Study Title: An Open-Label, Single Arm Phase II Study of Nivolumab in Combination with Ipilimumab in Subjects with Advanced Neuroendocrine Tumors

Johns Hopkins Protocol #: J17156 / IRB00151698

BMS Protocol #: CA209-9JL

Principal Investigator: Christine L. Hann, MD, PhD
Associate Professor of Oncology
Johns Hopkins University School of Medicine
201 N. Broadway, Room 8123
Baltimore, MD 21287
Phone: (410) 502-0678
Fax: (410) 614-9334
Email: chann1@jhmi.edu

Lead UAD Study Coordinator & Lead Regulatory: Amanda Barnes, BS, CCRP
Clinical Research Program Specialist
201 N. Broadway, Suite 8120
Baltimore, MD 21287
Phone: (410) 502-8737
Email: abarne13@jhmi.edu

Lead UAD Research Nurse: Joanne Riemer, RN
CO Sr. Research Nurse III
201 N. Broadway, Suite 8120
Phone: (443) 287-4114
Email: Jriemer3@jhmi.edu

IND #: 136301

IND Sponsor: Julie R. Brahmer, MD

Supplied Agents:

Nivolumab (BMS-936558)
Ipilimumab (NSC #732442)

Protocol Type / Version # / Version Date: Original/ Version 1/ December 22, 2016
Revision/ Version 2/ March 31, 2017
Revision/ Version 3/July 28, 2017

Revision/ Version 3.1/August 14, 2017
Revision/ Version 3.2/September 1, 2017
Revision/ Version 3.3/November 17, 2017
Revision/ Version 4.0/ April 26, 2019
Revision/ Version 4.1/ July 10, 2019
Revision/ Version 4.2/ July 16, 2019
Revision/ Version 4.3/ July 24, 2019
Revision/ Version 5.0/ September 25, 2019
Revision/ Version 6.0/ March 5, 2020
Revision/ Version 6.1/ April 17, 2020
Revision/ Version 6.2/ July 27, 2020
Revision/ Version 6.3/ May 25, 2021
Revision/ Version 6.4/ November 23, 2021

Table of Contents

1. OBJECTIVES

1.1 Primary Objective

1.1.1 To determine the objective response rate (ORR) of advanced, progressive, well-differentiated nonfunctional NET of the lung, pancreas or gastrointestinal (GI) tract treated with nivolumab plus ipilimumab.

1.2 Secondary Objectives

1.2.1 To assess safety and tolerability of nivolumab plus ipilimumab by quantification of treatment dose interruptions and characterization of toxicities of the combination of nivolumab and ipilimumab in subjects with advanced well-differentiated nonfunctional NET of the lung, pancreas or GI tract.

1.2.2 To assess efficacy via progression free survival (PFS) at 6 months, 12 and 24 months of the combination of nivolumab and ipilimumab in subjects with advanced well-differentiated nonfunctional NET of the lung, pancreas or GI tract.

1.2.3 To further assess efficacy via median PFS, disease control rate (DCR), duration of response (DOR) and overall survival (OS) of the combination of nivolumab and ipilimumab in subjects with advanced well-differentiated nonfunctional NET of the lung, pancreas or GI tract.

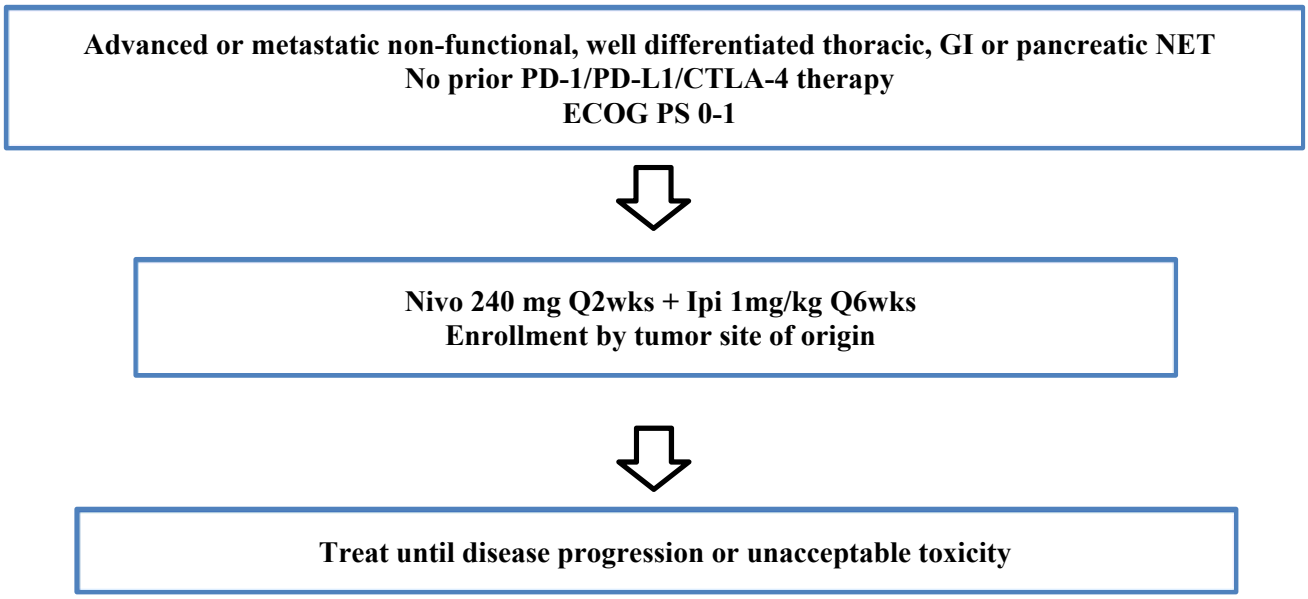
1.3 Exploratory Objectives

1.3.1 To assess immunogenicity, response characteristics, and predictors of toxicity of nivolumab in combination with ipilimumab by evaluating peripheral blood mononuclear cells (PBMCs), sera, plasma and tumor samples collected in treated subjects.

1.4 Study Design

The study population will include subjects with advanced thoracic, GI and pancreatic neuroendocrine tumors. We propose an open-label, single arm phase 2 study of nivolumab in combination with ipilimumab. All subjects will be assigned to receive Nivolumab: 240 mg IV q2 weeks plus ipilimumab: 1 mg/kg IV q6 weeks.

STUDY SCHEMA



2. BACKGROUND

2.1 Neuroendocrine tumors (NETs)

Well-differentiated neuroendocrine tumors (NETs), often referred to as carcinoid tumors, are a heterogeneous group of malignancies originating in neuroendocrine cells throughout the body(1). They are anatomically, functionally and histopathologically distinguished in an effort to optimize their care. Based on population-based registries, about 51% of NETs originate in the gastrointestinal (GI) tract , 27% in the lungs and 6% in the pancreas(1). Functional NETs cause carcinoid syndrome, due to hormonal hypersecretion. In the ~25% of patients with functional NETs, symptoms are often managed by a somatostatin analogue, such as octreotide or lanreotide. These medications have also been shown to delay tumor progression in advanced GI NETs (2, 3); as such they are commonly used in this disease setting, although are not FDA-approved for this indication. Nonfunctional NET (~70%) patients often develop symptoms due to tumor growth, such as intestinal obstruction, pain and bleeding for GI NETs, and asthma, chronic obstructive pulmonary disease and pneumonia for lung NETs (4-7). At presentation, 5-44% of patients with GI NET and 28% of patients with lung NET have advanced disease, and progression is typically associated with poor outcomes. Advanced or metastatic NETs, irrespective of function or histopathologic grade, are incurable with current treatment regimens.

Recently, everolimus has been FDA approved for the treatment of progressive, well-differentiated nonfunctional pancreatic, bronchopulmonary and GI NETs [Everolimus FDA]. The RADIANT trials were integral to this treatment approval. RADIANT-1 was a Phase II trial that evaluated Everolimus in patients with metastatic pancreatic NETs with

disease progression after cytotoxic chemotherapy; results revealed median progression free survival (mPFS) of 9.7-16.7 months as stratified by prior octreotide therapy (8). RADIANT-2 was a Phase III trial that evaluated Everolimus in advanced, non-functional NETs of the lung or GI tract which revealed mPFS of 11 months as compared to 3.9 months in the placebo group (9). RADIANT-3 was a Phase III trial that evaluated Everolimus in advanced, low-grade or intermediate grade pancreatic NET that revealed an 11 month mPFS compared to 4.6 months with placebo (10). RADIANT-4 was a Phase III trial that evaluated Everolimus in advanced, non-functional NETs of the lung or GI NET that reported an 11 month mPFS compared to a 3.9 month mPFS with placebo (11).

