Consent Form (ICF) except for alopecia.
  - Adequate bone marrow, liver and liver function as assessed by the following laboratory requirements:
    - Total bilirubin ≤ 1.5 x the upper limits of normal (ULN), except for subjects with Gilbert Syndrome who can have bilirubin <3.
    - Alanine aminotransferase (ALT) and aspartate amino-transferase (AST) ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer or stent placement)

- Alkaline phosphastase limit ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
- Serum creatinine <2 x ULN
- Hematologic parameters as follows:
  - Platelet count ≥ 100,000 /mm^3
  - Hemoglobin (Hb) ≥ 9 g/dL
  - Absolute neutrophil count (ANC) ≥1000/mm^3
  - Blood transfusion to meet the inclusion criteria will be allowed.

- Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity of 25 IU/L or equivalent units of HCG) performed within24 hours prior to the start of nivolumab Post-menopausal women (defined as no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test.
- Subjects (men and women) of childbearing potential must agree to use adequate contraception beginning at the signing of the ICF until at least 3 months after the last dose of study drug. The definition of adequate contraception will be based on the judgment of the principal investigator or a designated associate.
- Patients with history of hepatitis B and hepatitis C will be eligible but patients with hepatitis B must be started on antiviral therapy prior to beginning study therapy
- Availability of archival tumor tissue for biomarkers analysis (FFPE block or cell block will be required). Specimen from primary site will be allowed. Patients must have at least 10 slides available. Repeat biopsy to obtain sufficient tissue for 10 slides is allowed.

4.2 Exclusion Criteria

- Subjects with active CNS metastases are excluded. If CNS metastases are treated and subjects are at neurologic baseline for at least 2 weeks prior to enrollment, they will be eligible but will need a Brain MRI prior to enrollment. Subjects must be off corticosteroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent).
- Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll
- Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of enrollment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways).
- Previous or concurrent cancer within 3 years prior to treatment start EXCEPT for curatively treated cervical cancer in situ, non-melanoma skin cancer, superficial bladder tumors [Ta (non-invasive tumor), Tis (carcinoma in situ) and T1 (tumor invades lamina propria)].
- Known history of human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS).

- Child Pugh B or C disease
- History of severe hypersensitivity reactions to other monoclonal antibodies
- History of allergy or intolerance to study drug components or Polysorbate-80-containing infusions
- Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results.
- History or concurrent condition of interstitial lung disease of any grade or severely impaired pulmonary function.
- Unresolved toxicity higher than CTCAE grade 1 attributed to any prior therapy/procedure excluding alopecia.
- Pregnant or breast-feeding patients. Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity of 25 IU/L or equivalent units of HCG) performed within 24 hours prior to the start of nivolumab and a negative result must be documented before start of treatment.
- Any illness or medical conditions that are unstable or could jeopardize the safety of the patient and his/her compliance in the study.

Excluded Therapies and Medications for Cancer

- Anticancer chemotherapy during the study or within 4 weeks of study enrollment. Subjects must have recovered from the toxic effects of the previous anti-cancer chemotherapy (with the exception of alopecia). Anti-cancer therapy is defined as any agent or combination of agents with clinically proven anti-tumor activity administered by any route with the purpose of affecting the malignancy, either directly or indirectly, including palliative and therapeutic endpoints.
- Hormonal therapy during the study or within 2 weeks of first study enrollment.
- Radiotherapy to target lesions during study or within 2 weeks of enrollment.
- An irradiated lesion is considered evaluable only if it has shown enlargement since the completion of last radiation.
- Bone marrow transplant or stem cell rescue.
- Investigational drug therapy outside of this trial during or within 4 weeks of first study treatment.

4.3 Withdrawal of Subjects from Study

4.3.1 Withdrawal

Subjects must discontinue investigational product for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason). A subject must be removed from the trial at his/her own request or at the request of his/her legally acceptable representative. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject

- Pregnancy will be reported as an SAE and the patient will be withdrawn. (Note: subjects who have been withdrawn from treatment with study drug because of pregnancy should not undergo CT scans [with contrast]/MRI or bone scans while pregnant.)
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
- Subject is lost to follow-up
- Death

All subjects who discontinue should comply with protocol specified follow-up and survival procedures. The ONLY exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form page.

Subjects **may be** withdrawn from the study for the following reasons:

- The subject is non-compliant with study drug, trial procedures, or both; including the use of anti-cancer therapy not prescribed by the study protocol.
- Severe allergic reaction to nivolumab
- The development of a second cancer.
- Development of another illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- Deterioration of ECOG performance status to 3 or 4.
- Use of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise skewing trial result.

Any subject removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable.

Any subject with progression of disease will come off of treatment. In all cases, the reason for withdrawal must be recorded in the CRF and in the subject's medical records.

4.3.2 Screen Failures/Dropouts/Replacements

A subject who discontinues study participation prematurely for any reasons except death, disease progression and severe toxicity is defined as a dropout.

Dropouts who did not receive at least one staging assessment (after 2 cycles or 8 weeks of treatment) will need to be replaced.

A subject who, consents to participate but does not qualify for treatment based upon the eligibility criteria is regarded a “screening failure”.

Patients who are screening failures will need to be replaced.

Patient who receive at least one staging assessment (after 2 cycles or 8 weeks of treatment), will be included in the analysis of disease response.

5. Treatment

5.1 Treatment to be administered

All patients will receive Nivolumab

Agent	Dose	Route	Schedule*	
Nivolumab	240mg	IV	q2weeks	until 16 weeks

**One cycle = 28 days*

Agent	Dose	Route	Schedule*	
Nivolumab	480mg	IV	q4weeks	from 17 weeks to end of study

5.1.1 Flat Dose Regimen

The safety and efficacy of 240 mg Q2W flat dose of nivolumab is expected to be similar to 3 mg/kg Q2W dosing regimen. Using the PPK model, exposure of nivolumab at 240 mg flat dose is identical to a dose of 3 mg/kg for subjects weighing 80 kg, which is the approximate median body weight in nivolumab clinical trials. Across the various tumor types in the clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy and safety has been found to be relatively flat. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of 240 mg flat dose compared to 3 mg/kg, it is expected that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab. Hence, a flat dose of 240 mg nivolumab is under investigation. Of note, 240 mg is identical to 3mg/kg for 80 kg patients; 80 kg is the median body weight.

5.2 Management of Toxicities Associated with Study Drug

Subjects will receive treatment with nivolumab as a 60 minute IV infusion, on Week 1, Day 1 and Week 3, Day 1 of a treatment cycle (every 2 weeks).

There will be no dose escalations or reductions of nivolumab allowed. This includes both the 240mg q 2 week portion of the study as well as the 480mg q 4 week portion of the study.

Subjects may be dosed no less than 12 days from the previous dose. There are no premedications recommended for nivolumab on the first cycle. If an acute infusion reaction is noted, subjects should be managed according to Section 5.2.5.

Treatment may be delayed for up to a maximum of 6 weeks from the last dose (See Sections 5.2.1 and 5.2.4.1).
Subjects will be monitored continuously for AEs while on study. Treatment modifications (eg dose delay or discontinuation) will be based on specific laboratory and adverse event criteria.

In some cases, the natural history of immunotherapy-related AEs of special interest can differ and be more severe than AEs caused by other therapeutic classes. Early recognition and management may mitigate severe toxicity. The management of organ specific toxicities is detailed through flow sheets in Appendix 1.

Summary of Safety

Most related AEs are thought to be due to the effects of inflammatory cells on specific tissues. In general, the approach to suspected nivolumab-related AEs is similar across any involved organ system. Safety management algorithms for organ-specific AEs are found in Appendix 1. Subjects should have a thorough diagnostic work-up to evaluate potential drug- and non-drug-related diagnoses. For suspected nivolumab-related AEs, based on the severity of the event, management with immunosuppressant may be necessary. In general, dose delays and observation are adequate for low-grade AEs. For moderate- and high-grade AEs, immunosuppression with corticosteroids should be utilized. Once the AE has begun to improve, corticosteroids can be tapered over approximately 3 weeks to 6 weeks (depending on the severity of the AE).

Immune Mediated Event Assessment

This assessment of AE is made by the individual investigator and should be based on clinical evidence such as:

- Responsiveness to treatment (e.g. steroids)
- Diagnostic test results (e.g. evidence of inflammation)
- Medical history (other illness, prior therapies, etc.)

An IMAE is an AE consistent with an immune-mediated mechanism or immune-mediated component (alternate etiology exacerbated by the induction of autoimmunity) for which non-inflammatory etiologies (e.g. infection or tumor progression) have been ruled out, and consideration given to evidence of inflammation such as tumor biopsies or responsiveness to steroids.

Likely reasons an event **is not** an IMAE:

- Likely due to concomitant drug/chemotherapy/radiation
- Documented evidence of tumor as cause
- Same grade event at baseline/history
- Event likely caused by infection

Likely reasons an event **is** an IMAE:

- Inflammation per pathology or endoscopy
- Improves/resolves after immunosuppression
- Similar to previous immune mediated event in same organ

Pulmonary Adverse Events

Pulmonary AEs have been observed following treatment with nivolumab and have occurred after a single dose and after as many as 48 treatments. The majority of cases reported were Grade 1 or 2, and subjects presented with either asymptomatic radiographic changes (eg, focal ground glass opacities and patchy infiltrates) or with symptoms of dyspnea, cough, or fever. Subjects with reported Grade 3 or 4 pulmonary AEs were noted to have more severe symptoms, more extensive radiographic findings, and hypoxia. At this time, no underlying risk factor, including prior radiotherapy, presence of lung metastases, or underlying pulmonary medical history, has been identified.

Guidelines on the recommended management of pneumonitis and other pulmonary AEs are found in Appendix 1. Early recognition and treatment of pneumonitis is critical to its management. Subjects should be advised to seek medical evaluation promptly if they develop new-onset dyspnea, cough, or fever or if they have worsening of these baseline symptoms. It is important

that an evaluation/work-up distinguishes between non-drug-related causes (eg, infection or progression of disease) and a possible drug-related pulmonary toxicity as the management of these events can be quite different. For symptomatic nivolumab-related pneumonitis, the principal treatment is corticosteroids (Appendix 1). All subjects with Grade 3-4 pneumonitis should discontinue nivolumab and initiate treatment with high doses of corticosteroids.

Gastrointestinal Adverse Events

Gastrointestinal AEs have been observed following treatment with nivolumab. Most cases of diarrhea were of low grade (Grade 1-2). Colitis occurred less frequently than diarrhea. High-grade cases of diarrhea and colitis were managed with corticosteroids and, in all cases, the events resolved.

The recommended management of GI AEs is provided in Appendix 1. Early recognition and treatment of diarrhea and colitis are critical to their management. Subjects should be advised to seek medical evaluation if they develop new-onset diarrhea, blood in stool, or severe abdominal pain or if they have worsening of baseline diarrhea. It is important that an evaluation/work-up distinguishes between non-drug-related causes (eg, infection or progression of disease) and a possible drug-related AE as the management can be quite different. The principal treatment for high-grade GI AEs is corticosteroids (Appendix 1). Caution should be taken in the use of narcotics in subjects with diarrhea, colitis, or abdominal pain as pain medicines may mask the signs of colonic perforation. Grade 3 diarrhea/colitis requires permanent discontinuation regardless of AE duration.

Diverticular Perforation

Given the high prevalence of diverticulosis and diverticulitis in the general population, it is expected that some nivolumab-treated subjects will have these conditions concurrently w ith their malignancy. While there is insufficient evidence to suggest that diverticulosis or diverticulitis is a predisposing factor for GI perforation following nivolumab administration, clinical caution should be exercised, as appropriate, for subjects on concomitant medications of corticosteroids, NSAID, or opioid analgesics. In addition, vigilance should be used for signs and symptoms of potential perforation, especially in subjects with known diverticular disease.

Hepatic Adverse Events

Hepatic AEs, including elevated liver function tests (LFTs) and, infrequently, drug induced liver injury (DILI), have been observed following treatment with nivolumab. Most cases were of low or moderate grade. Higher-grade hepatic AEs, including DILI, were managed with corticosteroids (with or without mycophenolate mofetil) and, in almost all cases, the events resolved.

The recommended management of hepatic AEs is provided in Appendix 1. Early recognition and treatment of elevated LFTs and DILI are critical to their management. Subjects should be advised to seek medical evaluation if they notice jaundice (yellow appearance of skin or sclera) or if they develop bruising, bleeding, or right-sided abdominal pain. Physicians should monitor LFTs prior to each nivolumab treatment. As LFT abnormalities are common in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (eg, infection, progression of disease, concomitant medications, or alcohol) and a possible drug-related AE as the management can be quite different. The principal treatment for high-grade hepatic AEs is corticosteroids (Appendix 1).

For any grade increase in AST or ALT, the investigator needs to ensure that it is not due to biliary obstruction or the introduction of new drugs. Biliary obstruction should be ruled out by imaging if needed. If the elevation of AST or ALT is due to biliary obstruction, and the biliary obstruction is treated, the study drug may be restarted upon return of the AST and ALT to baseline or grade 2.

For any grade increase in bilirubin, the investigator needs to ensure that it is not due to biliary obstruction or the introduction of new drugs. Biliary obstruction should be ruled out by imaging if needed. If the elevation of bilirubin is due to biliary obstruction, and the biliary obstruction is treated, the study drug may be restarted upon return of the bilirubin to baseline or Grade 1.

Endocrinopathies

Endocrinopathies have been observed following treatment with nivolumab. Most cases were of low or moderate grade. The events have typically been identified through either routine periodic monitoring of specific laboratories (e.g., TSH) or as part of a work-up for associated symptoms (e.g., fatigue). Events may occur within weeks of beginning treatment, but also have been noted to occur after many months (while still on treatment). More than 1 endocrine organ may be involved (e.g., hypophysitis [pituitary inflammation] may need to be evaluated at the time adrenal insufficiency or thyroid disorder is suspected). Moderate- to high-grade cases were managed with hormone replacement therapy and, in some cases, with the addition of corticosteroids. In some cases, nivolumab treatment was held until adequate hormone replacement was provided.

Guidelines on the recommended management of endocrinopathies are provided in Appendix 1. Early recognition and treatment of endocrinopathies are critical to its management. Subjects should be advised to seek medical evaluation if they notice new-onset fatigue, lightheadedness, or difficulty with vision or if baseline fatigue worsens. As fatigue is common in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (e.g., progression of disease, anemia, concomitant medications, or depression) and a possible drug-related AE as the management can be quite different. The principal management of endocrinopathies is hormone replacement therapy. For subjects with moderate- or high-grade events, corticosteroids may also be used (Appendix 1).

Skin Adverse Events

Rash and pruritus were the most common skin AEs observed following treatment with nivolumab. The rash was typically focal with a maculopapular appearance occurring on the trunk, back, or extremities. Most cases have been of low or moderate grade. In some cases, rash and pruritus resolved without intervention. Topical corticosteroids have been used for some cases of rash. Anti-histamines have been used for some cases of pruritus. More severe cases responded to systemic corticosteroids.

Subjects should be advised to seek medical evaluation if they notice new-onset rash. Early consultation with a dermatology specialist and a biopsy should be considered if there is uncertainty as to the cause of the rash, or if there is any unusual appearance or clinical feature associated with it. Other drugs that may cause rash should be considered in the differential and, if possible, discontinued.

The principal treatment for skin AEs, such as rash and pruritus, consists of symptomatic management. Topical corticosteroids can be used for low- to moderate-grade focal rash.

Systemic corticosteroids should be used for diffuse and high-grade rash.

Renal Adverse Events

Elevated creatinine and biopsy-confirmed tubulointerstitial nephritis and allergic nephritis have been infrequently observed following treatment with nivolumab. The frequency of renal AEs may be greater with nivolumab combination therapies than with nivolumab monotherapy. Most cases were Grade 2 or 3 and based on creatinine elevation. Subjects with a history of RCC or prior nephrectomy did not appear to be at higher risk. Events were managed with corticosteroids and, in all cases, renal function partially or fully improved.

The recommended management of renal AEs is provided in Appendix 1. Physicians should monitor creatinine regularly. As creatinine abnormalities are common in subjects with cancer and other comorbidities, it is important that an evaluation/work-up distinguishes between non-drug-related causes (e.g., dehydration, concomitant medications, hypotension, or progression of disease) and a possible drug-related AE as the management can be quite different. The principal treatment for renal AEs is corticosteroids (Appendix 1).

Neurologic Adverse Events

Neurologic AEs have been uncommonly observed following treatment with nivolumab. Neurologic AEs can manifest as central abnormalities (e.g., aseptic meningitis, encephalopathy, or encephalitis) or peripheral sensory/motor neuropathies (e.g., Guillain-Barre Syndrome, myasthenia gravis complicated with sepsis and fatality).

The recommended management of neurologic AEs is provided in Appendix 1. Early recognition and treatment of neurologic AEs is critical to its management. Subjects should be advised to seek medical evaluation if they notice impairment in motor function (e.g., weakness), changes in sensation (e.g., numbness), or symptoms suggestive of possible central nervous system abnormalities such as new headache or mental status changes. As neurologic symptoms can be common in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (e.g., progression of disease, concomitant medications, or infection) and a possible drug-related AE as the management can be quite different. The principal treatments for neurologic toxicity are dose delay, corticosteroids, and IV immunoglobulin as outlined in the safety algorithm (Appendix 1). For high-grade related neurological AEs, nivolumab should be discontinued.