Thoracic NETs are histopathologically subdivided into typical carcinoid (TC) and atypical carcinoid (AC) tumors(12) and comprise 2.2% of lung cancers diagnosed in the US annually (7, 13). AC is the more common and more aggressive phenotype. There is a paucity of data regarding systemic therapy for advanced thoracic NET disease outside of the recently published RADIANT-4, and is based mainly on small retrospective series and subgroup analyses of predominant gastrointestinal neuroendocrine tumor clinical trials, leading to a lack of definitive data for systemic regimen recommendations outside of everolimus placebo (11). Forde et al., reported on a systematic analysis of thoracic NET patients at Johns Hopkins. The response rate to platinum plus etoposide chemotherapy for both advanced TC and AC was 23.5% (14).

GI NETs arise in the stomach, intestine, appendix, colon or rectum with an incidence of approximately 8000 cases annually in the US(15). The 5-yr OS rates in advanced well and moderately-differentiated neuroendocrine tumors range from 14-54% by anatomic location. The PROMID study showed an improvement in time to tumor progression in advanced midgut NET patients treated with octretotide LAR (long acting release (2) The recent advances of use of Everolimus in the RADIANT series have shown improved outcomes in some endpoints, leading to FDA approval, but does not frequently cause a response with tumor shrinkage (9, 11).

Pancreatic NETs account for <4% of all pancreatic cancers; about half of them are functional, benign tumors. Non-functional pancreatic NETs are more likely to be malignant. The CLARINET trial showing significant improvement in PFS in pancreatic NET patients treated with lanreotide vs. placebo (3). Based on the results of RADIANT-1 and RADIANT-3, everolimus is FDA-approved and commonly used in advanced pancreatic NET (8, 10). Sunitinib can also be used in this patient population (16).

2.2 PD-L1 Expression in NETs

PD-L1 staining in gastro-entero-pancreatic (GEP) NETs has been reported in by Kim et al.; of 24 foregut GEP-NETs, PD-L1 staining was observed in 21.9%, was significantly associated with high-grade classification and predicted for poorer survival (17). In a series of 66 GEP NETs, Pinato et al., reported a lower rate of PD-L1 staining (9%) but high PD-L2 (50%) (18). Fan et al., reported high PD-L1 (59%) and PD-1 (51%) staining in pulmonary NET tissue compared to cancer-adjacent tissue from 80 cases (19). Multivariate analyses revealed that expression of PD-L1 and PD-1 were negatively associated with survival time.

2.3 Nivolumab and Ipilimumab

Immunotherapeutic approaches have demonstrated clinical efficacy in several cancer types, including melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), head and neck cancer, bladder and hormone-refractory prostate cancer (20). Tumors modulate and evade the host immune response through a number of mechanisms, including down regulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands. T cell checkpoint regulators such as CTLA-4 and programmed death-1 (PD-1, CD279) are cell surface molecules that, when engaged by their cognate ligands, induce signaling cascades down-regulating T cell activation and proliferation. PD-1 and CTLA-4 are both co-inhibitory molecules, but evidence suggests that they use distinct mechanisms to limit T cell activation.

CTLA-4 mediated signals are inhibitory to T cell-dependent immune responses (21). Ipilimumab is a fully human monoclonal IgG1κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4 with B7 molecules on APCs, with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA 4/B7 interaction. Ipilimumab was approved by FDA for the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma.

Nivolumab (BMS-936558) is a fully human, IgG4 (kappa) isotype mAb that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response. In clinical trials, nivolumab has demonstrated activity in several tumor types, including melanoma, renal cell cancer (RCC), and NSCLC leading to widespread FDA-approval (22).

2.3.1 Combination treatment with nivolumab and ipilimumab

Multiple studies in several cancer types have evaluated the safety and efficacy of combination on nivolumab and ipilimumab. In both melanoma and non-small cell lung cancer (NSCLC) these data show that the combination of nivolumab and ipilimumab is well tolerated and associated with promising durable responses. In melanoma, CA209004 (MDC1106-04) was a phase Ib study in subjects with previously treated advanced melanoma. CA209069 and CA209067, a phase 2 and phase 3 studies, respectively, in treatment- naïve subjects with advanced melanoma (23, 24). This final study reported significantly improved PFS and ORR with the combination of nivolumab and ipilimumab versus ipilimumab alone in previously untreated melanoma. The mPFS was 6.9 mos in the nivolumab group compared with 11.5 mos in the nivolumab-plus-ipilimumab group.

CA209012, was an open-label, phase 1, multicohort study in treatment-naïve subjects with advanced NSCLC. In this study, multiple dosing regimens were explored. The final report included 78 patients randomly assigned to: 1) nivolumab 3mg/kg every 2 weeks plus ipilimumab 1mg/kg every 6 weeks or 2) nivolumab 3mg/kg every 2 weeks plus ipilimumab 1mg/kg every 12 weeks (25).

Grade 3-4 treatment related AEs were reported in 37% and 33% of subjects respectively, most commonly increased lipase, pneumonitis and adrenal insufficiency, colitis. Confirmed responses were reported in 47% in the ipilimumab 6 week cohort and 38% of the ipilimumab 12-week cohort.

2.4 Study Rationale

Subjects with progressive, non-functional advanced or metastatic thoracic, GI or pancreatic well-differentiated NETs are have few treatment options. The only FDA approved treatment regimen offers little response potential. In currently unpublished data with inhibitory immune checkpoint agents, patients with NET have shown promising clinical benefit. This therapy offers a novel approach to potentially provide long term benefit, but must be further explored.

The safety profile of nivolumab plus ipilimumab is characterized by immune-related toxicities, such as diarrhea, rash, pneumonitis, liver toxicity, and endocrinopathies (Nivolumab, Ipilimumab Investigator's Brochures). The frequencies and intensities of these events in the combination are variable and depend on the specific doses and schedule used. In the dosing schedules selected, these events were mostly low grade and manageable with the use of corticosteroids. Nivolumab and ipilimumab combination therapy has shown improved efficacy over either agent alone in melanoma.

2.4.1 Rationale for Single Arm Design

This study will use a single arm open-label design. The objective of this study is to evaluate the objective response rate of combination nivolumab and ipilimumab in advanced, well-differentiated neuroendocrine tumors. Durability of response, and PFS will also be described.

Response rates to everolimus, the only FDA approved regimen for this patient population, are well documented in the RADIANT trials. The ORR to everolimus in advanced, progressive low-intermediate grade pancreatic NET was 5% (vs. 2% with placebo), and 2% in advanced, progressive well-differentiated nonfunctional lung and GI NET (vs. 1% with placebo) (10, 11).

2.4.2 Rationale for Exploratory Correlative Studies

Exploratory correlative studies will be performed to evaluate immune system activation and for potential biomarker identification. The specific studies proposed include: 1) assessment of immune cell composition by IHC, gene expression profiling and cytokine production within the TME; 2) whole genome or exome sequencing to assess mutational load and potentially identify predictors of response or resistance; 3) plasma-based markers to correlate with response.

Paired pre-treatment and on treatment core biopsies will be mandatory for patients on the part 2 of this study and optional for patients on part 1. Biopsies at time of progression will be optional. Blood samples will be collected prior to treatment and during treatment as described in the study calendar.

2.4.2.1 Tissue studies

Tumor Microenvironment (TME) Analysis

Quantification, qualification and distribution of immune cell infiltrates may correlate to response and clinical outcome. The densities and distribution of effector T cells (Teff) including CD8, CD45RO, CXCR3 and CD69+ cells; expression of immune suppressive signals including PD-1, PD-L1, PD-L2, LAG3, TIM3, and IDO1; immune activation signals including CD137(4-1BB), 4-1BBL, OX40, OX40L, CD40, and CD40L on T cells and macrophages, and the expression of T helper cell differentiation markers including Tbet (for Th1), GATA3 (for Th2), ROR γ T (for Th17), and Foxp3 (for Treg) have been found to be clinically relevant (Lutz et al. 2014). The balance between Teff and regulatory T cell (Treg) function is an area of active study as well.

Quantitative Gene Expression

Evaluation of the balance between various immune cell types (Th1 vs. Th2; M1 vs M2; Teff vs. Treg) is imperative to understand the qualitative and quantitative effect of dual checkpoint blockade. The expression signatures of certain genes already found to be potentially linked to clinical benefit in other tumor types should be compared to the gene expression signatures found to correlate with response in NET patients. Intra-tumoral cytokine array analysis will also further describe the immunogenic tumor microenvironment.

Intratumoral Antigen Specific T cell Response

Tumor antigen-specific T cells that traffic into the tumor are the most relevant T cells to study when evaluating antitumor immune responses. Both peripheral (peripheral blood lymphocytes, (PBL)) and tumor-infiltrating lymphocytes (TIL) T-cell receptor (TCR) repertoires will identify T cells that expand following treatment. Peripheral and TIL TCR repertoire comparisons will be used to identify any T cell clones that are induced or expanded in PBL by combination treatment and also enriched in TIL. This data will be used to determine if T cells in PBL and TIL undergo clonal expansion following treatment, and if so, whether the T cell clones traffic to the carcinoid TME.

Whole exome sequencing to detect somatic alterations

Next generation sequencing may be performed to identify of genomic correlates of response and resistance. Nonsynonymous missense mutations identified will be used to predict mutant peptides and generate a neoantigen signature for each tumor using a computational pipeline we have developed. A separate targeted capture and sequencing analysis of the TCR will be performed to assess T cell clonality

2.4.2.2 Serum and Plasma Studies:

Various factors that may impact the immunomodulatory properties and efficacy of nivolumab and ipilimumab will be investigated in peripheral blood specimens

taken from all subjects prior to or during treatment. Data from these investigations will be evaluated for associations with response, survival, and/or safety (adverse event) data. Plasma samples will be obtained at baseline, on treatment and at progression.

Circulating Tumor DNA (ctDNA)
Non-invasive genomic approaches to determine somatic mutations that detect residual disease are being developed at our institution. Cancer-specific genomic alterations in circulating cell free DNA (ctDNA) are being evaluated for potential to assess ability to predict disease response or progression prior to conventional CT imaging. Peripheral tumor-specific mutations found following disease progression can be compared to the patient's genomic tumor profile to evaluate for potential matching resistance mutations.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Subjects with histologically confirmed advanced, progressive, well-differentiated nonfunctional NET of the pancreas, lung or gastrointestinal (GI) tract per the 8th International Association for the Study of Lung Cancer classification (IASLC) or the American Joint Committee on Cancer (AJCC) Staging Handbook, 7th edition. Progession must be documented over the prior 12 months.

3.1.2 Measurable disease by CT or MRI per RECIST 1.1 criteria (Appendix 3); radiographic tumor assessment performed within 28 days before treatment. Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site after the completion of radiation therapy.

3.1.3 Prior therapy, including everolimus, octreotide, surgery, chemoradiation, is all permitted after being properly noted. This prior therapy must have been completed at least 28 days prior to study enrollment.

3.1.4 Patients with lung NETs must have progressed after at least 1 line of therapy. Patients with GI NETs must have had at least 2 lines of prior therapy.

3.1.5 Subjects are to have tumor tissue sample available at central lab for PD -L1 IHC testing during the screening period. Subjects can initiate therapy before the result of IHC testing.

3.1.6 (Stage 2 only) Subjects must be willing to undergo 2 sets of core needle biopsies (pre-treatment and at 6-8 weeks on therapy) if there are lesions amenable to biopsy. Subjects without a lesion amendable to biopsy will still be permitted to enroll provided they have an archival tumor sample for PD-L1 IHC testing. An optional core biopsy will be requested at progression.

3.1.7 ECOG performance status ≤ 1 (see Appendix 1)

3.1.8 Prior palliative radiotherapy to non-CNS lesions must have been completed at least 2 weeks prior to treatment. Subjects with symptomatic tumor lesions at baseline that may require palliative radiotherapy within 4 weeks of first treatment are strongly encouraged to receive palliative radiotherapy prior to treatment.

3.1.9 Patients must have normal organ and marrow function as defined below:

- WBC	≥1,500/mcL
- absolute neutrophil count	≥1,000/mcL
- hemoglobin	≥ 8.0 g/dL
- platelets	≥75,000/mcL
- total bilirubin	≤ 1.5 x institutional ULN (patients with Gilbert's syndrome may have serum bilirubin ≤ 3 x ULN)
- AST/ALT	≤ 3 × institutional ULN (≤ 5 x ULN in the presence of liver metastases)
- creatinine	≤ 1.5 × institutional ULN or creatinine clearance (CrCl) ≥ 40 mL/min (if using the Cockcroft-Gault formula below): *Female*: $CrCl = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$ *Male:* $CrCl = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$

3.1.10 Age ≥18 years of age

3.1.11 Patients must have recovered from adverse events due to prior treatment to ≤ grade 1, except for alopecia and sensory neuropathy ≤ grade 2.

3.1.12 Patients must be able to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Subjects with poorly differentiated or small cell carcinoma histology

3.2.2 Subjects with disease that is amenable to surgical resection.

3.2.3 Subjects with history of or active symptoms of carcinoid or hormonal syndromes are permitted if symptoms are controlled with a somatostatin analog.

3.2.4 Hepatic intra-arterial embolization or peptide receptor radionuclide therapy (PRRT) within 4-8 weeks; cryoablation, radiofrequency ablation or trans-arterial chemoembolization of hepatic metastases within ≤ 4 weeks of study enrollment

3.2.5 Subjects with symptomatic untreated CNS metastases are excluded.

3.2.5.1 Subjects are eligible if CNS metastases are asymptomatic or adequately treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to first treatment.

3.2.5.2 In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent) for at least 2 weeks prior to first treatment.

3.2.6 Subjects with carcinomatous meningitis

3.2.7 Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before first treatment.

3.2.8 Pregnant or breast-feeding women

3.2.9 Women of child-bearing potential, who are biologically able to conceive, and not employing two forms of highly effective contraception. Highly effective contraception must be used throughout the trial and up to 8 weeks after the last dose of study drug (e.g. male condom with spermicidal; diaphragm with spermicide; intra-uterine device). Women of child-bearing potential, defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months), must have a negative serum pregnancy test ≤ 14 days prior to starting study drug.

3.2.10 Subjects with an active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

3.2.11 Other active malignancy requiring concurrent intervention.

3.2.12 Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first treatment. Inhaled or topical steroids, and adrenal replacement steroid 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

3.2.13 Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.

3.2.14 Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

3.2.15 Known medical condition that, in the investigator's opinion, would increase the risk associated with study participation or study drug administration or interferes with the interpretation of safety results.

3.2.16 Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways

3.2.17 Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection

3.2.18 History of allergy or hypersensitivity to study drug components

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. TREATMENT PLAN

4.1 Agent Administration

4.1.1 Study Treatment: all subjects will receive the following:

Table 1: Regimen Description

REGIMEN DESCRIPTION					
Agent	***Premedication***	***Dose***	***Route***	***Frequency***	***Cycle Length***
Nivolumab	No prophylactic pre-medication will be given unless indicated by previous experience in an individual subject per **Section 5.5**	240 mg	IV over 30 minutes*	Every 2 weeks	6 weeks (42 days)
Ipilimumab	No prophylactic pre-medication will be given unless indicated by previous experience in an individual subject per **Section 5.5**	1 mg/kg	IV over 30 minutes*	Every 6 weeks	

*Infusion times are approximate (+/- 10 min) and may be adjusted based on subject tolerability.

4.1.2 Cycle length

One cycle is defined as 42 days.

4.1.3 Dosing

Nivolumab and ipilimumab will be administered on the same day. Separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The second infusion will always be ipilimumab and will start no sooner than 30 minutes after completion of the nivolumab infusion. Subjects who require small volumes may infuse over < 60 minutes but no less than 20 minutes.

Nivolumab and ipilimumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution.

Dosing calculations for ipilimumab should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the prior dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. There will be no dose modifications allowed.

Subjects may be dosed with nivolumab no less than 12 days from the previous dose. There are no premedications recommended.

Doses of nivolumab and/or ipilimumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment. For more details, see **Section 5.2** (dose delays).