Uveitis and Visual Complaints

Immune therapies have been uncommonly associated with visual complaints. Inflammation of components within the eye (e.g., uveitis) is an uncommon, but clinically important, event. An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers, and retina. Topical corticosteroids may be used to manage low-grade events. Low-grade events that do not resolve and high-grade events should be managed with systemic corticosteroids. Complaints of double vision should also prompt medical evaluation. In addition to ocular inflammatory events, a work-up should also consider pituitary inflammation as a cause.

Others

Other clinically significant immune-mediated adverse reactions can occur with nivolumab. Immune-mediated adverse reactions may occur after discontinuation of nivolumab therapy. For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, permanently discontinue or withhold nivolumab, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, consider initiation of corticosteroid taper and continue to taper over at least 1 month. Consider restarting nivolumab after completion of corticosteroid taper based on the severity of the event.

Overdose, Warnings, and Precautions
There is no available information concerning overdose with nivolumab. Depending on the symptoms and/or signs leading to the suspicion of overdose, supportive medical management should be provided. There is no specific antidote.

Precautions for Women of Childbearing Potential

The nonclinical findings of increased late-stage pregnancy loss and early infant deaths/euthanasia in nivolumab-exposed pregnant monkeys suggest a potential risk to human pregnancy if there is continued treatment with nivolumab during pregnancy. Given the potential risk suggested by preliminary data from nonclinical and clinical data, dosing during pregnancy will continue to be prohibited. In addition, women of childbearing potential (WOCBP) receiving nivolumab will be instructed to adhere to contraception for a period of 23 weeks after the last dose of nivolumab. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of nivolumab.

These durations have been calculated using the upper limit of the half-life for nivolumab (25 days) and are based on the recommendation that WOCBP use contraception for 5 half-lives plus 30 days, and men who are sexually active with WOCBP use contraception for 5 half-lives plus 90 days after the last dose of nivolumab. Females should not breastfeed while receiving nivolumab and for any subsequent protocol-specified period.

5.2.1 Dose Delay Criteria

Tumor assessments for all subjects should continue as per protocol even if dosing is interrupted.

Nivolumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or clinically insignificant laboratory abnormalities do not require a treatment delay
- Any Grade 3 drug-related skin adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for blood counts, AST, ALT, or total bilirubin:
  - Grade 3 lymphopenia or leukopenia does not require dose delay
  - Grade 2 anemia does not require a dose delay
- If a subject has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
- If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 or Grade 2 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity

- A sudden increase in transaminases that the investigator determines is secondary to dislocation of a stent will not be counted as an AE. Treatment should be held until stent replacement can be performed and only resumed once LFTs have returned to the patient's baseline
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

5.2.2 Criteria to Resume Dosing

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

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline AST/ALT or total bilirubin in the Grade 1 or 2 toxicity range may resume treatment in the presence of return to Grade 1 or 2 AST/ALT OR total bilirubin, respectively
- Subjects who started out with normal baseline LFTs who develop combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 5.2.4.1) should have treatment permanently discontinued
- Drug-related pulmonary toxicity or diarrhea/colitis must have resolved to baseline before treatment is resumed. Grade 3 or 4 diarrhea/colitis require permanent discontinuation of the drug regardless of duration. Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment

If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 5.2.4.1

5.2.3 Treatment Beyond Disease Progression

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

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

1. Investigator-assessed clinical benefit, and do not have rapid disease progression
2. Continue to meet all other study protocol eligibility criteria
3. Tolerance of study drug
4. Stable performance status
5. Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)

If the subject appears to be deriving clinical benefit despite disease progression, the decision to continue treatment beyond disease progression should be discussed with the Principal Investigator and documented in the study records.

A radiographic assessment/ scan should be performed within six (6) weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

If the principal investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Time and Events Schedule. The decision to continue treatment should be discussed and documented in the study records.

5.2.4 Treatment Discontinuation Criteria

Tumor assessments for all subjects should continue as per protocol even if dosing is discontinued.

5.2.4.1 Nivolumab Dose Discontinuation

Nivolumab treatment should be permanently discontinued for the following:

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

Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions: Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation

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

1. Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
2. Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
    a. AST or ALT > 10x ULN
    b. Total bilirubin > 5x ULN
    c. In subjects with normal baseline LFTs, the development concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN

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

1. Grade 4 neutropenia ≥ 7 days
2. Grade 4 lymphopenia or leukopenia
3. Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset

Any dosing interruption lasting > 6 weeks with the following exceptions:

1. Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Principal Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
2. Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Principal Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Principal Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
3. Any adverse event, laboratory abnormality, or concurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

Global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression (ie radiographic confirmation) even after discontinuation of treatment.

5.2.5 Treatment of Nivolumab-Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthalgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

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

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

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

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

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the

infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit.

For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

For Grade 3 or 4 symptoms: Follow guidelines for Grade 2 infusion reaction as above and permanently discontinue study drug.

5.3 Study Treatment, Drug Ordering, and Pharmacy Reference Information

Nivolumab 100 mg (10 mg/mL) will be packaged in an open-label fashion. Ten nivolumab, 10 mL vials will be packaged within a carton, and are not subject or treatment arm specific. The appearance of the solution is clear to opalescent, colorless to pale yellow liquid that may contain particles. It should be stored between 2 and 8 degrees Celsius and should be protected from light and freezing.

Treatment should be initiated within 28 days of enrollment. Treatment will be continued until disease progression, discontinuation due to toxicity, withdrawal of consent, or the study ends.

Treatment will be administered at a dose of 240 mg every 2 weeks for 16 weeks and then at 480 mg every 4 weeks until disease progression or unacceptable toxicity for up to 24 months. Treatment can continue at the discretion of the investigator if clinical benefit is noted.

For full information regarding nivolumab drug ordering as well as pharmacy reference material, please see Appendix 2 and Table 3.

5.3.1 Handling and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately. Nivolumab vials must be stored in the refrigerator at 2-8°C, protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g. required diluents, administration sets).

Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

After nivolumab has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours. For details on prepared drug storage and use time under room temperature/light and refrigeration, please refer to the current Nivolumab Investigator Brochure.

Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyolefin bags have been observed.

Nivolumab is to be administered as a 60 minute IV infusion, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline (per institutional standard of care).

Details regarding the mixing and concentrations of the dose (preparation) and administration can be found in the current Investigator brochure for nivolumab.

5.3.2 Blinding

This is an open-label trial. There will be no randomization or blinding.

5.3.3 Drug Logistics and Accountability

All study drugs will be stored at the investigational site in accordance with good clinical practice (GCP) and GMP requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate / Contract Research Organization [CRO]), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the sponsor study file; the site-relevant elements, of this information will be available in the ISF. The responsible site personnel will confirm receipt of study drug and will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed upon and specified procedures.

5.3.4 Treatment Compliance

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

5.3.5 Destruction and Return of Study Drug

Destruction of Study Drug For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site. Any unused study drugs can only be destroyed after being inspected and reconciled by the

responsible BMS Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (e.g. cytotoxics or biologics). On-site destruction is allowed provided the following minimal standards are met:

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

If conditions for destruction cannot be met, the responsible BMS Study Monitor will make arrangements for return of study drug. It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

5.3.6 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible BMS Study Monitor. It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

5.4 Prior and Concomitant Therapy

5.4.1 Prohibited Concomitant Anti-cancer Therapy:

CYP3A4 Inhibitors and Inducers

The following strong CYP3A4 inhibitors should be avoided during the study. This includes (but is not limited to):

- Ketoconazole
- Itraconazole
- Clarithromycin
- Atazanvir
- Indinavir
- Nefazodone
- Nelfinavir
- Ritonavir
- Saquinavir
- Teithromycin
- Voriconazole

The following medications are prohibited during the study (unless utilized to treat a drug-related

adverse event):

• Immunosuppressive agents
• Immunosuppressive doses of systemic corticosteroids (except as stated in Section 5.4.3).
• Any concurrent antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of biliary tract cancers).

Palliative and supportive care for disease related symptoms (including local radiotherapy, bisphosphonates and RANK-L inhibitors) may be offered to all subjects prior to first dose of study therapy (prior radiotherapy must have been completed at least 2 weeks prior to enrollment).

5.4.2 Other Restrictions and Precautions

- Subjects with active, known or suspected autoimmune disease.
- Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of enrollment.
- Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

5.4.3 Permitted Therapy

- Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).
- Physiologic replacement doses of systemic corticosteroids (e.g., prednisone ≤ 10 mg/day) are permitted.
- A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.
- The potential for overlapping toxicities with radiotherapy and nivolumab currently is not known. Therefore, palliative radiotherapy is not recommended while receiving nivolumab. If palliative radiotherapy is required, then nivolumab should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolve to Grade ≤ 1 prior to resuming nivolumab. Only non-target bone lesions that do not include lung tissue in the planned radiation field may receive palliative radiotherapy. Details of palliative radiotherapy should be documented in the source records and electronic case report form (eCRF). Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and adverse events. If warranted, symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression.

6. Study Assessments and Procedures

6.1 Table 1: Screening Assessments and Procedures

Screening examinations will only be performed after having received the subject's written informed consent.

Screening Assessments and Procedures *to be completed within 28 days of enrollment*		
Procedure	**Screening Visit**	**Notes**
Eligibility Assessments		
Informed Consent	**X**	
Inclusion/Exclusion Criteria	**X**	
Medical History	**X**	
Safety Assessments		
Vital Signs and Oxygen saturation	**X**	**Temperature, BP, HR, RR, O_2 saturation by pulse oximetry (also monitor amount of supplemental oxygen if applicable)** **Obtain vital signs at screening visit and within 72 hours of first dose**
Physical Measurements (including Performance Status)	**X**	**Includes Height and Weight, and ECOG status**
Clinic Visit	**X**	
Laboratory Tests	**X**	**Labs performed within 21 days prior to first dose of study drug:** **CBC with differential, Serum chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and bicarbonate, glucose), AST, ALT, total bilirubin, direct bilirubin, alkaline phosphatase, albumin, LDH, TSH, free T3, free T4, HBV surface antigen, HCV RNA. CA 19-9**
Pregnancy Test	**X**	**Performed within 7 days prior to first dose study drug (serum or urine for WOCBP only)**
Concomitant Medication collection	**X**	
Radiographic Tumor Assessment (Chest, abdomen, pelvis)	**X**	**Should be performed within 28 days prior to first dose. CT/MRI of brain (with contrast) should only be performed in subjects with a known history of treated brain metastases.** **Additional sites of known or suspected disease (including CNS) should be imaged at the screening visit and at subsequent on-study assessments.**
Archived Tumor Tissue or Recent Tumor Biopsy (for IHC)	**X**	**May be archival or recent sample. 1 formalin-fixed paraffin embedded tumor tissue block or cell block is needed (or 10 slides).**

6.2 Table 2: On Study Assessments

Procedure	C1D1	C1D8	C1D15(±5 days)	C2D1(±5 days)	C4D1(±5 days)	End of every 2nd cycle(±5 days)	Subsequent Cycles[a]	EOT[b]	Notes
Vital signs and Oxygen Saturations	X	X	X	X	X		X	X	Temperature, BP, HR, RR, O_2 saturation by pulse oximetry (also monitor amount of supplemental oxygen if applicable) prior to dosing and at any time a subject has any new or worsening respiratory symptoms
AE and SAE Assessment	Continuously								Assessed using NCI CTCAE v. 4.0
Physical Measurements *including Performance Status*	X	X	X	X	X		X	X	Includes Weight and ECOG status
Complete blood count *Results obtained prior to dosing on infusion days*	X	X	X	X	X		X	X	Includes WBC count with differential, hemoglobin, hematocrit, and platelet count
Serum Chemistry Tests	X	X	X	X	X		X	X	Serum chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and bicarbonate, glucose), LDH
Clinic Visit	X	X	X	X	X		X	X	
Liver Function Testing *Results obtained within 72 hours prior to dosing on infusion days*	X	X	X	X	X		X	X	Includes aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, and albumin
Additional Testing						X			Tumor measurement/disease assessment according to RECIST 1.1, CA 19-9 assessment, Pregnancy Test Urine or Serum (for WOCBP only), TSH (reflex to free T3 and free T4 if abnormal results)

[a]Treatment is to be given every 2 weeks for 16 weeks (4 cycles) and then will be given once every 4 weeks thereafter as per Section 5.3

[b] The EOT disease assessment with radiographic imaging is required if it has been > 28 days since the last disease assessment

7. Adverse Events

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

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:

The 5 categories for AE grading are:

1. Not related
2. Not Likely
3. Possible
4. Probable
5. Definite

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.)

All AEs will be monitored until resolution or, if the AE is determined to be chronic, a cause is identified. If an AE is considered potentially related to study treatment and remains ongoing at the conclusion of the study, the event will be followed until resolution, stabilization, or initiation of treatment that confounds the ability to assess the event. AEs will be collected for a minimum of 30 days from the end of treatment. All SAEs must be collected from when the patient begins the study drug to within 100 days of discontinuation of dosing or until the patient begins another anti-cancer therapy.

7.1 Safety Monitoring

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology and blood chemistry parameters and regular physical examinations. Adverse events will be evaluated continuously throughout the study. Safety and tolerability will be assessed according to the NIH/NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) that is available at:
http://evs.nci.nih.gov/ftp1/CTCAE/About.html

7.1.1 Internal Safety Monitoring

The Moffitt Protocol Monitoring Committee (PMC) meets monthly and reviews accrual, patterns and frequencies of all adverse events, protocol violations and when applicable, internal audit results.
The PMC, upon review of any agenda item, may approve the study for continuation, require revisions, suspend or close a protocol.

Data will be captured in OnCore, Moffitt's Clinical Trials Database. Regulatory documents and case report forms will be reviewed routinely according to Moffitt's Monitoring Policies.

7.2 Serious Adverse Events

A S***erious AE (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires subject hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 7.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (e.g., any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Information about all serious adverse events will be collected and recorded. To ensure patient safety, each serious adverse event must be reported to the PI and to BMS expeditiously (see below for BMS requirements). Moffitt Cancer Center and all participating sites will report SAEs by completing an SAE report in ONCORE, the electronic data capture system and a Medwatch Form online at http://www.fda.gov/medwatch The SAE must be reported by email (affiliate.research@moffitt.org) to the MCRN within 2 working days.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 7.4 for reporting pregnancies).

NOTE:
The following hospitalizations are not considered SAEs:

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Elective surgery, planned prior to signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission for purpose other than remedying ill health state and was 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 (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)

7.2.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected from when the patient begins the study drug to within 100 days of discontinuation of dosing or until the patient begins another anti-cancer therapy. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

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

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

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, as well as pregnancies, must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

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

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

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

All SAEs should be followed to resolution or stabilization.

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

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

MedWatch SAE forms should be sent to the FDA at:

MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

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

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

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

For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection in the protocol.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization. All SAEs should be followed to resolution or stabilization.The Sponsor will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com). Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. BMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. 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.

7.3 Non-serious Adverse Events

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

The collection of nonserious AE information should begin at initiation of study drug.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 7.2). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

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

7.4 Laboratory Test Abnormalities

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

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

Wherever possible the clinical, rather than the laboratory term, should be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

7.5 Pregnancy

Following initiation of the investigational product, if it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 7.2.1.

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

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

7.6 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 (see Section 7.2.1 for reporting details).

7.7 Other Safety Considerations

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

For recommendations regarding suspected pulmonary toxicity, diarrhea and colitis, suspected hepatotoxicity (including asymptomatic LFT elevations), or suspected endocrinopathy, please see Section 5.2 and Appendix 1.

8. Statistical Considerations

8.1 Sample Size Determination

Patients will be accrued to the protocol according to a Simon two-stage design.[31] Based on patient response (CR + PR after 2 cycles), as defined by RECIST 1.1 criteria, we will either conclude that the therapy is effective or ineffective. The two-stage design has the smallest effective sample size with the following two properties:

(1) if the true response rate is less than or equal to 5% , we will conclude that the therapy is ineffective with probability of at least 0.07 (alpha), and
(2) if the true response rate is at least 20%, we will conclude that the therapy is effective with probability at least 0.90 (power).

At least one of eighteen patients must respond (CR or PR) in the first stage to proceed to the second stage. At any point when it is realized that this cannot happen, the study will be stopped and the therapy will be considered ineffective.

If there are at least 4 patients with stable disease for 16 weeks (2 restaging assessments), the principal investigator will discuss proceeding to the second stage of the study with the BMS medical team. This would require an amended protocol to define a successful trial result.

The second stage of this study will involve an additional 14 patients. The study will have met its primary endpoint of response rate if there are at least four patients out of thirty two patients who have a response.