4.2 General Concomitant Medication and Supportive Care Guidelines

4.2.1 Prohibited and/or Restricted Treatments

4.2.1.1 Systemic immunosuppressive agents are prohibited during the study, unless they are utilized to treat an adverse event. Allopurinol to prevent gout flares is allowed.

4.2.1.2 Concurrent administration of any anti-cancer therapies (investigational or approved) is also prohibited with the exception of subjects in the survival period of the study. This includes somatostatin analogues.

4.2.1.3 Any medicinal herbal preparation unless prescribed by the treating physician. All concomitant medications including prescribed medicinal herbal preparations must be documented.

4.2.1.4 G-CSF (granulocyte-colony stimulating factor) will be permitted. However, the use of these agents is allowed as per their respective label indications/institutional guidelines to treat neutropenia that occurs on study. G-CSF must not be used for the treatment of cancer or for any primary prophylaxis while on study.

4.2.1.5 Any non-oncology live viral vaccine therapies used for the prevention of infectious diseases within 12 weeks prior to study drug is prohibited. The use of the inactivated seasonal influenza vaccine will be permitted on study without restriction.

4.2.1.6 Alcohol consumption while on study is strongly discouraged due to the potential to confound interpretation of hepatotoxic events.

4.2.1.7 Routine use of acetaminophen use is strongly discouraged

4.2.2 Permitted Therapy

4.2.2.1 Regular concomitant use of bisphosphonates and RANK-L inhibitors for prevention or reduction of skeletal-related events in patients with bone metastases is allowed if initiated prior to first dose of study therapy.

4.2.2.2 Subjects are permitted the use of anti-emetic medications (with the exception of dexamethasone and/or other systemically administered steroids) at the treating physician's discretion.

4.2.2.3 Subjects are permitted the use of full-dose anti-coagulation (i.e. warfarin, enoxaparin, rivaroxaban, etc.) at the treating physician's discretion.

4.2.2.4 Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).

4.2.2.5 Adrenal replacement steroid doses $\leq$ 10 mg daily prednisone are permitted.

4.2.2.6 A brief (less than 2 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.

4.2.2.7 Palliative local therapy, including palliative radiation therapy- and palliative surgical resection, is permitted prior to discontinuation of study treatment for subjects who do not have evidence of overall clinical or radiographic progression per RECIST 1.1.

Subjects requiring palliative local therapy should be evaluated for objective evidence of disease progression prior to the initiation of such therapy, particularly if the most recent tumor assessment was more than 4 weeks prior to the start of local therapy. If progression per RECISTv1.1 is identified on any tumor assessments prior to the initiation of palliative local therapy, then subjects must either discontinue study drug treatment or they must meet criteria to continue treatment beyond progression (**Section 5.3**) in order to resume immunotherapy after palliative local therapy.

The potential for overlapping toxicities with radiotherapy and nivolumab plus ipilimumab currently is not known; however, anecdotal data suggests that it is tolerable. As concurrent radiotherapy and nivolumab /ipilimumab have not been formally evaluated, in cases where palliative radiotherapy is required for a tumor lesion, then nivolumab /ipilimumab 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 or ipilimumab.

4.3 Dosing Criteria

To account for drug quantities supplied within each vial and to minimize wasted unused investigational drug, pharmacy may adjust the calculated drug dose +/- 10% for each patient. All patients dosed within these parameters will be considered dosed at full dose.

4.4 Definition of an Overdose for this Protocol

Patients dosed > 10% above their calculated drug dose will be considered over-dosed.

4.5 Contraception, Use in Pregnancy, Use in Nursing

See **Section 3.2.8**

4.6 Duration of Therapy

Treatment will be continued for up to 2 years or discontinuation due to toxicity, withdrawal of consent, or study closure. Subjects may discontinue either drug and remain on the other agent if certain circumstances are met (**Section 5.2.7**).

4.7 Off Study/Safety Follow-up Visit

The post-treatment follow-up begins when the decision to discontinue a subject from all treatment is made.

Subjects who discontinue treatment for reasons other than disease progression will continue to have tumor assessments (if clinically feasible) according to the schedule in **Section 9** until progression is confirmed.

Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after the last dose of study medication.

4.8 Duration of Follow Up

After completion of the first two follow-up visits, subjects will be followed every 3 months for survival until death, withdrawal of consent, or study closure. Survival follow-up visits may be performed by phone or email contact or office visit (**Section 9**). At that time of this request, each subject will be contacted to determine their survival status unless the subject had withdrawn consent for all contact.

Study assessments are to be collected as outlined in study calendar in **Section 9**.

4.9 Criteria for Removal from Study Treatment

Patients will be removed from the study for any of the following reasons:

- Disease progression as defined in **Section 11**.
- Patient non-compliance or request to withdraw from all therapy and follow up. Patients who withdraw from therapy only may continue to be followed for study specified follow up secondary endpoints.
- Pregnancy.
- Unacceptable toxicity that in the treating physician's discretion places the patient at risk

for future significant harm.

- Intercurrent illness that prevents continuation of therapy or follow up.

4.10 Treatment Beyond Progression

Treatment beyond initial investigator-assessed RECIST 1.1-defined progression is permitted if the subject has investigator-assessed clinical benefit and is tolerating treatment, as specified in **Section 6.3**

4.11 Duration of Study

The analysis of the primary endpoint ORR will be performed six months after the last subject's first treatment. Additional survival follow-up may continue for up to 5 years from the primary analysis. The study will end once survival follow-up has concluded.

5. DOSING REDUCTIONS/DOSE DELAYS

5.1 Dose Reductions

Recommended Dose Modifications for OPDIVO (Nivolumab)

Adverse Reaction	Severity	Dose Modification
Colitis	Grade 2 diarrhea or colitis	Withhold dose[a]
	Grade 3 diarrhea or colitis	Withhold dose[a] when administered as a single agent
		Permanently discontinue when administered with ipilimumab
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose[a]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis	AST or ALT > 3 - 5 x ULN or total bilirubin > 1.5 - 3 x ULN	Withhold dose[a]
	AST or ALT > 5 ULN or total bilirubin > 3 x ULN	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose[a]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose[a]
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose[a]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine > 1.5 – 6 x ULN	Withhold dose[a]
	Serum creatinine > 6 x ULN	Permanently discontinue

Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose[a]
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose[a]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction: First occurrence Recurrence of same Grade 3 adverse reactions	Withhold dose[a] Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Grade 3 myocarditis	Permanently discontinue
	Requirement for ≥ 10 mg per day prednisone or equivalent for > 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

* Toxicity was graded per NCI CTCAE v4.

[a] Resume treatment when adverse reaction improves to Grade 0 or 1.

Recommended Treatment Modifications for Immune-Mediated Adverse Reactions of YERVOY (Ipilimumab)

Target/Organ System	Adverse Reaction	Treatment Modification
Endocrine	Symptomatic endocrinopathy	Withhold dose Resume in patients with complete or partial resolution of adverse reactions (Grade 0 to 1) and who are receiving < 7.5 mg prednisone or equivalent per day.
	• Symptomatic reactions lasting 6 weeks or longer • Inability to reduce corticosteroid dose to < 7.5 mg prednisone or equivalent per day	Permanently discontinue
Ophthalmologic	Grade 2 through 4 reactions • not improving to Grade 1 within 2 weeks while receiving topical therapy or • requiring systemic treatment	Permanently discontinue
All Other	Grade 2	Withhold dose Resume in patients with complete or partial resolution of adverse reactions (Grade 0 to 1) and who are receiving < 7.5 mg prednisone or equivalent per day.

	• Grade 2 reactions lasting 6 weeks or longer • Inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day • Grade 3 or 4	Permanently discontinue

The NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 will be used to grade adverse events.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study.

Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

Due to the prolonged half-life associated with monoclonal antibodies, no dose reductions of either study agent are planned.

5.2 Dosing Delays

- In addition to the dose modifications in 6.1, any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects that have drug-related toxicities that meet the criteria for dose delay, should have both drugs (ipilimumab and Nivolumab) delayed until retreatment criteria are met.

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

5.2.1 Criteria for Permanent Discontinuation of Nivolumab and Ipilimumab

- In addition to the treatment discontinuation parameters in 6.1, any treatment-related event that leads to delay in dosing lasting >12 weeks from ipilimumab dosing OR > 6 weeks from nivolumab dosing requires discontinuation, with the following exceptions:
    - Dosing delays within those time frames to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
    - Dosing delays lasting >12 weeks of ipilimumab or > 6 weeks of nivolumab from the previous dose that occur for non-drug-related reasons may be allowed.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued dosing.

Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

5.2.2 Criteria to Resume Nivolumab Dosing

- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the IND Sponsor.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.
- Any Grade 3 drug-related laboratory abnormality (except lymphopenia, AST, ALT, or total bilirubin or asymptotic lipase or amylase). Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require does delay. The IND Sponsor should be consulted prior to resuming nivolumab in such subjects.

5.2.3 Criteria to Resume Ipilimumab Dosing

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT or total bilirubin.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the IND Sponsor.
- Treatment-related dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation.
- Ipilimumab may not be resumed sooner than 6 weeks (+/- 5days) after the prior ipilimumab dose.
- In general, subjects who meet criteria to resume ipilimumab will also have met criteria to resume nivolumab, so it should be feasible to synchronize dosing of both drugs when resuming ipilimumab. In order to facilitate this, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted +/- 5 day window, as long as consecutive nivolumab doses are given at least 12 days apart.
- Any Grade 3 drug-related laboratory abnormality (except lymphopenia, AST, ALT, or total bilirubin or asymptotic lipase or amylase). Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require does delay. The IND Sponsor should be consulted prior to resuming nivolumab in such subjects.

5.2.4 Rescheduling:

Nivolumab may be delayed until the next planned ipilimumab dose if the next ipilimumab dose is scheduled within the next 12 days. This will permit periodic ipilimumab dosing to be synchronized with nivolumab dosing.

Ipilimumab should be dosed at the specified interval regardless of any delays in intervening nivolumab doses. However, in order to maintain periodic synchronized dosing of ipilimumab and nivolumab, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted +/- 5 day window, as long as consecutive nivolumab doses are given at least 12 days apart. Ipilimumab may be delayed

beyond the 5 day window if needed to synchronize with the next nivolumab dose.

If an ipilimumab dose is delayed beyond 6 weeks from the prior ipilimumab dose, then subsequent ipilimumab doses should rescheduled to maintain the 6 week interval between consecutive ipilimumab doses.

5.2.5 Continuing Nivolumab or Ipilimumab as monotherapy:

The assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of ipilimumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for nivolumab or ipilimumab (Drug 1) but not for the other (Drug 2), treatment with Drug 1 may continue if Drug 2 is discontinued.

5.3 Treatment Beyond Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD (26).

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

- Investigator-assessed clinical benefit and no rapid disease progression
- Subject is tolerating study treatment
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)

The decision to continue treatment beyond initial investigator-assessed progression should be discussed with the IND Sponsor and documented in the study records. A follow-up scan should be performed within six (6) weeks +/- 5 days of original PD to determine whether there has been a decrease in the tumor size, or continued progression of disease. Subsequent scans should be performed every twelve (12) weeks until further progression is determined.

If the 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 on study calendar (**Section 9**).

For the subjects who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. Nivolumab and ipilimumab treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which

must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

5.4 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity.

Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

The above algorithms are found in both the Nivolumab and Ipilimumab Investigator Brochures, as well as in **Appendix 2**.

5.5 Management of Nivolumab or Ipilimumab Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the IND Sponsor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

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

5.5.1 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 325 to 1000 mg at least 30 minutes before additional nivolumab or ipilimumab administrations.

5.5.2 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 or ipilimumab 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 or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).

For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg should be administered at least 30 minutes before nivolumab or ipilimumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

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

Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

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

6. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

This study will use the descriptions and grading scales found in the revised National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 for adverse event reporting that can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Information about all AEs, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded, and followed as appropriate.

All AEs and SAEs experienced by subjects will be collected and reported from the first dose of nivolumab, throughout the study, and will only be followed for 4 weeks unless related to the investigational agent. All SAEs will be collected for 100 days after the last dose of nivolumab. Subjects who have an ongoing AE related to the study procedures and/or medication(s) may continue to be periodically contacted by a member of the study staff until the event is resolved or determined to be irreversible by the investigator.

Laboratory abnormalities: Laboratory abnormalities present at the screening visit will be recorded as pre-treatment signs and symptoms. After study treatment administration, all grade 3 and 4 clinical laboratory results that represent an increase in severity from baseline will be reported as adverse events. A grade 1 or 2 clinical laboratory abnormality should be

6.1 Definitions

6.1.1 Adverse Event

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

BMS will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320.

6.1.2 Serious Adverse Event

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

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Potential drug induced liver injury (DILI) is also considered an important medical event. (See **Section 6.5.3** for the definition of potential DILI.)
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

- Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See **Section 6.5.4** for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see **Section 6.5** for reporting details).

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

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

6.2 Relationship

The relationship of an AE to the administration of the study drug is to be assessed by the principal investigator according to the following definitions:

- No (unrelated, not related, no relation): The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.
- Yes (related): The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The following factors should also be considered:

- The temporal sequence from study drug administration - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication - The other medications the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study drug - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

6.3 Expectedness

Expected adverse events are those which are expected to occur, according to previous clinical experience, and are listed in the Investigator Brochure. The expectedness of an SAE will be assessed by the Principal Investigator.

Unexpected adverse event: An adverse event which varies in nature, intensity, or frequency from information on the investigational drug/agent provided in the Investigator's Brochure, package insert, or safety reports. Any adverse event that is not included in the informed consent is considered "unexpected".

Expected (known) adverse event: An adverse event which has been reported in the Investigator's Brochure. An adverse event is considered "expected," only if it is included in the informed consent document as a risk.

6.4 Handling of Expedited Safety Reports

In accordance with local regulations, BMS and the IND Sponsor will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).

- Other important findings which may be reported by the as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (e.g., animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.
- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
- In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

6.5 Reporting

6.5.1 General

All SAEs, regardless of causality to study drug and/or administration device, will be reported promptly to the Principal Investigator (e-mail: Chann1@jhmi.edu and Lead Study Coordinator), within 24 hours of recognition of the event. If this falls on a weekend or holiday, an email notification is acceptable but must be followed by an SAE reporting form on the next business day.

The principal investigator will notify the appropriate regulatory agencies of any serious adverse event due to any cause during the course of this investigation. These include the Johns Hopkins Cancer Center Data and Safety Monitoring Committee, and the Johns Hopkins Medical Institutional Review Board (JHM-IRB) of The Johns Hopkins Medical Institutions. The required reporting time period is 3 days for fatal events, and 10 days for all other events.

For studies conducted under an Investigator IND, 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 or similar form. It MUST include the institutional **AND** BMS study ID [per study Agreement]

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/

The Lead Study Coordinator shall fax or e-mail the SAEs to BMS at:
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
SAE Email Address: Worldwide.Safety@BMS.com

6.5.2 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 SAEs.

6.5.3 Potential Drug Induced Liver Injury (DILI)

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

1) ALT or AST elevation > 3 times the institutional upper limit of normal (ULN)
   AND
2) Total bilirubin > 2 times the institutional ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
   AND
3) No other immediately apparent possible causes of AST/ALT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.5.4 Pregnancy Reporting

Although pregnancy and lactation are not considered AEs, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial or within 23 weeks days of completing the trial. This also includes the pregnancy of a male subject's female partner who has provided written consent to provide information regarding pregnancy that occurs during the trial or within 31 weeks days of completing the trial. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as SAEs (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported to the IND sponsor and BMS.

6.5.5 Institutional Review Board (IRB)

All serious adverse events will be reported to the IRB per institutional standards within 3 business days of recognition of the adverse event if the event is related and expected, related and unexpected, or related and fatal or life-threatening due to administration of the investigational product. Follow-up information will be submitted to the IRB as soon as relevant information is available.

6.5.6 Food and Drug Administration (FDA)

All reporting to the FDA will be completed by the IND Sponsor (Julie R. Brahmer, MD, MSc; fax: (410) 550-54457; e-mail: brahmju@jhmi.edu)

6.5.3.1 Expedited IND Safety Reports:

7 Calendar-Day Telephone or Fax Report: The Sponsor is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the investigational agent. Such reports are to be telephoned or faxed (301-796-9845) to the FDA within 7 calendar days of

first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

15 Calendar-Day Written Report: The Sponsor is required to notify the FDA of any serious adverse event that is unexpected and possibly related to the investigational agent in a written IND Safety Report.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA within 15 calendar days of first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

6.5.3.2 IND Annual Reports

In accordance with the regulation 21 CFR § 312.33, the Sponsor shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the adverse events and progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.33 for a list of the elements required for the annual report. All IND annual reports will be submitted to the FDA by the Sponsor-Investigator.