8.1.1 Rationale for an expansion of the study

In March, 2018, it was determined that the Simon-2 stage results led to the rejection of the null hypothesis, and conclusion that the therapy was promising, as 5 of 32 patients had partial responses. Two additional patients were also enrolled due to confusion regarding the evaluability of two patients, with best responses of PD and SD. Thus 5 of 34 patients overall have had PRs (note:5 patients did not have any follow-up RECIST assessments; 4 patients had clinical progression, while a 5th patient withdrew consent). The study team would like to enroll an additional cohort of 20 patients, which would give us a total sample size of 54 patients, for which the 6-month PFS and OS rates are the primary endpoints to be estimated. Presuming no censorship of patients in the first six months after starting treatment, we will be able to estimate the 6-month PFS and 6-month OS rates with a 95% confidence interval half-width of 13.3% (Normal approximation to the binomial calculation). Current 6—month estimates from the study are 41% for PFS, and 73% for OS. Notably, the last of the 10 deaths to date occurred at 6.4 months, and 15 patients have exceeded that time by an average of 5.0 months, suggesting that there will be a high rate of long-term survivors. Thus, the expansion would provide additional valuable information on this promising therapy.

8.2 Populations for Analyses

All enrolled subjects: All subjects who signed an informed consent form and were registered into the IVRS. Analyses of the patients enrolled into the study but not treated and the reason for not being treated will be performed on the data set of all enrolled subjects.

All treated subjects: All subjects who received at least one dose of nivolumab.

This is the primary dataset for dosing and safety.

Response Evaluable Subjects: treated subjects whose change in the sum of diameters of target lesions was assessed (ie. target lesion measurements were made at baseline and at least one on-study tumor assessment.)

8.3 Endpoint Definitions

8.3.1 Primary Endpoint

The primary objective in the study will be measured by the primary endpoint of ORR (CR + PR) as measured by RECIST 1.1 criteria.

8.3.2 Secondary Endpoints

8.3.2.1 Overall Survival (OS)

OS is defined as the time from enrollment to the date of death. A subject who has not died will be censored at last known date alive. OS will be followed continuously while subjects are on the study drugs and every 3 months via in-person or phone contact after subjects discontinue the study drugs.

8.3.2.2 Progression Free Survival (PFS)

PFS is defined as the time from first treatment to the date of the first documented tumor progression as determined by the investigator (per RECIST 1.1), or death due to any cause.

Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were enrolled. Subjects who started any subsequent anti-cancer therapy (including on-treatment palliative RT of non-target bone lesions or CNS lesions) without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on initiation of the subsequent anti-cancer therapy.

8.3.2.3 Safety and Tolerability

Safety and tolerability objective will be measured by the incidence of adverse events, serious adverse events, deaths, and laboratory abnormalities.

Adverse event assessments and laboratory tests are performed at baseline, and continuously throughout the study at the beginning of each subsequent cycle.

8.3.2.4 Immune Response Criteria

In addition to evaluation by RECIST criteria, subjects will be evaluated using the immune response criteria.[32] In this classification, the overall response is determined as follows:

- Immune response CR (irCR) is a complete disappearance of all lesions (whether measurable or not, and no new lesions) with confirmation by a repeat, consecutive assessment no less than 4 weeks from the first documentation.
- Immune response PR (irPR) is a decrease in tumor burden of greater than or equal to 50% relative to baseline. This must be confirmed by a consecutive assessment at least 4 weeks after the first documentation.
- Immune response SD (irSD) is classified as those who do not meet criteria for irCR or irPR and who do not have irPD
- Immune response PD (irPD) is an increase in tumor burden of greater than or equal to 25%relative to the minimum recorded tumor burden which must be confirmed by a repeat, consecutive assessment no less than 4 weeks from the first documentation.

8.3.3 Exploratory Endpoints

Immune Signature
An immune signature using the Kew CancerPlex® Panel will be performed on all patients and correlated to outcome. Tumor profiling will be conducted in a CAP/CLIA-certified laboratory, licensed by MA and 48 other states (KEW Group Inc.). DNA will be extracted from FFPE tissue sections (20 um equivalent), slides, cell blocks, from FNAs or effusions, or cell pellets, followed by hybrid-capture next-generation sequencing. Rapid sequencing runs are employed to generate at least 200x sequencing depth coverage (500x, in average), and mutational analysis will be performed using the KEW Clinical Genomics Analytical pipeline. The coding regions and portions of the introns of 400+ genes will sequenced. The assay simultaneously surveys multiple classes of genomic abnormalities including single nucleotide substitutions (SNP), small insertions/deletions (indels), copy number alterations (CNV), and translocations. Analytic sensitivity for SNP calls is 98.9%-100% at 95% confidence interval, specificity is 99.99%; for indels sensitivity is 99.8%-100% at 95% confidence interval and specificity is 99.99%.

This analysis will include targeted exome sequencing for the 400 genes and will also generate an immune signature panel that reports the frequency of mutations in the sample. It will include testing for loci at the mismatch repair genes so that microsatellite instability can be assessed.

The slides should be sent to
Domenico Coppola
Moffitt Cancer Center, Dep of pathology
12902 Magnolia Drive MCC- Lab
Tampa FL33612

9. Data Recording

9.1 Institutional Review Board (IRB) Approval and Consent

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

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

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

9.2 Required Documentation

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

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

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

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

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

The requirements of the protocol and all associated procedures and processes will be reviewed

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

a. Registration Procedures

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

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

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

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

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

b. Data Management and Monitoring/Auditing

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

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

c. Adherence to the Protocol

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

d. Emergency Modifications

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

For Institutions Relying on Moffitt's IRB:

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

For Institutions Relying on Their Own IRB:

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

e. Record Retention

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

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

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

f. Obligations of Investigators

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

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

9.3 Ethical and Legal Aspects

a. Ethical and Legal Conduct of the Study

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

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

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

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

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

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

b. Subject Information and Consent

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

Only if the subject/legal representative or proxy consenter voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator and other

information provider (if any) will personally sign and date the form. The subject/legal representative or proxy consenter will receive a copy of the signed and dated form.

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

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

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

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

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

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

c. Publication policy

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

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

d. Confidentiality

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

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

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Appendix 1: Immune Adverse Event Management Algorithms

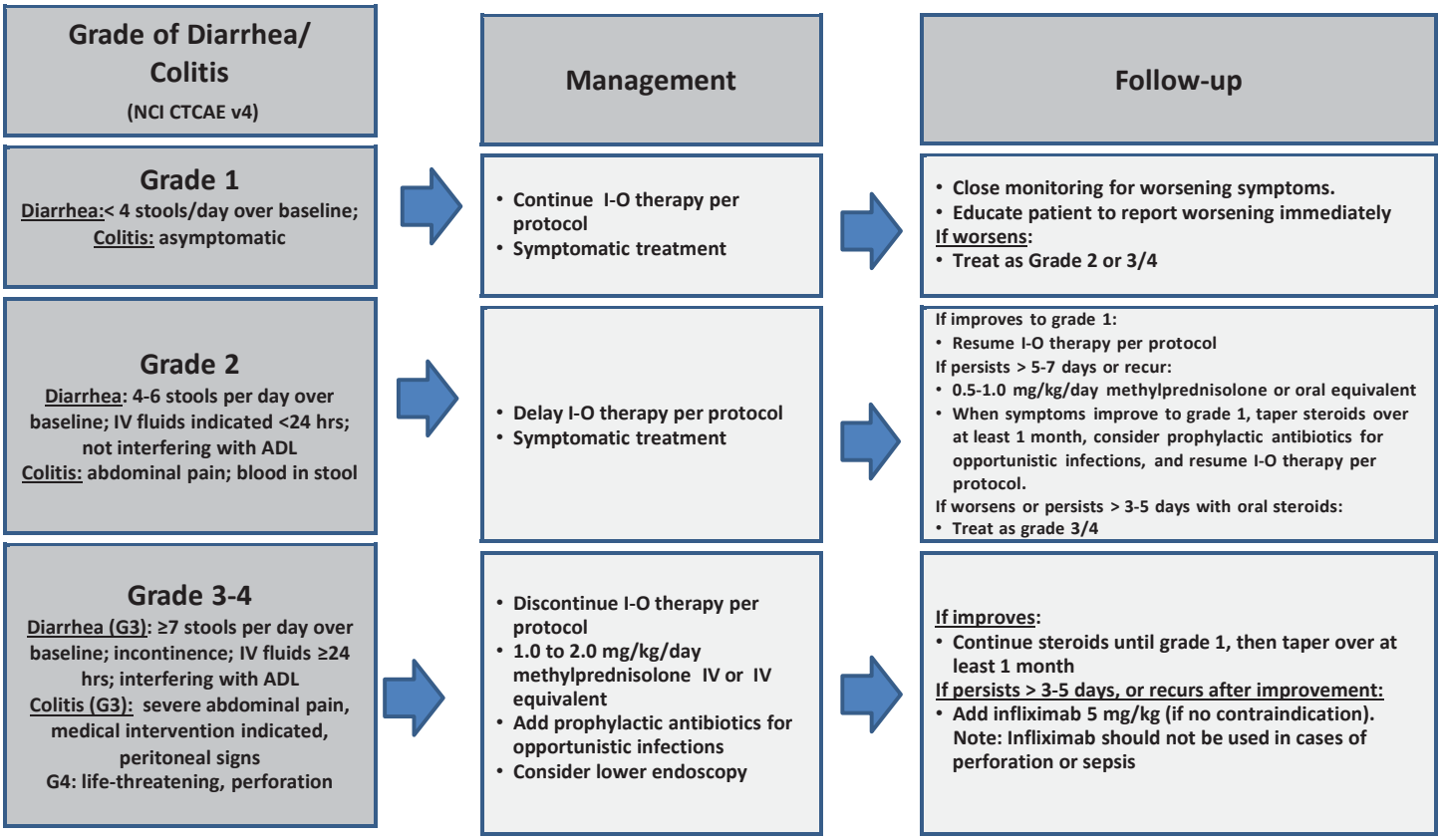
These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens. A general principle is that differential diagnoses should be diligently evaluated 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 ManagementAlgorithm

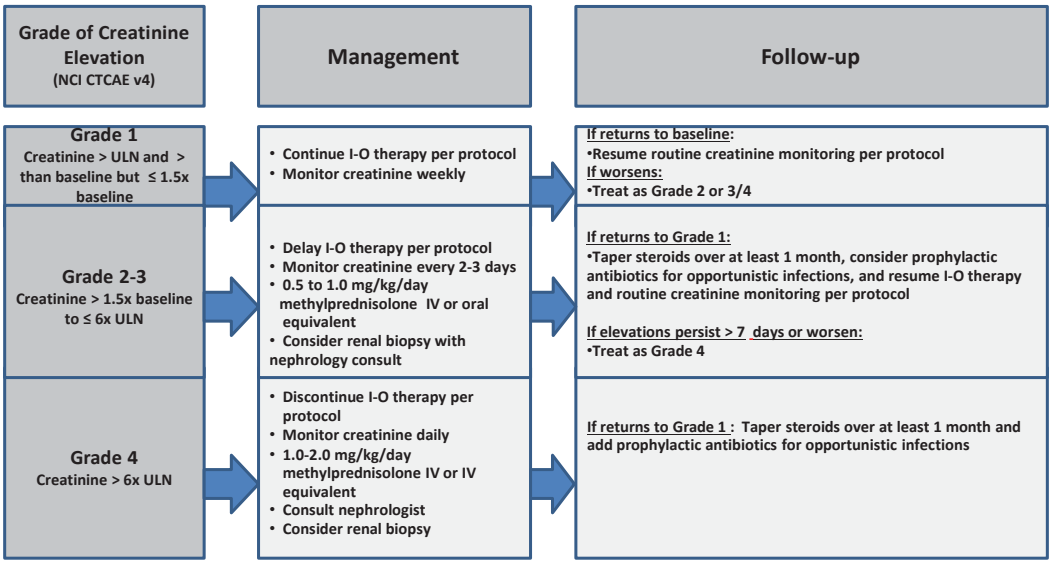
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

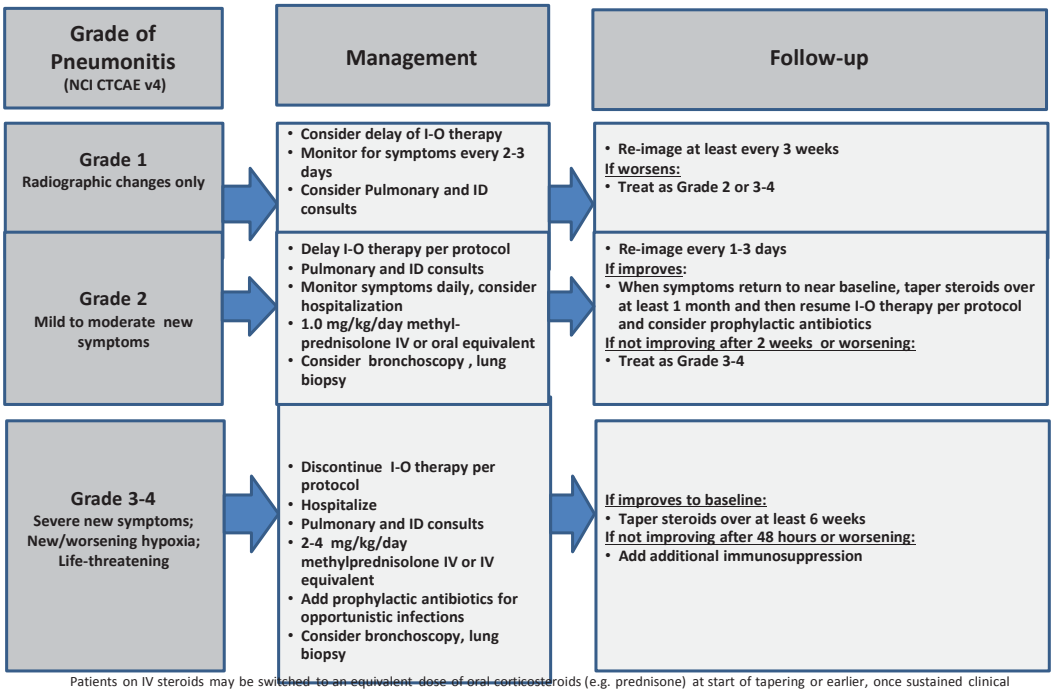
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

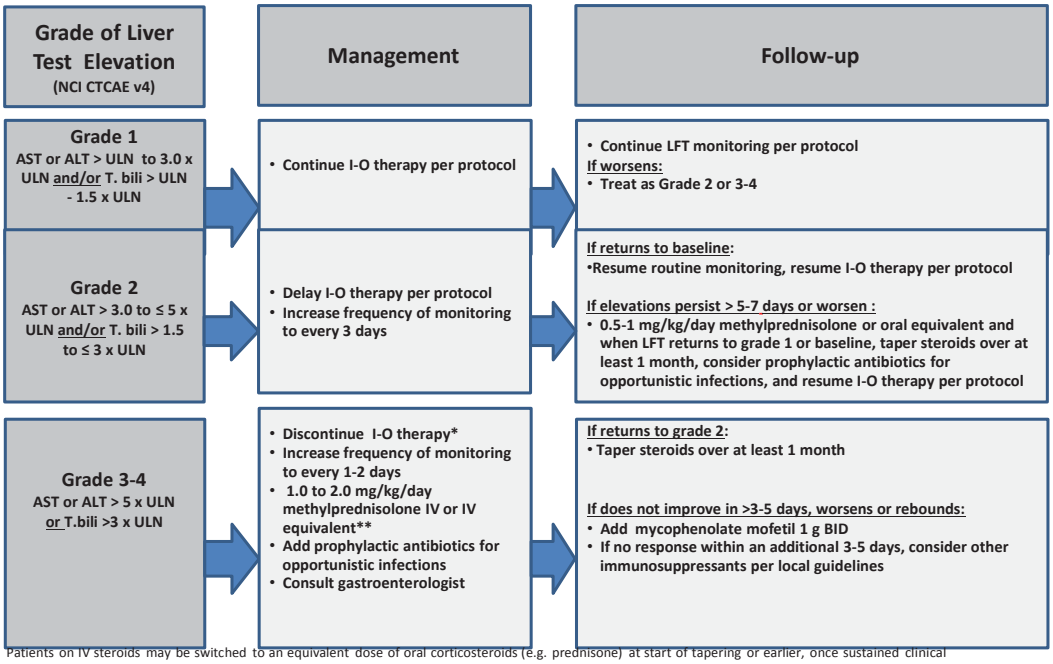
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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.