6.6 Adverse Events of Interest

6.6.1 Definition of immune-mediated adverse events (IMAEs)

Immune-mediated AEs are specific events (that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis) for which subjects received immunosuppressive medication for treatment of the event, with the exception of endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which are included regardless of treatment since these events are often managed without immunosuppression.

IMAEs include events, regardless of causality, occurring within 100 days of the last dose.

Table 2 below provides a summary of the IMAEs category and their respective Preferred Terms (PTs).

Table 2: Preferred Terms Included in Analysis of IMAEs to Support Warnings and Precautions

IMAE Category	**Preferred Terms included under IMAE Category**
Pneumonitis	Pneumonitis, Interstitial lung disease
Diarrhea/Colitis	Diarrhea, Colitis, Enterocolitis

Table 2: Preferred Terms Included in Analysis of IMAEs to Support Warnings and Precautions	
IMAE Category	**Preferred Terms included under IMAE Category**
Hepatitis	Hepatotoxicity, Hepatitis, Hepatitis acute, Autoimmune Hepatitis, AST increased, ALT increased, Bilirubin increased, ALP increased
Adrenal insufficiency	Adrenal Insufficiency
Hypothyroidism/Thyroiditis	Hypothyroidism, Thyroiditis, Thyroiditis acute (collapsed with thyroiditis for frequency), Autoimmune thyroiditis (collapsed with thyroiditis for frequency)
Hyperthyroidism	Hyperthyroidism
Hypophysitis	Hypophysitis
Diabetes mellitus	Diabetes mellitus, Diabetic Ketoacidosis
Nephritis and renal dysfunction	Nephritis, Nephritis allergic, Tubulointerstitial nephritis

7. PHARMACEUTICAL INFORMATION

7.1 Product Information Table

Table 3:	**Product Description**				
Product Description and Dosage Form	**Potency**	**Primary Packaging (Volume)/ Label Type**	**Secondary Packaging (Qty) /Label Type**	**Appearance**	**Storage Conditions (per label)**
Nivolumab[a]	100 mg (10 mg/mL)	10 mL vial	5 vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect form light and freezing
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	40 mL vial	5 vials per carton/Open-label	Clear, colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing.

*Nivolumab may be labeled as BMS-936558-01 Solution for Injection

7.2 Nivolumab

7.2.1 Agent Accountability

The IND sponsor or the Sponsor's representative shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply,

storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

7.2.2 Mode of Action

Nivolumab is a fully human monoclonal immunoglobulin (Ig) G4 antibody that binds to the PD-1 cell surface membrane receptor, a negative regulatory molecule expressed by activated T and B lymphocytes. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T cell responses to both foreign antigens as well as self-antigens.

7.2.3 Description

Nivolumab Injection, 100 mg/vial (10 mg/mL) is a clear to opalescent, colorless to pale, yellow liquid; light (few) particulates may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriamine pentacetic acid and polysorbate 80 (Tween™ 80), pH 6.0 and includes a 0.7-mL overfill to account for vial, needle, and syringe (VNS) holdup. It is supplied in 10-cc type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals.

7.2.4 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements. Open-label cartons will be supplied with 5 vials per carton.

7.2.5 Preparation

Nivolumab injection should infused undiluted (10 mg/mL) or be diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. The total volume of infusion must not exceed 160 mL. 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. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves. Detailed instructions on the preparation of nivolumab for administration will be provided in the Procedures Manual.

7.2.6 Storage

Clinical supplies must be stored in a secure, limited-access location. Nivolumab vials must be stored at a temperature of 2°C to 8°C and should be protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

7.2.7 Stability

The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°-8°C, 36°-46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

7.2.8 Route of Administration

Nivolumab is to be administered as a 30 minute IV infusion, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified dose. 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.

7.2.9 Subject Care Implications

The overall safety experience with nivolumab is based on experience in approximately 1500 subjects as either a monotherapy or in combination with other therapeutics. In general for monotherapy, the safety profile is similar across tumor types. The one exception is pulmonary inflammation AEs which may be numerically greater in subjects with NSCLC possibly because in some cases it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes. The most frequently reported treatment related AE is fatigue which is almost always low grade.

Most related AEs are thought to be due to the effects of inflammatory cells on specific tissues. A variety of PTs have been used to describe similar kinds of organ-related AEs with the result being that AE frequency tables organized by PTs can lead to underestimation of the frequency of similar kinds of organ-related AEs. To address this issue, select AE categories were created. Select AE categories group together the most common and impactful PTs by organ category. These categories include the following: pulmonary, gastrointestinal, hepatic, dermatologic, endocrine, and renal AEs. It is also useful to consider the management of nivolumab-related AEs by organ category as the diagnostic workup often requires excluding other potential diagnoses and when appropriate instituting specific management principles as outlined in this protocol and Appendix 2.

7.2.10 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from BMS or designee, the amount dispensed to, and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. 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. BMS will be notified of all destruction of

study drug.

7.3 Ipilimumab

7.3.1 Agent Accountability

The IND sponsor or the Sponsor's representative shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

7.3.2 Mode of Action

Ipilimumab is a fully human immunoglobulin ($IgG_1\kappa$) that is specific for the CTLA-4 antigen expressed on a subset of activated T-cells. CTLA-4 interaction with the B7 molecule, one of its ligands expressed on professional antigen presenting cells, can down-regulate T-cell response. Ipilimumab is, thought to act by blocking the interaction of CTLA-4 with the B7 ligand, resulting in a blockade of the inhibitory effect of T-cell activation. The CTLA-4/B7 creates the interaction.

7.3.3 Description

Ipilimumab injection, 200 mg/40 mL (5 mg/mL), is formulated as a clear to slightly opalescent, colorless to pale yellow, sterile, nonpyrogenic, single-use, isotonic aqueous solution that may contain particles. Ipilimumab injection, 200 mg/40 mL, is supplied in 50-cc Type I flint glass vials, stoppered with gray butyl stoppers and sealed with aluminum seals. The drug product is formulated at a concentration of 5 mg/mL at a pH of 7.0. in sodium chloride, TRIS-hydrochloride, diethylenetriamine pentacetic acid, mannitol, polysorbate 80 (Tween™ 80), and water, and includes a 0.7-mL overfill to account for vial, needle, and syringe (VNS) holdup.

7.3.4 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements. Open-label cartons will be supplied with 5 vials per carton.

7.3.5 Preparation

The drug can be diluted with 0.9% normal saline or 5% Dextrose Injection to concentrations between 1 mg/mL and 4 mg/mL. It is not to be administered as an IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents. Recommended safety measures for preparation and handling of ipilimumab include laboratory coats and gloves. Detailed instructions on the preparation of ipilimumab for administration will be provided in the Pharmacy Manual.

7.3.6 Storage

Clinical supplies must be stored in a secure, limited-access location. Ipilimumab vials must be stored at a temperature of 2°C to 8°C and should be protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

7.3.7 Stability

The administration of ipilimumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored in IV infusion bags (PVC, non-PVC/non-DEHP) or glass infusion containers under refrigeration conditions (2°-8°C, 36°-46°F) with protection from light and from freezing or at temperature/room light (20-25°C, 68-77°F) for up to 24 hours. This would include any time in transit and the total time for infusion.

7.3.8 Route of Administration

Ipilimumab is to be administered as a 30 minute IV infusion, using a volumetric pump with a 0.2 to 1.2 micron in-line filter at the protocol-specified dose. 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 (approximately 30-50mL).

7.3.9 Subject Care Implications

The overall safety experience with ipilimumab is based on experience in approximately 19,500 subjects as either a monotherapy or in combination with other therapeutics. The safety profile of ipilimumab is generally consistent across these trials with a) the majority adverse events (AEs) being inflammatory in nature, which is consistent with the proposed mechanism of action of ipilimumab; b) the same types of such immune-mediated events in the gastrointestinal (GI) tract (eg, diarrhea and colitis), skin (eg, pruritus and rash), liver (eg, transaminase elevations), endocrine glands (including the thyroid, pituitary and adrenal glands, manifested by hypothyroidism, hypophysitis with hypopituitarism, or adrenal insufficiency, respectively), and nervous system (eg, motor neuropathy with or without sensory neuropathy) being reported; and c) most of these events being manageable using symptomatic or immuno-suppressive therapy as recommended through detailed diagnosis and management guidelines as outlined in this protocol and **Appendix 2**.

7.3.10 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from BMS or designee, the amount dispensed to, and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. 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. BMS will be notified of all destruction of study drug.

8. Correlative Studies collection and handling

Correlative studies will be performed to evaluate immune system activation and for potential biomarker identification. A variety of factors that could potentially predict clinical response to nivolumab and ipilimumab will be investigated in tumor specimens and in peripheral blood obtained prior to first dose of study drug, on study and potentially progression, as outlined in the **Study Calendar**. Baseline and on treatment tumor assessment of response, immune reactivity and gene expression will be performed on all patients during the second stage of this trial. Plasma samples will be collected on all patients for ctDNA and immunogenicity studies.

8.1 Tumor Tissue Studies

Archival or recently collected FFPE tumor tissue (in the form of paraffin embedded block or unstained slides, as described in **Section 8.1.1**) collected prior to enrollment, will be requested for all patients participating in this study.

Pre-treatment and on-treatment biopsies of patients on Stage 2 will also be collected as per the **Study Calendar**. A biopsy sample of subjects who experience progression at any time while on treatment is optional, but strongly encouraged for the purposes of understanding mechanisms of resistance to therapy.

Several analyses will be completed and are described briefly below.

8.1.1 Tumor Tissue Handling

A formalin-fixed, paraffin-embedded (FFPE) tumor tissue block (preferred) or 10 unstained slides of tumor sample (archival or recent) for biomarker evaluation must be available and submitted for correlative studies in order for a subject to be enrolled as described in the **Laboratory Manual**. If fewer than 10 slides are available, the Principal Investigator may still approve enrollment of subjects upon review of the case. Excisional, incisional or core needle biopsies are strongly preferred, however samples collected via endobronchial ultrasound (EBUS) guided biopsy (using a 22g needle or larger) and transbronchial lung biopsy (TBLB) are acceptable. In certain cases, the Principal Investigator may approve submission of samples collected via other methods.

If a new biopsy is taken (i.e. no archival tissue is available), up to 5 core biopsies are recommended at baseline. Otherwise, up to 4 core biopsies should be collected at baseline and at other time points per the Study Calendar. An assessment of biopsy quality by a pathologist is encouraged at the time of the procedure. The tumor tissue that is obtained from these biopsies will be allocated to FFPE, fresh frozen and for RNA later as described in the **Laboratory Manual**. The investigator, in consultation with the radiology staff, must determine the degree of risk associated with the procedure and find it acceptable. Biopsies may be done with local anesthesia or conscious sedation. Institutional guidelines for the safe performance of biopsies should be followed. Excisional biopsies may be performed to obtain tumor biopsy samples. Invasive procedures that require general anesthesia should not be performed to obtain a biopsy specimen. However, if a surgical procedure is performed for a clinical indication, excess tumor tissue may be used for research purposes with the consent of the subject.

A pathology report should be provided with tumor samples.

8.1.2 Tumor microenvironment (TME) analysis by IHC

Immunohistochemistry (IHC) will be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within FFPE tumor tissue before, during and after exposure to therapy. These IHC analyses will include, but not necessarily be limited to, the following markers relevant to the PD-L1/PD-1 and CTLA-4 pathways will be performed on FFPE slides of treated patients: densities and distribution of effector T cells (Teff) including CD8, CD45RO, CXCR3 and CD69+ cells, expression of immune suppressive signals including PD-1, PD-L1, PD-L2, LAG3, TIM3, and IDO1, immune activation signals including CD137(4-1BB), 4-1BBL, OX40, OX40L, CD40, and CD40L on T cells and macrophages, and the expression of T helper cell differentiation markers including Tbet (for Th1), GATA3 (for Th2), ROR γ T (for Th17), and Foxp3 (for Treg) will be assessed as previously described (Lutz et al. 2014).

Quantification of IHC on immune markers will be conducted by Aperio's Immune Analysis Software Program as described previously (Lutz et al. 2014) and will be supervised by an on-site pathologist. A specific evaluation will be whether the combination of nivolumab and ipilimumab collaboratively suppress the Treg pathway and enhance effector T cell infiltration.

8.1.3 Genomic assessment and gene expression

DNA or RNA extracted from tumor provided may be used for whole genome or exome sequencing to identify mutational load and transcriptional expression. Sequencing of pre- and on-treatment biopsies may be compared to evaluate for predictors of response or resistance. Gene expression will be quantified by nanostring assays to assess whether the combination of nivolumab and ipilimumab influences immune cells within the tumor microenvironment. The gene expression signatures listed in **Table 4** and the signature found to correlate with responses to the study treatment will be evaluated.

Next-generation sequencing may be used to examine the TCR repertoire in peripheral blood lymphocytes (PBL) and TIL from FFPE sections from the pre- or on-treatment biopsies, to identify if TCR clonal expansion is taking place. TCR repertoires in PBL vs TIL may also be compared from the same patients to identify any T cell clones that are induced or expanded in PBL by combination treatment and also enriched in TIL. This data may be used to determine if T cells in PBL and TIL undergo clonal expansion following treatment, and if so, whether the T cell clones traffic to the carcinoid TME.

Nonsynonymous missense mutations identified may be used to predict mutant peptides and generate a neoantigen signature for each tumor using a computational pipeline we have developed. A separate targeted capture and sequencing analysis of the T cell receptor may be performed to assess T cell clonality.

Table 4. Immune-Related Gene Expression Signatures (27).

IFN γ	Expanded Immune	TCR Signaling	De Novo
IDO1 CXCL10 CXCL9 HLA-DRA STAT1 IFNG	CD3D NKG7 IDO1 HLA-E CIITA CXCR6 CD3E LAG3 CCL5 TAGAP GZMK CXCL10 CD2 STAT1 HLA-DRA GZMB CXCL13 IL2RG EOSMES	CD27 TIGIT CD8A CD3D GRAP2 LCK PTPRCAP CD4 CCL5 IL2RB IKZF3 CD3G CD74	IKZF3 SAMHD1 CD38 HLA-DPB1 TIGIT CRTAM CD27 IL2RB CD8A AMICA1 TARP CXCL9 CD74 CD3D HLA-C LY9 CD3G GPR18 CD4 HLA-B IL18 HLA-DRA IGJ CX3CR1 B2M IRF1 CXCL10 IGSF6 BST2 SIT1 FASLG PTPN7 LCK

IFN interferon; TCR = T-cell receptor

8.1.4 Cytokine arrays

If fresh frozen biopsy specimens are available, they may be used in a cytokine array analysis by a well-established protocol in the Zheng Lab using a commercially available cytokine protein array (R&D).

8.2 Serum and Plasma Marker Studies

Various factors may impact the immunomodulatory properties and efficacy of nivolumab and ipilimumab will be investigated in peripheral blood specimens taken from all subjects prior to or during treatment. Data from these investigations will be evaluated for associations with response, survival, and/or safety (adverse event) data. Plasma samples will be obtained at time-points indicated in the **Study Calendar (Section 9)**. Non-invasive genomic approaches may be used in order to determine somatic mutations that detect residual disease in the patient's circulation.

Several analyses will be completed and are described briefly below.

8.2.1 circulating tumor DNA (ctDNA)

Using blood samples collected prospectively after initiation of study treatment, measurements of cancer-specific genomic alterations in ctDNA may be analyzed to assess if they can predict disease progression prior to conventional CT imaging. Comparison of detection of somatic mutations in ctDNA and the sensitivity and specificity of the plasma analysis approach for detection of somatic alterations may be evaluated by comparison of the mutation data from the plasma to the sequence information obtained from analysis of the matching tumor samples.

Tumor- specific mutations found in the circulation after disease progression may be compared to the genomic profile of the recurrent tumors and the presence of matching resistance mutations in ctDNA may be confirmed.

8.2.2 Peripheral Blood Mononuclear Cells (PBMCs)

PBMCs taken at time points on **Study Calendar (Section 9)** may be analyzed by flow cytometry or other methods (e.g., ELIspot) to assess immune cell activity.

8.2.3 Serum Soluble Factors

To understand the prevalence of circulating proteins and the impact they may have on the clinical activity of nivolumab and ipilimumab, the protein concentrations of a panel of cytokines, chemokines, and other relevant immunomodulatory, serum-soluble factors (e.g., soluble PD-L1) may be investigated at baseline and during treatment.