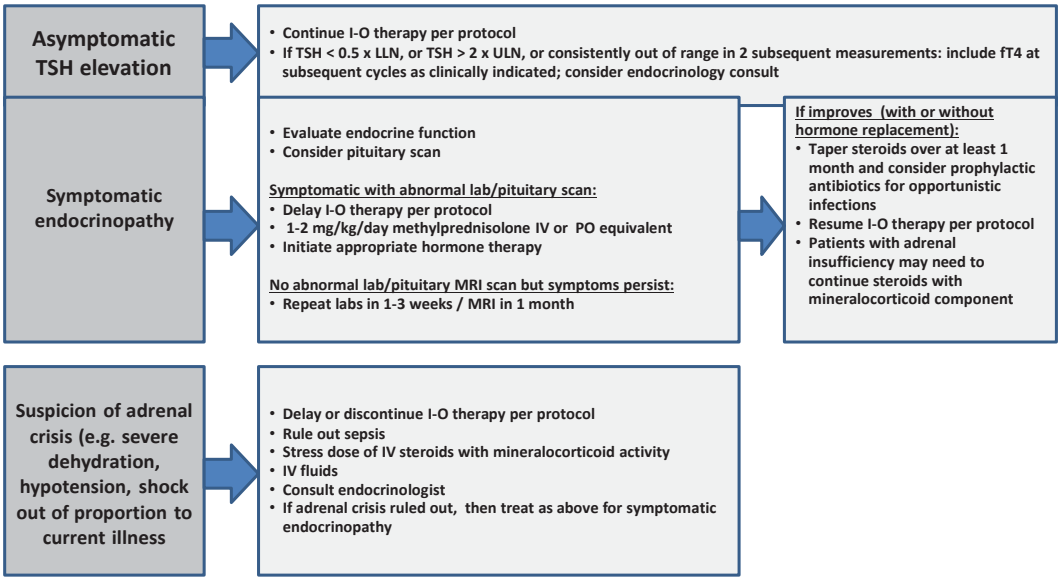
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Endocrinopathy Management Algorithm

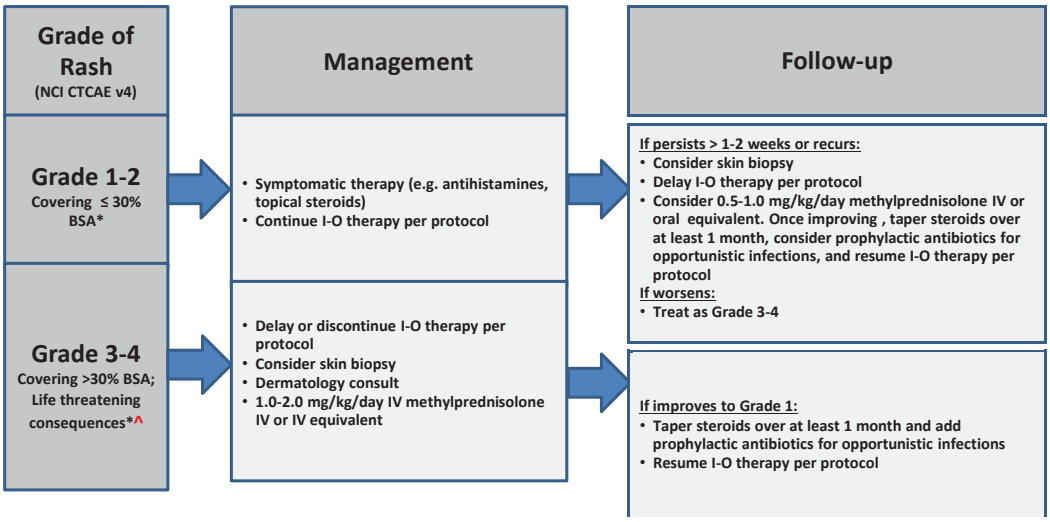
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

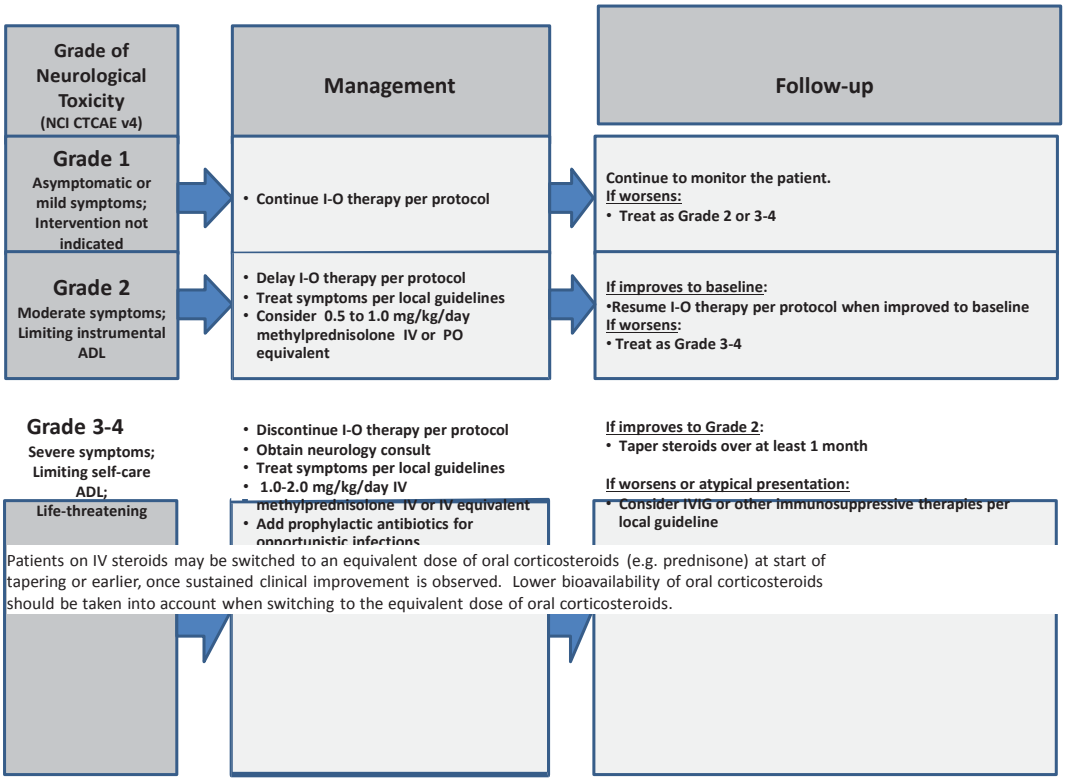
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

Appendix 2: Nivolumab Drug Ordering and Pharmacy Reference Material

Initial Orders

- *Following submission and approval of the required regulatory documents, a supply of nivolumab may be ordered from by completing a Drug Request Form provided by BMS for this specific trial.*
- *The initial order should be limited to the amount needed for two doses. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All drug products will be shipped by courier in a temperature-controlled container. It is possible that sites may have more than one nivolumab clinical study ongoing at the same time. It is imperative that only drug product designated for this protocol number be used for this study.*
- *Pharmacy supplies not provided by BMS: Empty IV bags/containers, approved diluents, In-line filters and infusion tubing*

Re-Supply

- *Drug re-supply request form should be submitted electronically at least 7 business days before the expected delivery date. Deliveries will be made Tuesday through Friday.*
- *When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose, and that shipments may take 14 business days from receipt of request. Drug is not patient-specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.*

Drug Excursions

- *Drug excursions should be reported immediately to BMS on the form provided with the study-specific drug order form*

Please refer to the most recent version of the nivolumab Investigator Brochure for additional information to be included as per institutional or regulatory standards.

TABLE 3: Product Information

Product Description:(Other names = MDX-1106, ONO-4538, anti-PD-1					
Product Description and Dosage Form	**Potency**	**Primary Packaging (Volume)/ Label Type**	**Secondary Packaging (Qty) /Label Type**	**Appearance**	**Storage Conditions (per label)**
Nivolumab (BMS-936558-01)* Injection drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL	100 mg/Vial (10 mg/mL).	Carton of 5 or 10 vials	10-cc Type 1 flint glass vials stoppered with butyl stoppers and sealed with aluminum seals.	Clear to opalescent, colorless to pale yellow liquid. May contain particles	**BMS-936558-01 Injection** must be stored at 2 to 8 degrees C (36 to 46 degrees F) and protected from light and freezing

Protocol #: MCC 18684

TITLE: A Phase II Investigator Sponsored Study of Nivolumab in Patients with Advanced Refractory Biliary Tract Cancers

Sponsor/IND Holder: H. Lee Moffitt Cancer Center

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MCRN Sites: City of Hope Cancer Center
Emory University- Winship Cancer Institute

Supplied Agent: Nivolumab

Protocol Version Date: 08/13/2019

Study Synopsis

Title	A Phase II Investigator Sponsored Study of Nivolumab in Patients with Advanced Refractory Biliary Tract Cancers
Clinical study phase	Phase II
Study objective(s)	**Primary Objective** The primary endpoint will be overall response rate (ORR). ORR is defined as complete responses (CR) plus partial responses (PR). **Secondary Objectives** • To determine the frequency and severity of adverse events and tolerability of the regimen in patients with advanced refractory BC receiving nivolumab • To determine the progression-free survival (PFS) in patients with advanced refractory BC receiving nivolumab. PFS is defined as the duration of time from start of treatment to time of progression or death, whichever comes first. • To determine the overall survival in patients with advanced refractory BC receiving nivolumab • To determine the overall response rate by the immune response criteria **Exploratory Objectives** Immunohistochemical staining and next generation sequencing will be performed with tumor samples to evaluate the correlation with clinical outcome in a descriptive analysis. .

Background	The outcome of patients with advanced biliary cancer remains dismal with the current standard of care options. There is currently an unmet medical need for patients with advanced BC who have failed systemic therapy. BC includes a heterogeneous group of cancers but data has suggested that there is an immune component to the development of these tumors and high PD-1 protein expression has been found. The second line setting therefore offers a unique opportunity to evaluate the activity of anti-PD1 immunotherapy agents like nivolumab.
Indication	Patients with advanced biliary tumor who have failed at least one prior line of systemic therapy.
Diagnosis and main criteria for inclusion	Patients must have histologically or cytologically documented carcinoma primary to the intra- or extra-hepatic biliary system or gall bladder with clinical and/or radiologic evidence of unresectable locally advanced or metastatic disease. Patients with ampullary carcinoma are not eligible. Patients must have failed one but no more than 3 prior lines of systemic chemotherapy for advanced biliary cancer. Patients who are intolerant to first line therapy will be allowed. Patients who had disease recurrence after first line therapy will be allowed. Patients who received adjuvant chemotherapy and had evidence of disease recurrence within 6 months of completion of the adjuvant treatment are also eligible. If patient received adjuvant treatment and had disease recurrence after 6 months, patients will only be eligible after failing one line of systemic chemotherapy used to treat the disease recurrence. Patients must have measurable disease, as defined by RECIST 1.1 criteria. Patients must not have been treated with any prior anti-PD1, anti-PDL1, or anti-CTLA4 agents
Study design	This is a multi-institutional phase II single arm two-stage design trial using nivolumab as a single agent.

Type of control	Patients will receive nivolumab at a dose of 240 mg IV every 2 weeks for 16 weeks and then 480 mg IV every 4 weeks until disease progression or unacceptable toxicity. After 2 cycles (1 cycle= 28 days), tumor response will be evaluated using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) as well as immune response criteria. Treatment beyond progressive disease (PD) will be allowed for pseudo progression as determined by clinical benefit or immune response criteria.
Number of subjects	52 evaluable
Plan for statistical analysis	The primary endpoint for this study will be response rate (CR + PR) at 4 months. We will use a Simon's Two-Stage Design in which the power is 0.9 and the type 2 error is 10%. The study will be expanded to the second stage if there is a 20% probability of response. At least 1 patient of the first 18 enrolled will need to have a complete or partial response for study continuation. Alternatively, if there are at least 4 patients with stable disease for 16 weeks (2 restaging assessments), the principal investigator will discuss proceeding to the second stage of the study with the BMS medical team. The second stage of this study will involve an additional 14 patients. The study will have met its primary endpoint of response rate if there are at least four patients in the nivolumab only arm who achieve a response. We anticipate an attrition rate of 10%, so about 40 patients will be recruited. Based on previous trials, we expect to enroll about 12 patients per year at our center and so will involve 2 other centers to complete enrollment within 18 months. Please see section 8.2 for rationale for the expansion of the study.

Schema

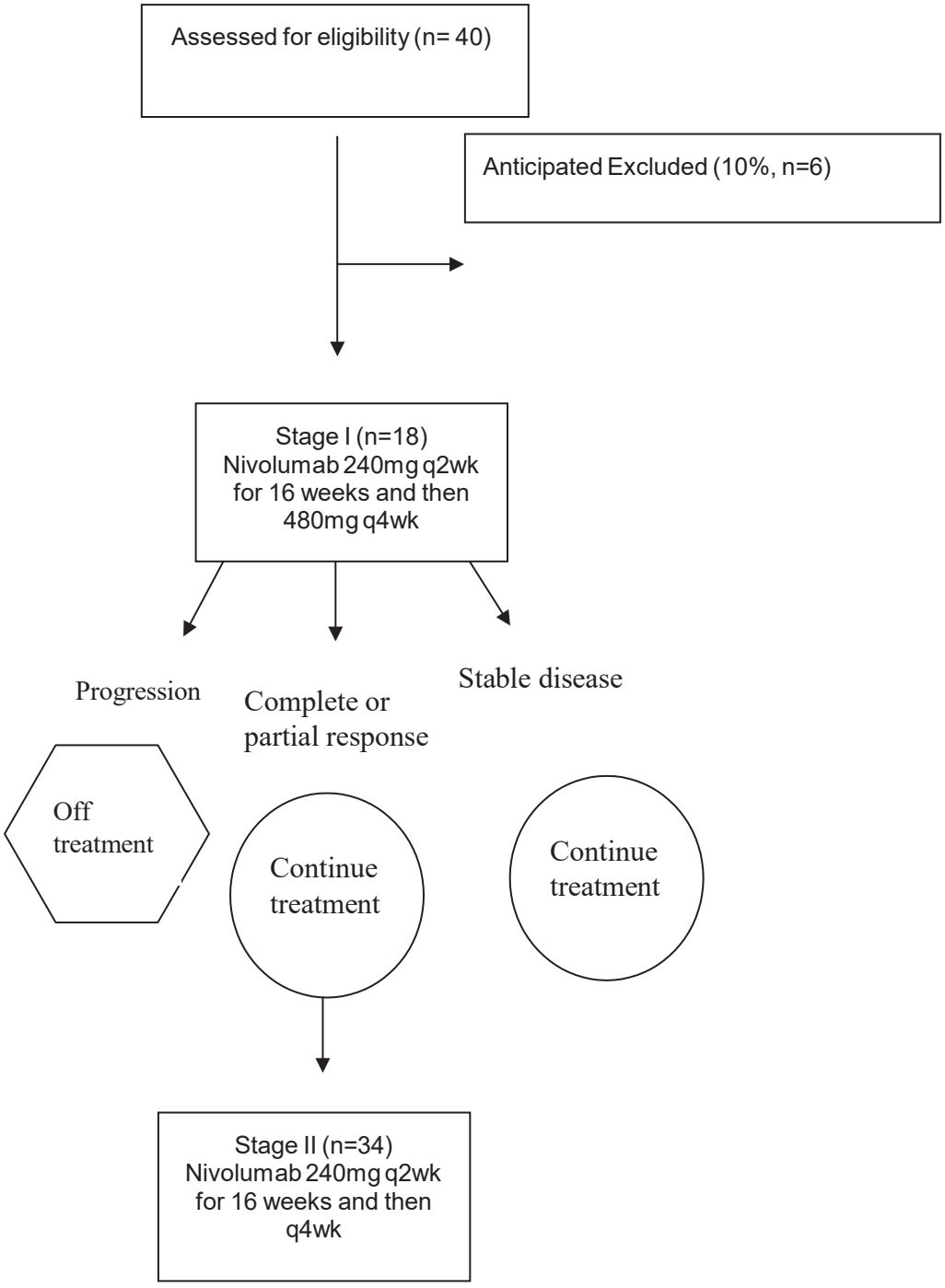
Assessed for eligibility (n= 40)
Anticipated Excluded (10%, n=6)
Stage I (n=18)
Nivolumab 240mg q2wk
for 16 weeks and then
480mg q4wk
Progression
Complete or
partial response
Stable disease
Off
treatment
Continue
treatment
Continue
treatment
Stage II (n=34)
Nivolumab 240mg q2wk
for 16 weeks and then
q4wk

Table of Contents

1. Introduction

1.1 Background

Biliary tract cancers (BTC) typically include intra and extrahepatic cholangiocarcinoma and cancers of the gallbladder. In the US in 2015, an estimated 2,600 intrahepatic cholangiocarcinomas and 10,000 cases of extrahepatic bile duct cancer. Of the latter, two thirds were gallbladder cancers.[1] This is a rare but aggressive group of malignancies with many patients presenting with advanced disease and overall dismal outcomes.[2]

The only cure for patients who present with local disease is surgical resection or liver transplantation. However, the rate of disease recurrence remains high even in resectable patients and there is no compelling data regarding the role for adjuvant therapy in this setting. Though meta-analyses have shown a nonsignificant overall survival benefit to adjuvant therapy,[3] there is limited prospective data on which agents are active in this disease.

However, the majority of patients present with unresectable disease and treatment options are very limited. Systemic chemotherapy has historically been disappointing in advanced BTC, though new combination regimens have shown activity. ABC-02, a randomized phase III study, enrolled 410 patients and compared gemcitabine plus cisplatin with gemcitabine alone.[4] The median overall survival (OS) and progression-free survival (PFS) were greater for gemcitabine plus cisplatin than for gemcitabine alone without significantly increased toxicity (OS: 11.7 *v* 8.1 months; log-rank *P* = .002; PFS: 8.0 *v* 5.0 months; *P* = .003). This drug combination set a new international standard of care for the first line treatment of advanced BTC. Based on phase II data, the combination of gemcitabine and oxaliplatin is also used in the first line setting after efficacy and tolerability were shown.[5]

Several phase II trials have evaluated various chemotherapy regimens in the second line setting, including FOLFOX (oxaliplatin, 5-fluorouracil, and leucovorin), oxaliplatin with capecitabine, and 5-fluorouracil and cisplatin.[6,7] However, there is no established regimen for treatment in patients with progression on first line therapy or refractory disease. The survival in this setting remains dismal at a median of less than 6 months.[8-10] Advances have been slow in part because of the tumor heterogeneity of BTCs.[11] There remains a significant need to identify novel agents and to treat this deadly disease.

Outcomes can perhaps be improved with greater understanding of the underlying disease biology. The development of BTC appears to be related to the immune system, and carcinogenesis has been linked to chronic parasitic infections as well as autoimmune conditions like primary sclerosing cholangitis.[12,13] In addition, patients with evidence of immune system activation, measured by higher levels of lymphocytes, have been shown to have improved prognosis.[14] Recent data suggests that the immune regulatory protein PD-1 is upregulated in intrahepatic cholangiocarcinoma tissues compared to cancer adjacent tumors.[15] It has also been shown that hilar cholangiocarcinomas may evade immunologic surveillance through the apoptosis of lymphocytes.[16]

In pre-clinical work at Moffitt Cancer Center, we found that cholangiocarcinoma tumors which stained positive for CD45R0 (lymph node like structure) were associated with improved median OS (63 months vs 18 months, P = 0.003).[17] These immune active tumors are likely to have escaped the inhibitory effects of programmed death ligand complex.

Immunotherapy has been evaluated in a few patients with BTCs. In one case report, a patient with a locally advanced intrahepatic cholangiocarcinoma was treated initially with surgical resection followed by adjuvant treatment with immunotherapy (CD3 activated T cells as well as dendritic

cells). She had no disease recurrence for over 3 years.[18] More recently, an anti-PD1 agent was recently evaluated in tumors with microsatellite instability in a phase II study.[19] Included in this cohort was one patient with mismatch repair deficient bile duct cancer who had a partial response with a 41% decrease in tumor size and a 93% decrease in tumor marker at 20 weeks.

1.2 Nivolumab

Human tumors have a myriad of genetic alterations leading to neoantigens which should be recognized by the host immune system. However, cancer can dysregulate immune checkpoint proteins as a way of evading the host immune system and ensuring survival.[20] Immunotherapy in oncology has been evaluated as a means of upregulating the host immune system so that tumors can be recognized as foreign and endogenous anti-tumor immunity can attack tumor cells. Immune checkpoint pathway inhibitors such as anti-CTLA4 and anti-PD-1 antibodies have been evaluated in the treatment of a variety of tumors.

Preclinical Studies

Programmed death 1 is a protein which limits T-cell activity in an effort to minimize autoimmunity.[21] When activated by ligands, PD-1 along with its costimulatory protein B7, decrease T cell activity which can allow tumors to escape immune recognition. Antibodies against PD-1 have been developed in an effort to increase T cell activity.

Nivolumab is a human monoclonal antibody that targets the programmed death-1 (PD-1) CD279 cell surface membrane receptor and inhibits PD-1 interaction with its ligands PD-L1 and PD-L2. PD-1 knockout mice develop autoimmune conditions from excessive T cell activity including glomerulonephritis and autoimmune cardiomyopathy.[22,23] In vitro, nivolumab has resulted in increased T-cell proliferation and interferon gamma release in mixed lymphocyte reaction.[24] In vivo, PD-1 blockade by a nivolumab analog resulted in enhanced anti-tumor response and tumor rejection in several murine models (BMS investigator's brochure). Nivolumab has been generally well tolerated in the preclinical setting. In toxicity studies of cynomolgus monkeys, nivolumab was tolerated at doses of 50mg/kg every 2 weeks. There was increased neonatal mortality in pregnant monkeys, in keeping with the role of PD-L1 in maintaining murine fetomaternal tolerance.[25]

Clinical Studies

Clinical Pharmacokinetics
Nivolumab has been tested in over 8600 human subjects with doses ranging from 0.1 to 10 mg/kg as both a single dose as well as multiple doses every few weeks. Steady state drug concentration was achieved by 12 weeks when nivolumab was administered at 3mg/kg every 2 weeks. Drug clearance has not been affected by age, gender, race, or tumor type. Though glomerular filtration rate and mild hepatic impairment have had an effect on clearance, it has not been clinically meaningful.

Clinical Efficacy
Nivolumab has been FDA approved for the treatment of metastatic melanoma, metastatic non-small cell lung cancer, and clear cell renal cancer based on the results of phase III studies.[26-29] The majority of responses have been durable and have exceeded 6 months. In melanoma, nivolumab has been approved in metastatic disease in the first line setting. In non-squamous lung cancer, it has been approved in advanced disease after progression on one prior treatment. Similarly, nivolumab is approved for the treatment of renal cell carcinoma patients who have progressed on previous therapy.

Clinical Safety
No maximum tolerated dose of nivolumab has been established at doses tested up to 10mg/kg. The safety profile is similar across tumor types and there has been no pattern of adverse effects with regards to incidence or severity based on dose level. Common drug related adverse effects have included pulmonary toxicity, GI toxicity, liver toxicity, and dermatologic toxicity, the majority of which have been manageable with supportive care, dose delay, or steroid treatments.

The overall safety experience with nivolumab is based on clinical experience in approximately 8,600 subjects. In general, for monotherapy, the safety profile is similar across tumor types. The most frequently reported treatment-related AE is fatigue, which is almost always of low grade.

Rationale:

The outcome of patients with advanced biliary cancer remains dismal with the current standard of care options. There is no established second line option for patients with advanced BC who have failed one prior systemic therapy.

Given that immune modulatory agents are known to have activity in BTCs,[30] we propose to evaluate the anti-PD1 agent nivolumab in advanced, refractory BTC, a rare malignancy in which there is a critical unmet clinical need.

2. Study Objectives

Primary Objective
To determine the disease response rate (Complete Response + Partial Response) in patients with advanced biliary tract cancers (BTC) receiving nivolumab as a single agent

Secondary Objectives
1. To determine the median progression free survival (PFS) and overall survival (OS) and response rate by immune response criteria in patients with advanced BTC receiving nivolumab

2. To determine the safety and tolerability of nivolumab in BTC

Exploratory Objectives

1. To explore potential correlations between mismatch repair status and outcome

2. To explore potential correlation of mutational burden and outcome, as evaluated by the Kew CancerPlex immune signature panel.

3. Study Design

This is a multi-institutional single arm study with two stage design using nivolumab in advanced BTC, who have failed or are intolerant to at least one line of therapy and no more than 3 lines of therapy. In the first stage, 18 patients will be accrued. If there is at least one response (or several patients with stable disease based on the study team's discretion), an additional 14 patients will be accrued for a total of 32 patients. Patients will receive nivolumab at a flat dose of 240mg every 2 weeks for 16 weeks (4 cycles). Response and progression will be evaluated using the new

international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1). The primary endpoint is disease response after 2 cycles of treatment (8 weeks). Patients with stable disease or disease response will continue on therapy until progression. Patients can continue on therapy if there is pseudo-progression which is defined by the immune response criteria or if they are having clinical benefit as determined by the investigator after discussion with the principal investigator.

4. Eligibility

4.1 Inclusion Criteria

- Patients must have histologically or cytologically documented carcinoma primary to the intra- or extra-hepatic biliary system or gall bladder with clinical and/or radiologic evidence of unresectable, locally advanced or metastatic disease. Patients with ampullary carcinoma are not eligible.

- Patients must have failed or are intolerant to one line of systemic treatment but no more than 3 prior lines of systemic chemotherapy for advanced BTC. Patients who received adjuvant chemotherapy and had evidence of disease recurrence within 6 months of completion of the adjuvant treatment are also eligible. If the patient received adjuvant treatment and had disease recurrence after 6 months, patients will only be eligible after failing or having intolerance to one line of systemic chemotherapy used to treat the disease recurrence.

- Age $\geq$ 18 years.

- Eastern Cooperative Oncology Group (ECOG) Performance Status Assessment of 0 or 1.

- The patient must have radiographic measurable disease per RECIST 1.1 criteria
  - Life expectancy of at least 12 weeks (3 months).
  - For patients who have received prior radiation, cryotherapy, radiofrequency ablation, therasphere, ethanol injection, transarterial chemoembolization (TACE) or photodynamic therapy, the following criteria must be met:
    - 28 days have elapsed since that therapy
    - Lesions that have not been treated with local therapy must be present and measureable
  - Subjects must be able to understand and be willing to sign the written informed consent form. A signed informed consent form must be appropriately obtained prior to the conduct of any trial-specific procedure. Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other study requirements.
  - All acute toxic effects of any prior treatment have resolved to NCI-CTCAE v4.0 Grade 1 or less at the time of signing the Informed Consent Form (ICF) except for alopecia.
  - Adequate bone marrow, liver and liver function as assessed by the following laboratory requirements:
    - Total bilirubin $\leq$ 1.5 x the upper limits of normal (ULN), except for subjects with Gilbert Syndrome who can have bilirubin <3.
    - Alanine aminotransferase (ALT) and aspartate amino-transferase (AST) $\leq$ 2.5 x ULN ($\leq$ 5 x ULN for subjects with liver involvement of their cancer or stent placement)

- Alkaline phosphastase limit ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
- Serum creatinine <2 x ULN
- Hematologic parameters as follows:
  - Platelet count ≥ 100,000 /mm^3
  - Hemoglobin (Hb) ≥ 9 g/dL
  - Absolute neutrophil count (ANC) ≥1000/mm^3
  - Blood transfusion to meet the inclusion criteria will be allowed.

- Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity of 25 IU/L or equivalent units of HCG) performed within24 hours prior to the start of nivolumab Post-menopausal women (defined as no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test.
- Subjects (men and women) of childbearing potential must agree to use adequate contraception beginning at the signing of the ICF until at least 3 months after the last dose of study drug. The definition of adequate contraception will be based on the judgment of the principal investigator or a designated associate.
- Patients with history of hepatitis B and hepatitis C will be eligible but patients with hepatitis B must be started on antiviral therapy prior to beginning study therapy
- Availability of archival tumor tissue for biomarkers analysis (FFPE block or cell block will be required). Specimen from primary site will be allowed. Patients must have at least 10 slides available. Repeat biopsy to obtain sufficient tissue for 10 slides is allowed.

4.2 Exclusion Criteria

- Subjects with active CNS metastases are excluded. If CNS metastases are treated and subjects are at neurologic baseline for at least 2 weeks prior to enrollment, they will be eligible but will need a Brain MRI prior to enrollment. Subjects must be off corticosteroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent).
- Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll
- Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of enrollment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways).
- Previous or concurrent cancer within 3 years prior to treatment start EXCEPT for curatively treated cervical cancer in situ, non-melanoma skin cancer, superficial bladder tumors [Ta (non-invasive tumor), Tis (carcinoma in situ) and T1 (tumor invades lamina propria)].
- Known history of human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS).

- Child Pugh B or C disease
- History of severe hypersensitivity reactions to other monoclonal antibodies
- History of allergy or intolerance to study drug components or Polysorbate-80-containing infusions
- Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results.
- History or concurrent condition of interstitial lung disease of any grade or severely impaired pulmonary function.
- Unresolved toxicity higher than CTCAE grade 1 attributed to any prior therapy/procedure excluding alopecia.
- Pregnant or breast-feeding patients. Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity of 25 IU/L or equivalent units of HCG) performed within 24 hours prior to the start of nivolumab and a negative result must be documented before start of treatment.
- Any illness or medical conditions that are unstable or could jeopardize the safety of the patient and his/her compliance in the study.

Excluded Therapies and Medications for Cancer

- Anticancer chemotherapy during the study or within 4 weeks of study enrollment. Subjects must have recovered from the toxic effects of the previous anti-cancer chemotherapy (with the exception of alopecia). Anti-cancer therapy is defined as any agent or combination of agents with clinically proven anti-tumor activity administered by any route with the purpose of affecting the malignancy, either directly or indirectly, including palliative and therapeutic endpoints.
- Hormonal therapy during the study or within 2 weeks of first study enrollment.
- Radiotherapy to target lesions during study or within 2 weeks of enrollment.
- An irradiated lesion is considered evaluable only if it has shown enlargement since the completion of last radiation.
- Bone marrow transplant or stem cell rescue.
- Investigational drug therapy outside of this trial during or within 4 weeks of first study treatment.

4.3 Withdrawal of Subjects from Study

4.3.1 Withdrawal

Subjects must discontinue investigational product for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason). A subject must be removed from the trial at his/her own request or at the request of his/her legally acceptable representative. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject

- Pregnancy will be reported as an SAE and the patient will be withdrawn. (Note: subjects who have been withdrawn from treatment with study drug because of pregnancy should not undergo CT scans [with contrast]/MRI or bone scans while pregnant.)
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
- Subject is lost to follow-up
- Death

All subjects who discontinue should comply with protocol specified follow-up and survival procedures. The ONLY exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form page.

Subjects **may be** withdrawn from the study for the following reasons:

- The subject is non-compliant with study drug, trial procedures, or both; including the use of anti-cancer therapy not prescribed by the study protocol.
- Severe allergic reaction to nivolumab
- The development of a second cancer.
- Development of another illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- Deterioration of ECOG performance status to 3 or 4.
- Use of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise skewing trial result.

Any subject removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable.

Any subject with progression of disease will come off of treatment. In all cases, the reason for withdrawal must be recorded in the CRF and in the subject's medical records.

4.3.2 Screen Failures/Dropouts/Replacements

A subject who discontinues study participation prematurely for any reasons except death, disease progression and severe toxicity is defined as a dropout.

Dropouts who did not receive at least one staging assessment (after 2 cycles or 8 weeks of treatment) will need to be replaced.

A subject who, consents to participate but does not qualify for treatment based upon the eligibility criteria is regarded a “screening failure”.

Patients who are screening failures will need to be replaced.

Patient who receive at least one staging assessment (after 2 cycles or 8 weeks of treatment), will be included in the analysis of disease response.

5. Treatment

5.1 Treatment to be administered

All patients will receive Nivolumab

Agent	Dose	Route	Schedule*	
Nivolumab	240mg	IV	q2weeks	until 16 weeks

**One cycle = 28 days*

Agent	Dose	Route	Schedule*	
Nivolumab	480mg	IV	q4weeks	from 17 weeks to end of study

5.1.1 Flat Dose Regimen

The safety and efficacy of 240 mg Q2W flat dose of nivolumab is expected to be similar to 3 mg/kg Q2W dosing regimen. Using the PPK model, exposure of nivolumab at 240 mg flat dose is identical to a dose of 3 mg/kg for subjects weighing 80 kg, which is the approximate median body weight in nivolumab clinical trials. Across the various tumor types in the clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy and safety has been found to be relatively flat. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of 240 mg flat dose compared to 3 mg/kg, it is expected that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab. Hence, a flat dose of 240 mg nivolumab is under investigation. Of note, 240 mg is identical to 3mg/kg for 80 kg patients; 80 kg is the median body weight.

5.2 Management of Toxicities Associated with Study Drug

Subjects will receive treatment with nivolumab as a 60 minute IV infusion, on Week 1, Day 1 and Week 3, Day 1 of a treatment cycle (every 2 weeks).

There will be no dose escalations or reductions of nivolumab allowed. This includes both the 240mg q 2 week portion of the study as well as the 480mg q 4 week portion of the study.

Subjects may be dosed no less than 12 days from the previous dose. There are no premedications recommended for nivolumab on the first cycle. If an acute infusion reaction is noted, subjects should be managed according to Section 5.2.5.

Treatment may be delayed for up to a maximum of 6 weeks from the last dose (See Sections 5.2.1 and 5.2.4.1).
Subjects will be monitored continuously for AEs while on study. Treatment modifications (eg dose delay or discontinuation) will be based on specific laboratory and adverse event criteria.

In some cases, the natural history of immunotherapy-related AEs of special interest can differ and be more severe than AEs caused by other therapeutic classes. Early recognition and management may mitigate severe toxicity. The management of organ specific toxicities is detailed through flow sheets in Appendix 1.

Summary of Safety

Most related AEs are thought to be due to the effects of inflammatory cells on specific tissues. In general, the approach to suspected nivolumab-related AEs is similar across any involved organ system. Safety management algorithms for organ-specific AEs are found in Appendix 1. Subjects should have a thorough diagnostic work-up to evaluate potential drug- and non-drug-related diagnoses. For suspected nivolumab-related AEs, based on the severity of the event, management with immunosuppressant may be necessary. In general, dose delays and observation are adequate for low-grade AEs. For moderate- and high-grade AEs, immunosuppression with corticosteroids should be utilized. Once the AE has begun to improve, corticosteroids can be tapered over approximately 3 weeks to 6 weeks (depending on the severity of the AE).

Immune Mediated Event Assessment

This assessment of AE is made by the individual investigator and should be based on clinical evidence such as:

- Responsiveness to treatment (e.g. steroids)
- Diagnostic test results (e.g. evidence of inflammation)
- Medical history (other illness, prior therapies, etc.)

An IMAE is an AE consistent with an immune-mediated mechanism or immune-mediated component (alternate etiology exacerbated by the induction of autoimmunity) for which non- inflammatory etiologies (e.g. infection or tumor progression) have been ruled out, and consideration given to evidence of inflammation such as tumor biopsies or responsiveness to steroids.

Likely reasons an event **is not** an IMAE:

- Likely due to concomitant drug/chemotherapy/radiation
- Documented evidence of tumor as cause
- Same grade event at baseline/history
- Event likely caused by infection

Likely reasons an event **is** an IMAE:

- Inflammation per pathology or endoscopy
- Improves/resolves after immunosuppression
- Similar to previous immune mediated event in same organ

Pulmonary Adverse Events

Pulmonary AEs have been observed following treatment with nivolumab and have occurred after a single dose and after as many as 48 treatments. The majority of cases reported were Grade 1 or 2, and subjects presented with either asymptomatic radiographic changes (eg, focal ground glass opacities and patchy infiltrates) or with symptoms of dyspnea, cough, or fever. Subjects with reported Grade 3 or 4 pulmonary AEs were noted to have more severe symptoms, more extensive radiographic findings, and hypoxia. At this time, no underlying risk factor, including prior radiotherapy, presence of lung metastases, or underlying pulmonary medical history, has been identified.

Guidelines on the recommended management of pneumonitis and other pulmonary AEs are found in Appendix 1. Early recognition and treatment of pneumonitis is critical to its management. Subjects should be advised to seek medical evaluation promptly if they develop new-onset dyspnea, cough, or fever or if they have worsening of these baseline symptoms. It is important

that an evaluation/work-up distinguishes between non-drug-related causes (eg, infection or progression of disease) and a possible drug-related pulmonary toxicity as the management of these events can be quite different. For symptomatic nivolumab-related pneumonitis, the principal treatment is corticosteroids (Appendix 1). All subjects with Grade 3-4 pneumonitis should discontinue nivolumab and initiate treatment with high doses of corticosteroids.

Gastrointestinal Adverse Events

Gastrointestinal AEs have been observed following treatment with nivolumab. Most cases of diarrhea were of low grade (Grade 1-2). Colitis occurred less frequently than diarrhea. High-grade cases of diarrhea and colitis were managed with corticosteroids and, in all cases, the events resolved.

The recommended management of GI AEs is provided in Appendix 1. Early recognition and treatment of diarrhea and colitis are critical to their management. Subjects should be advised to seek medical evaluation if they develop new-onset diarrhea, blood in stool, or severe abdominal pain or if they have worsening of baseline diarrhea. It is important that an evaluation/work-up distinguishes between non-drug-related causes (eg, infection or progression of disease) and a possible drug-related AE as the management can be quite different. The principal treatment for high-grade GI AEs is corticosteroids (Appendix 1). Caution should be taken in the use of narcotics in subjects with diarrhea, colitis, or abdominal pain as pain medicines may mask the signs of colonic perforation. Grade 3 diarrhea/colitis requires permanent discontinuation regardless of AE duration.

Diverticular Perforation

Given the high prevalence of diverticulosis and diverticulitis in the general population, it is expected that some nivolumab-treated subjects will have these conditions concurrently w ith their malignancy. While there is insufficient evidence to suggest that diverticulosis or diverticulitis is a predisposing factor for GI perforation following nivolumab administration, clinical caution should be exercised, as appropriate, for subjects on concomitant medications of corticosteroids, NSAID, or opioid analgesics. In addition, vigilance should be used for signs and symptoms of potential perforation, especially in subjects with known diverticular disease.

Hepatic Adverse Events

Hepatic AEs, including elevated liver function tests (LFTs) and, infrequently, drug induced liver injury (DILI), have been observed following treatment with nivolumab. Most cases were of low or moderate grade. Higher-grade hepatic AEs, including DILI, were managed with corticosteroids (with or without mycophenolate mofetil) and, in almost all cases, the events resolved.

The recommended management of hepatic AEs is provided in Appendix 1. Early recognition and treatment of elevated LFTs and DILI are critical to their management. Subjects should be advised to seek medical evaluation if they notice jaundice (yellow appearance of skin or sclera) or if they develop bruising, bleeding, or right-sided abdominal pain. Physicians should monitor LFTs prior to each nivolumab treatment. As LFT abnormalities are common in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (eg, infection, progression of disease, concomitant medications, or alcohol) and a possible drug-related AE as the management can be quite different. The principal treatment for high-grade hepatic AEs is corticosteroids (Appendix 1).

For any grade increase in AST or ALT, the investigator needs to ensure that it is not due to biliary obstruction or the introduction of new drugs. Biliary obstruction should be ruled out by imaging if needed. If the elevation of AST or ALT is due to biliary obstruction, and the biliary obstruction is treated, the study drug may be restarted upon return of the AST and ALT to baseline or grade 2.

For any grade increase in bilirubin, the investigator needs to ensure that it is not due to biliary obstruction or the introduction of new drugs. Biliary obstruction should be ruled out by imaging if needed. If the elevation of bilirubin is due to biliary obstruction, and the biliary obstruction is treated, the study drug may be restarted upon return of the bilirubin to baseline or Grade 1.

Endocrinopathies

Endocrinopathies have been observed following treatment with nivolumab. Most cases were of low or moderate grade. The events have typically been identified through either routine periodic monitoring of specific laboratories (e.g., TSH) or as part of a work-up for associated symptoms (e.g., fatigue). Events may occur within weeks of beginning treatment, but also have been noted to occur after many months (while still on treatment). More than 1 endocrine organ may be involved (e.g., hypophysitis [pituitary inflammation] may need to be evaluated at the time adrenal insufficiency or thyroid disorder is suspected). Moderate- to high-grade cases were managed with hormone replacement therapy and, in some cases, with the addition of corticosteroids. In some cases, nivolumab treatment was held until adequate hormone replacement was provided.

Guidelines on the recommended management of endocrinopathies are provided in Appendix 1. Early recognition and treatment of endocrinopathies are critical to its management. Subjects should be advised to seek medical evaluation if they notice new-onset fatigue, lightheadedness, or difficulty with vision or if baseline fatigue worsens. As fatigue is common in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (e.g., progression of disease, anemia, concomitant medications, or depression) and a possible drug-related AE as the management can be quite different. The principal management of endocrinopathies is hormone replacement therapy. For subjects with moderate- or high-grade events, corticosteroids may also be used (Appendix 1).

Skin Adverse Events

Rash and pruritus were the most common skin AEs observed following treatment with nivolumab. The rash was typically focal with a maculopapular appearance occurring on the trunk, back, or extremities. Most cases have been of low or moderate grade. In some cases, rash and pruritus resolved without intervention. Topical corticosteroids have been used for some cases of rash. Anti-histamines have been used for some cases of pruritus. More severe cases responded to systemic corticosteroids.

Subjects should be advised to seek medical evaluation if they notice new-onset rash. Early consultation with a dermatology specialist and a biopsy should be considered if there is uncertainty as to the cause of the rash, or if there is any unusual appearance or clinical feature associated with it. Other drugs that may cause rash should be considered in the differential and, if possible, discontinued.

The principal treatment for skin AEs, such as rash and pruritus, consists of symptomatic management. Topical corticosteroids can be used for low- to moderate-grade focal rash.

Systemic corticosteroids should be used for diffuse and high-grade rash.

Renal Adverse Events

Elevated creatinine and biopsy-confirmed tubulointerstitial nephritis and allergic nephritis have been infrequently observed following treatment with nivolumab. The frequency of renal AEs may be greater with nivolumab combination therapies than with nivolumab monotherapy. Most cases were Grade 2 or 3 and based on creatinine elevation. Subjects with a history of RCC or prior nephrectomy did not appear to be at higher risk. Events were managed with corticosteroids and, in all cases, renal function partially or fully improved.

The recommended management of renal AEs is provided in Appendix 1. Physicians should monitor creatinine regularly. As creatinine abnormalities are common in subjects with cancer and other comorbidities, it is important that an evaluation/work-up distinguishes between non-drug-related causes (e.g., dehydration, concomitant medications, hypotension, or progression of disease) and a possible drug-related AE as the management can be quite different. The principal treatment for renal AEs is corticosteroids (Appendix 1).

Neurologic Adverse Events

Neurologic AEs have been uncommonly observed following treatment with nivolumab. Neurologic AEs can manifest as central abnormalities (e.g., aseptic meningitis, encephalopathy, or encephalitis) or peripheral sensory/motor neuropathies (e.g., Guillain-Barre Syndrome, myasthenia gravis complicated with sepsis and fatality).

The recommended management of neurologic AEs is provided in Appendix 1. Early recognition and treatment of neurologic AEs is critical to its management. Subjects should be advised to seek medical evaluation if they notice impairment in motor function (e.g., weakness), changes in sensation (e.g., numbness), or symptoms suggestive of possible central nervous system abnormalities such as new headache or mental status changes. As neurologic symptoms can be common in subjects with cancer, it is important that an evaluation/work-up distinguishes between non-drug-related causes (e.g., progression of disease, concomitant medications, or infection) and a possible drug-related AE as the management can be quite different. The principal treatments for neurologic toxicity are dose delay, corticosteroids, and IV immunoglobulin as outlined in the safety algorithm (Appendix 1). For high-grade related neurological AEs, nivolumab should be discontinued.

Uveitis and Visual Complaints

Immune therapies have been uncommonly associated with visual complaints. Inflammation of components within the eye (e.g., uveitis) is an uncommon, but clinically important, event. An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers, and retina. Topical corticosteroids may be used to manage low-grade events. Low-grade events that do not resolve and high-grade events should be managed with systemic corticosteroids. Complaints of double vision should also prompt medical evaluation. In addition to ocular inflammatory events, a work-up should also consider pituitary inflammation as a cause.

Others

Other clinically significant immune-mediated adverse reactions can occur with nivolumab. Immune-mediated adverse reactions may occur after discontinuation of nivolumab therapy. For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, permanently discontinue or withhold nivolumab, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, consider initiation of corticosteroid taper and continue to taper over at least 1 month. Consider restarting nivolumab after completion of corticosteroid taper based on the severity of the event.

Overdose, Warnings, and Precautions
There is no available information concerning overdose with nivolumab. Depending on the symptoms and/or signs leading to the suspicion of overdose, supportive medical management should be provided. There is no specific antidote.

Precautions for Women of Childbearing Potential

The nonclinical findings of increased late-stage pregnancy loss and early infant deaths/euthanasia in nivolumab-exposed pregnant monkeys suggest a potential risk to human pregnancy if there is continued treatment with nivolumab during pregnancy. Given the potential risk suggested by preliminary data from nonclinical and clinical data, dosing during pregnancy will continue to be prohibited. In addition, women of childbearing potential (WOCBP) receiving nivolumab will be instructed to adhere to contraception for a period of 23 weeks after the last dose of nivolumab. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of nivolumab.

These durations have been calculated using the upper limit of the half-life for nivolumab (25 days) and are based on the recommendation that WOCBP use contraception for 5 half-lives plus 30 days, and men who are sexually active with WOCBP use contraception for 5 half-lives plus 90 days after the last dose of nivolumab. Females should not breastfeed while receiving nivolumab and for any subsequent protocol-specified period.

5.2.1 Dose Delay Criteria

Tumor assessments for all subjects should continue as per protocol even if dosing is interrupted.

Nivolumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or clinically insignificant laboratory abnormalities do not require a treatment delay
- Any Grade 3 drug-related skin adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for blood counts, AST, ALT, or total bilirubin:
  - Grade 3 lymphopenia or leukopenia does not require dose delay
  - Grade 2 anemia does not require a dose delay
- If a subject has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
- If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 or Grade 2 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity

- A sudden increase in transaminases that the investigator determines is secondary to dislocation of a stent will not be counted as an AE. Treatment should be held until stent replacement can be performed and only resumed once LFTs have returned to the patient's baseline
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

5.2.2 Criteria to Resume Dosing

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

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline AST/ALT or total bilirubin in the Grade 1 or 2 toxicity range may resume treatment in the presence of return to Grade 1 or 2 AST/ALT OR total bilirubin, respectively
- Subjects who started out with normal baseline LFTs who develop combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 5.2.4.1) should have treatment permanently discontinued
- Drug-related pulmonary toxicity or diarrhea/colitis must have resolved to baseline before treatment is resumed. Grade 3 or 4 diarrhea/colitis require permanent discontinuation of the drug regardless of duration. Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment

If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 5.2.4.1

5.2.3 Treatment Beyond Disease Progression

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

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

1. Investigator-assessed clinical benefit, and do not have rapid disease progression
2. Continue to meet all other study protocol eligibility criteria
3. Tolerance of study drug
4. Stable performance status
5. Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)

If the subject appears to be deriving clinical benefit despite disease progression, the decision to continue treatment beyond disease progression should be discussed with the Principal Investigator and documented in the study records.

A radiographic assessment/ scan should be performed within six (6) weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

If the principal investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Time and Events Schedule. The decision to continue treatment should be discussed and documented in the study records.

5.2.4 Treatment Discontinuation Criteria

Tumor assessments for all subjects should continue as per protocol even if dosing is discontinued.

5.2.4.1 Nivolumab Dose Discontinuation

Nivolumab treatment should be permanently discontinued for the following:

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

Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions: Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation

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

1. Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
2. Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
    a. AST or ALT > 10x ULN
    b. Total bilirubin > 5x ULN
    c. In subjects with normal baseline LFTs, the development concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN

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

1. Grade 4 neutropenia ≥ 7 days
2. Grade 4 lymphopenia or leukopenia
3. Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset

Any dosing interruption lasting > 6 weeks with the following exceptions:

1. Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Principal Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
2. Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Principal Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Principal Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
3. Any adverse event, laboratory abnormality, or concurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

Global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression (ie radiographic confirmation) even after discontinuation of treatment.

5.2.5 Treatment of Nivolumab-Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthalgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

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

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

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

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

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the

infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit.

For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

For Grade 3 or 4 symptoms: Follow guidelines for Grade 2 infusion reaction as above and permanently discontinue study drug.

5.3 Study Treatment, Drug Ordering, and Pharmacy Reference Information

Nivolumab 100 mg (10 mg/mL) will be packaged in an open-label fashion. Ten nivolumab, 10 mL vials will be packaged within a carton, and are not subject or treatment arm specific. The appearance of the solution is clear to opalescent, colorless to pale yellow liquid that may contain particles. It should be stored between 2 and 8 degrees Celsius and should be protected from light and freezing.

Treatment should be initiated within 28 days of enrollment. Treatment will be continued until disease progression, discontinuation due to toxicity, withdrawal of consent, or the study ends.

Treatment will be administered at a dose of 240 mg every 2 weeks for 16 weeks and then at 480 mg every 4 weeks until disease progression or unacceptable toxicity for up to 24 months. Treatment can continue at the discretion of the investigator if clinical benefit is noted.

For full information regarding nivolumab drug ordering as well as pharmacy reference material, please see Appendix 2 and Table 3.

5.3.1 Handling and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately. Nivolumab vials must be stored in the refrigerator at 2-8°C, protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g. required diluents, administration sets).

Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

After nivolumab has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours. For details on prepared drug storage and use time under room temperature/light and refrigeration, please refer to the current Nivolumab Investigator Brochure.

Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyolefin bags have been observed.

Nivolumab is to be administered as a 60 minute IV infusion, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline (per institutional standard of care).

Details regarding the mixing and concentrations of the dose (preparation) and administration can be found in the current Investigator brochure for nivolumab.

5.3.2 Blinding

This is an open-label trial. There will be no randomization or blinding.

5.3.3 Drug Logistics and Accountability

All study drugs will be stored at the investigational site in accordance with good clinical practice (GCP) and GMP requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate / Contract Research Organization [CRO]), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the sponsor study file; the site-relevant elements, of this information will be available in the ISF. The responsible site personnel will confirm receipt of study drug and will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed upon and specified procedures.

5.3.4 Treatment Compliance

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

5.3.5 Destruction and Return of Study Drug

Destruction of Study Drug For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site. Any unused study drugs can only be destroyed after being inspected and reconciled by the

responsible BMS Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (e.g. cytotoxics or biologics). On-site destruction is allowed provided the following minimal standards are met:

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

If conditions for destruction cannot be met, the responsible BMS Study Monitor will make arrangements for return of study drug. It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

5.3.6 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible BMS Study Monitor. It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

5.4 Prior and Concomitant Therapy

5.4.1 Prohibited Concomitant Anti-cancer Therapy:

CYP3A4 Inhibitors and Inducers

The following strong CYP3A4 inhibitors should be avoided during the study. This includes (but is not limited to):

- Ketoconazole
- Itraconazole
- Clarithromycin
- Atazanvir
- Indinavir
- Nefazodone
- Nelfinavir
- Ritonavir
- Saquinavir
- Teithromycin
- Voriconazole

The following medications are prohibited during the study (unless utilized to treat a drug-related

adverse event):

• Immunosuppressive agents
• Immunosuppressive doses of systemic corticosteroids (except as stated in Section 5.4.3).
• Any concurrent antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of biliary tract cancers).

Palliative and supportive care for disease related symptoms (including local radiotherapy, bisphosphonates and RANK-L inhibitors) may be offered to all subjects prior to first dose of study therapy (prior radiotherapy must have been completed at least 2 weeks prior to enrollment).

5.4.2 Other Restrictions and Precautions

- Subjects with active, known or suspected autoimmune disease.
- Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of enrollment.
- Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

5.4.3 Permitted Therapy

- Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).
- Physiologic replacement doses of systemic corticosteroids (e.g., prednisone ≤ 10 mg/day) are permitted.
- A brief (less than 3 weeks) course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.
- The potential for overlapping toxicities with radiotherapy and nivolumab currently is not known. Therefore, palliative radiotherapy is not recommended while receiving nivolumab. If palliative radiotherapy is required, then nivolumab should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolve to Grade ≤ 1 prior to resuming nivolumab. Only non-target bone lesions that do not include lung tissue in the planned radiation field may receive palliative radiotherapy. Details of palliative radiotherapy should be documented in the source records and electronic case report form (eCRF). Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and adverse events. If warranted, symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression.

6. Study Assessments and Procedures

6.1 Table 1: Screening Assessments and Procedures

Screening examinations will only be performed after having received the subject's written informed consent.

Screening Assessments and Procedures *to be completed within 28 days of enrollment*		
Procedure	**Screening Visit**	**Notes**
Eligibility Assessments		
Informed Consent	**X**	
Inclusion/Exclusion Criteria	**X**	
Medical History	**X**	
Safety Assessments		
Vital Signs and Oxygen saturation	**X**	**Temperature, BP, HR, RR, O_2 saturation by pulse oximetry (also monitor amount of supplemental oxygen if applicable)** **Obtain vital signs at screening visit and within 72 hours of first dose**
Physical Measurements (including Performance Status)	**X**	**Includes Height and Weight, and ECOG status**
Clinic Visit	**X**	
Laboratory Tests	**X**	**Labs performed within 21 days prior to first dose of study drug:** **CBC with differential, Serum chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and bicarbonate, glucose), AST, ALT, total bilirubin, direct bilirubin, alkaline phosphatase, albumin, LDH, TSH, free T3, free T4, HBV surface antigen, HCV RNA. CA 19-9**
Pregnancy Test	**X**	**Performed within 7 days prior to first dose study drug (serum or urine for WOCBP only)**
Concomitant Medication collection	**X**	
Radiographic Tumor Assessment (Chest, abdomen, pelvis)	**X**	**Should be performed within 28 days prior to first dose. CT/MRI of brain (with contrast) should only be performed in subjects with a known history of treated brain metastases.** **Additional sites of known or suspected disease (including CNS) should be imaged at the screening visit and at subsequent on-study assessments.**
Archived Tumor Tissue or Recent Tumor Biopsy (for IHC)	**X**	**May be archival or recent sample. 1 formalin-fixed paraffin embedded tumor tissue block or cell block is needed (or 10 slides).**

6.2 Table 2: On Study Assessments

Procedure	C1D1	C1D8	C1D15(±5 days)	C2D1(±5 days)	C4D1(±5 days)	End of every 2nd cycle(±5 days)	Subsequent Cycles[a]	EOT[b]	Notes
Vital signs and Oxygen Saturations	X	X	X	X	X		X	X	Temperature, BP, HR, RR, O_2 saturation by pulse oximetry (also monitor amount of supplemental oxygen if applicable) prior to dosing and at any time a subject has any new or worsening respiratory symptoms
AE and SAE Assessment	Continuously								Assessed using NCI CTCAE v. 4.0
Physical Measurements *including Performance Status*	X	X	X	X	X		X	X	Includes Weight and ECOG status
Complete blood count *Results obtained prior to dosing on infusion days*	X	X	X	X	X		X	X	Includes WBC count with differential, hemoglobin, hematocrit, and platelet count
Serum Chemistry Tests	X	X	X	X	X		X	X	Serum chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and bicarbonate, glucose), LDH
Clinic Visit	X	X	X	X	X		X	X	
Liver Function Testing *Results obtained within 72 hours prior to dosing on infusion days*	X	X	X	X	X		X	X	Includes aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, and albumin
Additional Testing						X			Tumor measurement/disease assessment according to RECIST 1.1, CA 19-9 assessment, Pregnancy Test Urine or Serum (for WOCBP only), TSH (reflex to free T3 and free T4 if abnormal results)

[a]Treatment is to be given every 2 weeks for 16 weeks (4 cycles) and then will be given once every 4 weeks thereafter as per Section 5.3

[b] The EOT disease assessment with radiographic imaging is required if it has been > 28 days since the last disease assessment

7. Adverse Events

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

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:

The 5 categories for AE grading are:

1. Not related
2. Not Likely
3. Possible
4. Probable
5. Definite

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.)

All AEs will be monitored until resolution or, if the AE is determined to be chronic, a cause is identified. If an AE is considered potentially related to study treatment and remains ongoing at the conclusion of the study, the event will be followed until resolution, stabilization, or initiation of treatment that confounds the ability to assess the event. AEs will be collected for a minimum of 30 days from the end of treatment. All SAEs must be collected from when the patient begins the study drug to within 100 days of discontinuation of dosing or until the patient begins another anti-cancer therapy.

7.1 Safety Monitoring

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology and blood chemistry parameters and regular physical examinations. Adverse events will be evaluated continuously throughout the study. Safety and tolerability will be assessed according to the NIH/NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) that is available at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

7.1.1 Internal Safety Monitoring

The Moffitt Protocol Monitoring Committee (PMC) meets monthly and reviews accrual, patterns and frequencies of all adverse events, protocol violations and when applicable, internal audit results.
The PMC, upon review of any agenda item, may approve the study for continuation, require revisions, suspend or close a protocol.

Data will be captured in OnCore, Moffitt's Clinical Trials Database. Regulatory documents and case report forms will be reviewed routinely according to Moffitt's Monitoring Policies.

7.2 Serious Adverse Events

A S***erious AE (SAE)*** is any untoward medical occurrence that at any dose:

- **7.2.1** results in death
- **7.2.2** is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- **7.2.3** requires subject hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- **7.2.4** results in persistent or significant disability/incapacity
- **7.2.5** is a congenital anomaly/birth defect
- **7.2.6** is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 7.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (e.g., any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Information about all serious adverse events will be collected and recorded. To ensure patient safety, each serious adverse event must be reported to the PI and to BMS expeditiously (see below for BMS requirements). Moffitt Cancer Center and all participating sites will report SAEs by completing an SAE report in ONCORE, the electronic data capture system and a Medwatch Form online at http://www.fda.gov/medwatch The SAE must be reported by email (affiliate.research@moffitt.org) to the MCRN within 2 working days.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 7.4 for reporting pregnancies).

NOTE:
The following hospitalizations are not considered SAEs:

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Elective surgery, planned prior to signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission for purpose other than remedying ill health state and was 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 (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)

7.2.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected from when the patient begins the study drug to within 100 days of discontinuation of dosing or until the patient begins another anti-cancer therapy. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

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

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

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, as well as pregnancies, must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

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

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

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

All SAEs should be followed to resolution or stabilization.

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

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

MedWatch SAE forms should be sent to the FDA at:

MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

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

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

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

For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection in the protocol.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization. All SAEs should be followed to resolution or stabilization.The Sponsor will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com). Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. BMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. 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.

7.3 Non-serious Adverse Events

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

The collection of nonserious AE information should begin at initiation of study drug.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 7.2). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

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

7.4 Laboratory Test Abnormalities

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

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

Wherever possible the clinical, rather than the laboratory term, should be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

7.5 Pregnancy

Following initiation of the investigational product, if it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 7.2.1.

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

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

7.6 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 (see Section 7.2.1 for reporting details).

7.7 Other Safety Considerations

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

For recommendations regarding suspected pulmonary toxicity, diarrhea and colitis, suspected hepatotoxicity (including asymptomatic LFT elevations), or suspected endocrinopathy, please see Section 5.2 and Appendix 1.

8. Statistical Considerations

8.1 Sample Size Determination

Patients will be accrued to the protocol according to a Simon two-stage design.[31] Based on patient response (CR + PR after 2 cycles), as defined by RECIST 1.1 criteria, we will either conclude that the therapy is effective or ineffective. The two-stage design has the smallest effective sample size with the following two properties:

8.1.1if the true response rate is less than or equal to 5% , we will conclude that the therapy is ineffective with probability of at least 0.07 (alpha), and
8.1.2if the true response rate is at least 20%, we will conclude that the therapy is effective with probability at least 0.90 (power).

At least one of eighteen patients must respond (CR or PR) in the first stage to proceed to the second stage. At any point when it is realized that this cannot happen, the study will be stopped and the therapy will be considered ineffective.

If there are at least 4 patients with stable disease for 16 weeks (2 restaging assessments), the principal investigator will discuss proceeding to the second stage of the study with the BMS medical team. This would require an amended protocol to define a successful trial result.

The second stage of this study will involve an additional 14 patients. The study will have met its primary endpoint of response rate if there are at least four patients out of thirty two patients who have a response.

8.2 Rationale for an expansion of the study

In March, 2018, it was determined that the Simon-2 stage results led to the rejection of the null hypothesis, and conclusion that the therapy was promising, as 5 of 32 patients had partial responses. Two additional patients were also enrolled due to confusion regarding the evaluability of two patients, with best responses of PD and SD. Thus 5 of 34 patients overall have had PRs (note:5 patients did not have any follow-up RECIST assessments; 4 patients had clinical progression, while a 5th patient withdrew consent). The study team would like to enroll an additional cohort of 20 patients, which would give us a total sample size of 54 patients, for which the 6-month PFS and OS rates are the primary endpoints to be estimated. Presuming no censorship of patients in the first six months after starting treatment, we will be able to estimate the 6-month PFS and 6-month OS rates with a 95% confidence interval half-width of 13.3% (Normal approximation to the binomial calculation). Current 6—month estimates from the study are 41% for PFS, and 73% for OS. Notably, the last of the 10 deaths to date occurred at 6.4 months, and 15 patients have exceeded that time by an average of 5.0 months, suggesting that there will be a high rate of long-term survivors. Thus, the expansion would provide additional valuable information on this promising therapy.

8.3 Populations for Analyses

All enrolled subjects: All subjects who signed an informed consent form and were registered into the IVRS. Analyses of the patients enrolled into the study but not treated and the reason for not being treated will be performed on the data set of all enrolled subjects.

All treated subjects: All subjects who received at least one dose of nivolumab.

This is the primary dataset for dosing and safety.

Response Evaluable Subjects: treated subjects whose change in the sum of diameters of target lesions was assessed (ie. target lesion measurements were made at baseline and at least one on-study tumor assessment.)

8.4 Endpoint Definitions

8.4.1 Primary Endpoint

The primary objective in the study will be measured by the primary endpoint of ORR (CR + PR) as measured by RECIST 1.1 criteria.

8.4.2 Secondary Endpoints

8.4.2.1 Overall Survival (OS)

OS is defined as the time from enrollment to the date of death. A subject who has not died will be censored at last known date alive. OS will be followed continuously while subjects are on the study drugs and every 3 months via in-person or phone contact after subjects discontinue the study drugs.

8.4.2.2 Progression Free Survival (PFS)

PFS is defined as the time from first treatment to the date of the first documented tumor progression as determined by the investigator (per RECIST 1.1), or death due to any cause.

Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were enrolled. Subjects who started any subsequent anti-cancer therapy (including on-treatment palliative RT of non-target bone lesions or CNS lesions) without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on initiation of the subsequent anti-cancer therapy.

8.4.2.3 Safety and Tolerability

Safety and tolerability objective will be measured by the incidence of adverse events, serious adverse events, deaths, and laboratory abnormalities.

Adverse event assessments and laboratory tests are performed at baseline, and continuously throughout the study at the beginning of each subsequent cycle.

8.4.2.4 Immune Response Criteria

In addition to evaluation by RECIST criteria, subjects will be evaluated using the immune response criteria.[32] In this classification, the overall response is determined as follows:

- Immune response CR (irCR) is a complete disappearance of all lesions (whether measurable or not, and no new lesions) with confirmation by a repeat, consecutive assessment no less than 4 weeks from the first documentation.
- Immune response PR (irPR) is a decrease in tumor burden of greater than or equal to 50% relative to baseline. This must be confirmed by a consecutive assessment at least 4 weeks after the first documentation.
- Immune response SD (irSD) is classified as those who do not meet criteria for irCR or irPR and who do not have irPD
- Immune response PD (irPD) is an increase in tumor burden of greater than or equal to 25%relative to the minimum recorded tumor burden which must be confirmed by a repeat, consecutive assessment no less than 4 weeks from the first documentation.

8.4.3 Exploratory Endpoints

Immunohistochemical stains

Archive tumor samples (paraffin-embedded tissue blocks or unstained slides) will be used for evaluation of expression of PD-L1, CD4, FOXP3, CD8, granzymen B, CD45RO, CD68 and CD163 using immunohistochemical (IHC) methods with commercial antibiodies. Paraffin blocks may be processed according to standard institutional protocols. This IHC scores including PD-L1, memory effector cells (CD8+granzyme B+CD45RO+), M2 macrophage (CD163+) and Treg

(CD4+FOXP3+) will be correlated with the clinical efficacy. Sections of formalin-fixed, paraffin-embedded tissue from the colon cancer will be cut and stained with the respective antibodies against PD-L1, CD4, CD8, granzyme B, FOXP3, CD163, CD68 and CD45RO. In brief, the slides will be immersed in citrate buffer solution for antigen retrieval and boiled in microwave for 10 min and washed in buffer solution. They will be incubated with primary antibody for 1 hr at room temperature and then washed in buffer solution. After 1 hr of incubation in the secondary antibody, the sections will be incubated with streptavidin-biotin-complex. Appropriate positive and negative controls will be used.

Immune Signature

An immune signature using next generation sequencing will be performed on all patients and correlated to outcome. Total RNA will be extracted from FFPE tissue sections or slides followed by hybrid-capture next-generation sequencing to evaluate gene expression profiles. First-strand complementary DNA was synthesized from random hexamer-primed RNA templates. Individual target-gene amplification will be multiplexed with 18S rRNA endogenous control and run in triplicate in 384-well format on fast real-time PCR systems. Normalized cycle threshold values for each amplified target gene replicated will be calculated. Resulting triplicate normalized cycle threshold values for individual target genes will be averaged, yielding a final value.

Tumor RNA seq, PD-L1, CD8 T cells, Tregs and macrophages will be reported as percentage measure. The percentage measurement will be summarized using mean (standard deviation).

9. Data Recording

9.1 Institutional Review Board (IRB) Approval and Consent

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

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

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

9.2 Required Documentation

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

to the IRB.

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

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

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

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

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

a. Registration Procedures

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

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

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

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

To register a patient send the completed signed eligibility checklist along with supporting

documentation to the MCRN via email at affiliate.research@moffitt.org or via fax at 813-745-5666, Monday through Friday between 8:00AM and 5:00PM(EST).

b. Data Management and Monitoring/Auditing

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

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

c. Adherence to the Protocol

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

d. Emergency Modifications

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

For Institutions Relying on Moffitt's IRB:

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

For Institutions Relying on Their Own IRB:

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

e. Record Retention

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

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

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

f. Obligations of Investigators

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

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

9.3 Ethical and Legal Aspects

a. Ethical and Legal Conduct of the Study

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

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

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

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

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

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

b. Subject Information and Consent

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

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

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

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

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

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

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

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

c. Publication policy

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

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

d. Confidentiality

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

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

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Appendix 1: Immune Adverse Event Management Algorithms

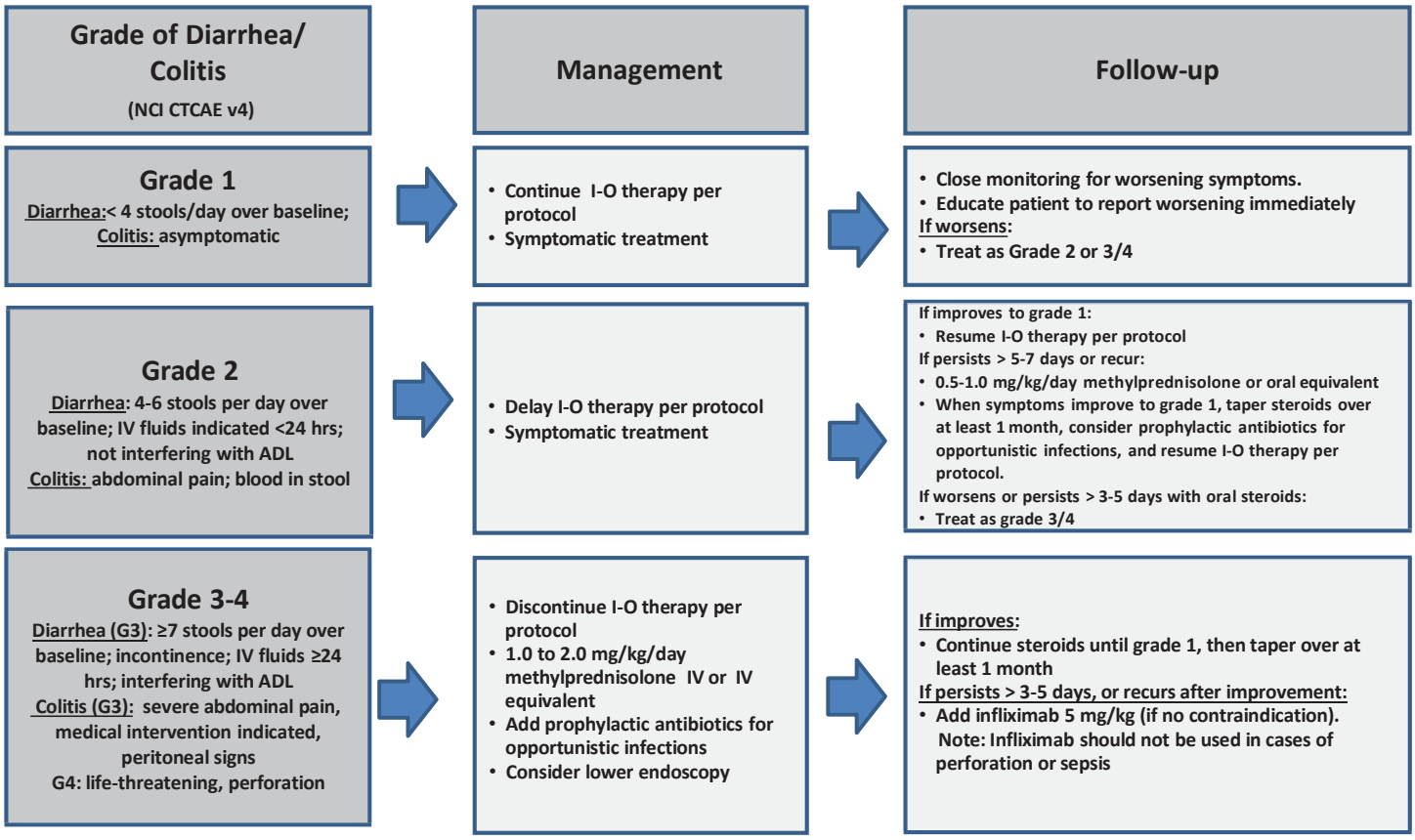
These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens. A general principle is that differential diagnoses should be diligently evaluated 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 ManagementAlgorithm

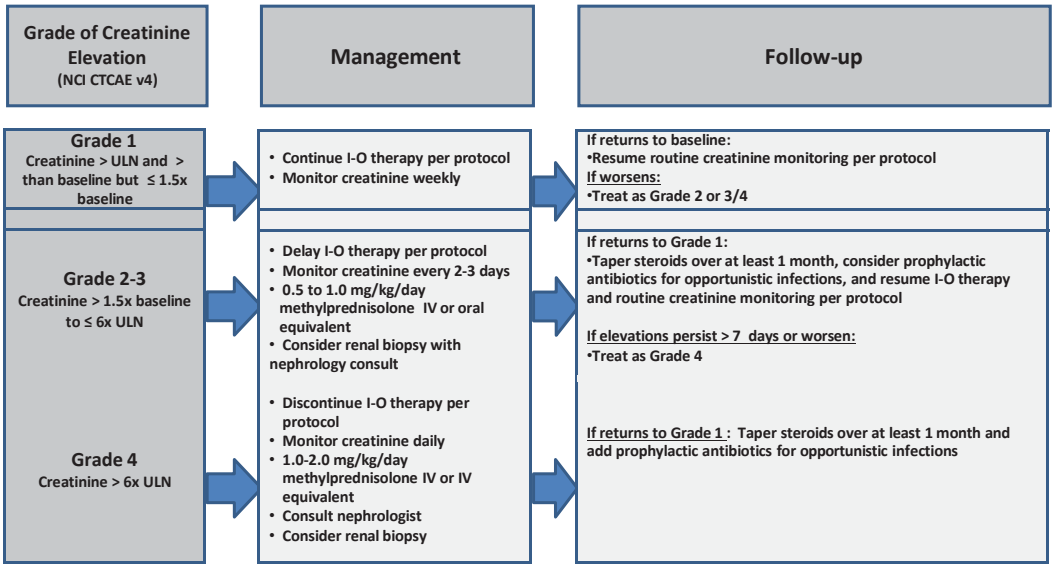
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

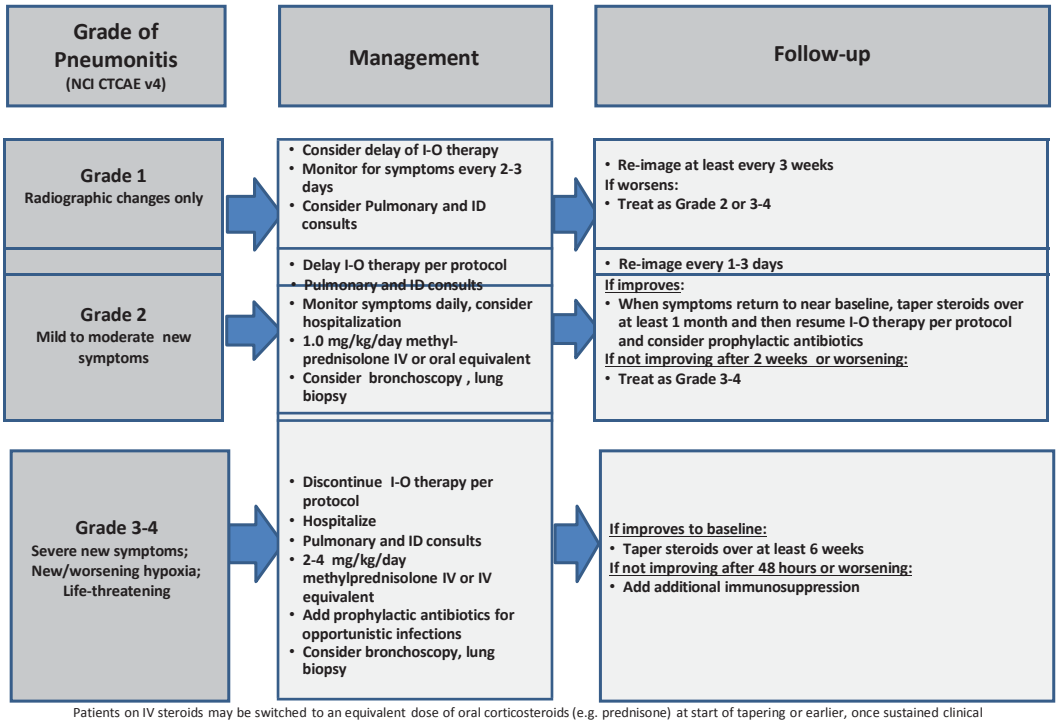
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

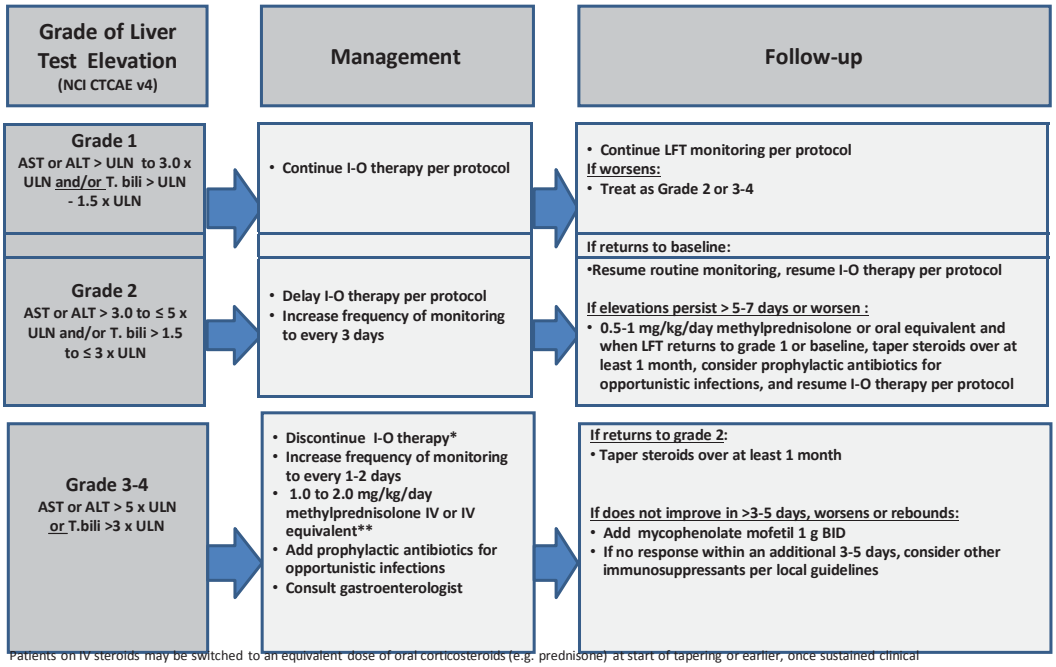
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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.



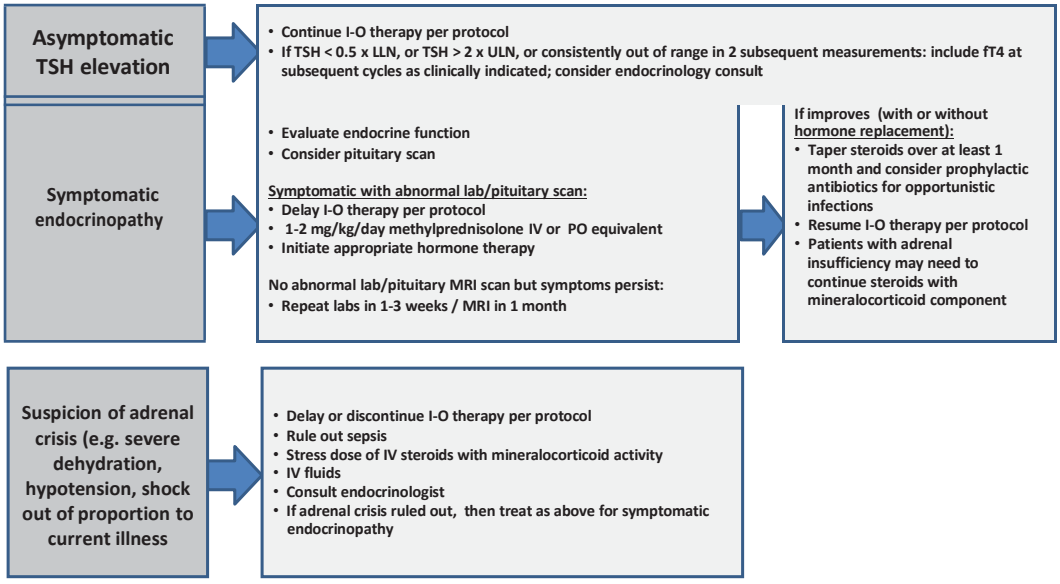
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Endocrinopathy Management Algorithm

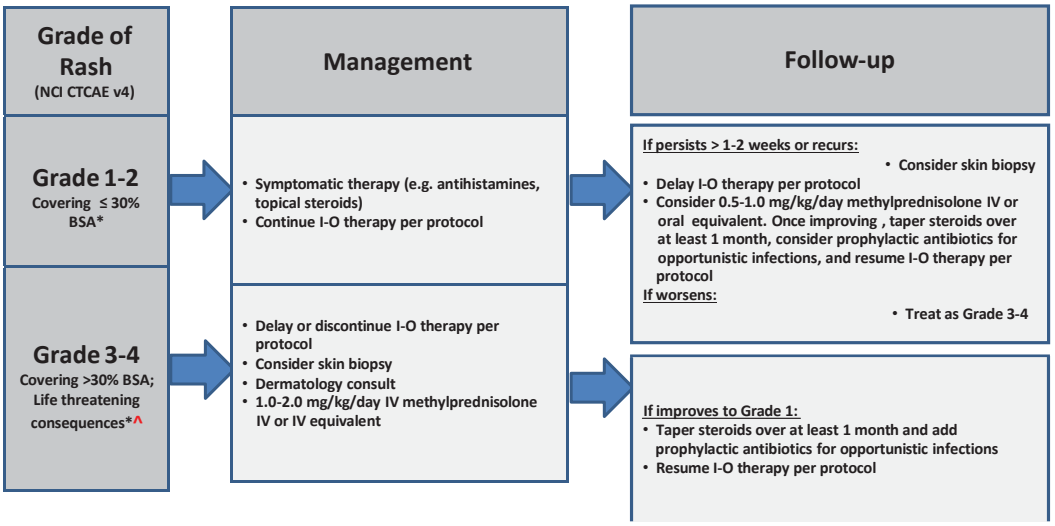
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

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

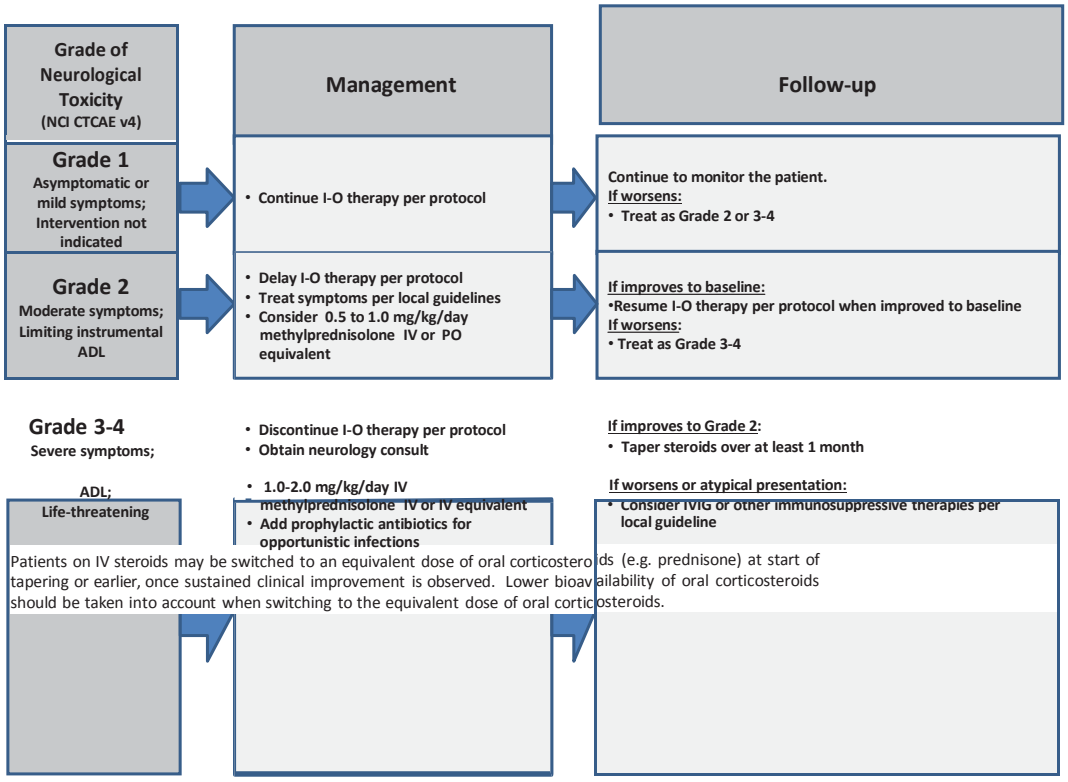


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

Appendix 2: Nivolumab Drug Ordering and Pharmacy Reference Material

Initial Orders

- *Following submission and approval of the required regulatory documents, a supply of nivolumab may be ordered from by completing a Drug Request Form provided by BMS for this specific trial.*
- *The initial order should be limited to the amount needed for two doses. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All drug products will be shipped by courier in a temperature-controlled container. It is possible that sites may have more than one nivolumab clinical study ongoing at the same time. It is imperative that only drug product designated for this protocol number be used for this study.*
- *Pharmacy supplies not provided by BMS: Empty IV bags/containers, approved diluents, In-line filters and infusion tubing*

Re-Supply

- *Drug re-supply request form should be submitted electronically at least 7 business days before the expected delivery date. Deliveries will be made Tuesday through Friday.*
- *When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose, and that shipments may take 14 business days from receipt of request. Drug is not patient-specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.*

Drug Excursions

- *Drug excursions should be reported immediately to BMS on the form provided with the study-specific drug order form*

Please refer to the most recent version of the nivolumab Investigator Brochure for additional information to be included as per institutional or regulatory standards.

TABLE 3: Product Information

Product Description:(Other names = MDX-1106, ONO-4538, anti-PD-1

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Nivolumab (BMS-936558-01)* Injection drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL	100 mg/Vial (10 mg/mL).	Carton of 5 or 10 vials	10-cc Type 1 flint glass vials stoppered with butyl stoppers and sealed with aluminum seals.	Clear to opalescent, colorless to pale yellow liquid. May contain particles	**BMS-936558-01 Injection** must be stored at 2 to 8 degrees C (36 to 46 degrees F) and protected from light and freezing