8.2.4 Single Nucleotide Polymorphisms (SNPs)

Whole blood will be collected from all subjects prior to treatment to generate genomic DNA for SNP analyses and serve as a reference for tumor mutational profiling. These analyses will focus on SNPs within genes associated with PD-1 and other immunoregulatory signaling pathways to determine if natural variation within those genes is associated with response to nivolumab and/or with AEs during treatment.

9. STUDY CALENDAR

	Screening (0-28 day pre-dose)	Cycle 1			Cycle 2, 3, etc.			End of Treatment (EOT) Assessment[n]	Follow-Up Visit 30 days post EOT/ 90 days post EOT	Survival/ FU visits[l]
		D1	D15	D29	D1	D15	D29			
CLINICAL ASSESSMENTS										
Informed consent	X									
Inclusion/Exclusion Criteria	X									
Demographics	X									
Medical history	X									
Physical exam[o]	X	X	X	X	X	X	X	X	X	
Vital signs, Height (baseline), Weight, O_2 Sat	X	X	X	X	X	X	X	X		
Height (baseline), Weight, O_2 Sat	X	X	X	X	X	X	X	X		
ECOG performance status	X	X	X	X	X	X	X	X	X	
CBC w/diff, plts	X	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X	X	
Serum chemistry[a]	X	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X	X	
Hepatitis Panel[b]	X									
TSH, Free T4, Free T3[c]	X				X			X		
EKG	X	X[f]								
Urinalysis	X									
Pregnancy Test (WOCBP only)[d]	X	X			X					
Tumor Assessment/Imaging[e]	X				X				X[m]	
TREATMENT										
Nivolumab		X[g]	X[g]	X[g]	X[g]	X[g]	X[g]			
Ipilimumab		X[g]			X[g]					
CORRELATIVE STUDIES										
Archival Tumor[h]	X									
Fresh Tumor Biopsy[i] (Second stage only)	X				X					
Plasma for Immunogenecity Studies (Second stage only)[j]		X	X	X	X				X	
Plasma for ctDNA (Second stage only)[j]		X	X	X	X				X	
OTHER ASSESSMENTS										
Concurrent meds	X	X	X	X	X	X	X	X	X	
Symptom/Toxicity Assessment[j]	X	X	X	X	X	X	X	X	X	

Survival Status/Subsequent Therapy										X

a: LDH, AST, ALT, ALP, T. bili, BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, phosphate, glucose, amylase, lipase, TSH, Free T4, Free T3, within 14 days prior to first dose.
b: Hep B/C (HBV sAg, HCV antibody or HCV RNA), within 28 days prior to first dose.
c: Thyroid Function Testing to be evaluated every 6 weeks
d: A serum or urine pregnancy testing is required prior to study enrollment/registration, also within 24 hours prior to D1 (and extension to 72 hours may be granted if unable to obtain within 24 hrs). Must be reassessed every 4 weeks.
e: CT scan of the chest and other relevant sites as well as MRI brain with gadolinium (or CT scan brain with contrast if MRI is contraindicated) will be performed ≤ 4 weeks prior to the start of therapy. For subsequent scans, may be done within +/- 7 days of intended visit.
f. Within 72 hrs prior to dosing to include CBC w/ differential, AST, ALT, ALP, T. bili, BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, LDH, phosphate, glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3). **Note:** C1D1 labs do not need to be repeated if they were performed within 14 days of dosing.
g. All treatments may be performed +/- 2 days of the intended treatment administration dates schedule for all cycles.
h: Recent sample or archival obtained. One (1) formalin-fixed paraffin embedded tumor tissue block or a minimum of 10 unstained tumor tissue sections are acceptable.
i: Mandatory fresh tissue will be collected for biomarker studies at baseline and on treatment (week 6-8) for patients enrolled in the second stage of the study.
j: Immunogenecity samples should be collected just before the administration of the first drug (preferably within 30 minutes).
k: Adverse event evaluation as per Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
l: Survival follow-up may be done via phone call for survival status and subsequent therapy
m: CT if the subject came off study for reasons other than PD
n: EOT assessments do not need to be repeated if performed within 14 days
o. In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in-person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participant's risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

10. DATA REPORTING / REGULATORY REQUIREMENTS

10.1 Data Management

Interim analysis of toxicity, outcome and ongoing scientific investigations will be performed at least annually by the Sidney Kimmel Comprehensive Cancer Center Data Safety Monitoring Board (SKCCC DSMB). The SKCCC DSMB Recommendation letter will state the timeline for the next required review. The SKCCC DSMB will review aspects of this trial that are outlined in the responsibilities section of the Data and Safety Monitoring Board (DSMB) Guidance. If the committee decides that amendments should be made to this trial, recommendations will be made in writing to the Study Principal Investigator. The study team will submit modifications to the IRB within 60 days of receipt from the DSMB. The Associate Director of Clinical Research, will arbitrate any disagreements between the DSMB and the study Principal Investigator. These changes may include early termination of accrual if deemed appropriate.

The SKCCC Compliance Monitoring Program will provide external monitoring for JHU-

affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring.

10.2 Safety Meetings

Scheduled meetings will take place at least on a monthly basis with the frequency dependent on the rate of subject accrual and will include the principal investigator, study coordinator(s), data manager(s), sub-investigators (as appropriate), collaborators (as appropriate), and biostatisticians (as appropriate) involved with the conduct of the protocol. During these meetings matters related to the following will be discussed: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for objectives.

10.3 Monitoring

The PI shall internally monitor the progress of the trial, including review and confirmation of all safety/treatment-related outcomes, response assessments, safety reports and/or any related source documentation.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect

For the purposes of this study, patients should be re-evaluated every 6 weeks. In addition to a baseline scan, confirmatory scans will also be obtained 6 (not less than 4) weeks following initial documentation of an objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Tumor lesions that are situated in a previously irradiated area may only be considered measurable if they are growing on pre-treatment imaging.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

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

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of Best Overall Response

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

Table 5: For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation
CR	Non-CR/ Non-PD	No	PR	≥4 wks. Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/ Non-PD/ not evaluated	No	PR	
SD	Non-CR/	No	SD	Documented at least once

	Non-PD/ not evaluated			≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

11.1.5 Duration of Response

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

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

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

11.1.6 Progression-Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11.1.7 Response Review

There is no independent or central review of the radiology assessments planned for this trial. It is the responsibility of each Principal Investigator to ensure that tumor assessments are reported per the RECIST 1.1 criteria outlined above.

12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

This is an open label, phase II clinical trial of nivolumab and ipilimumab in subjects with advanced, well-differentiated nonfunctional NET of the pancreas, lung or gastrointestinal (GI) tract. The primary endpoint is ORR defined as RECIST 1.1 partial response (PR) or complete response (CR).

Simon two-stage design (28) was used to evaluate the primary endpoint, with details as described in section 12.2.

12.2 Sample Size/Accrual Rate

The optimal two-stage design to test the null hypothesis that $P \leq 0.050$ versus the alternative that $P \geq 0.150$ has an expected sample size of 29.51 and a probability of early termination of 0.736. If the regimen is actually not effective, there is a 0.097 probability of concluding that it is (the target for this value was 0.100). If the regimen is actually effective, there is a 0.199 probability of concluding that it is not (the target for this value was 0.200). After testing the drug on 20 patients in the first stage, the trial will be terminated if 1 or fewer respond. If the trial goes on to the second stage, a total of 56 patients will be studied. If the total number responding is less than or equal to 4, the regimen is rejected.

Assuming a 15% screening failure rate, it is estimated that approximately 64 subjects will be enrolled in order to achieve 56 treated subjects.

12.3 Analysis and Summary of Endpoints

12.3.1 Primary Endpoints

The primary endpoint is ORR (per RECIST v1.1 criteria) among all treated subjects. All treated subjects is defined as all subjects who received at least one complete dose of nivolumab and ipilimumab. ORR is defined as the number of subjects with a best overall response (BOR) of confirmed CR or PR, divided by the number of treated subjects.

BOR is defined as the best response designation, recorded between baseline and the date of objectively documented progression per RECIST 1.1 or the date of initiation of palliative local therapy or the date of initiation of subsequent anticancer therapy,

whichever occurs first. For subjects without documented progression or palliative local therapy or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. For subjects who continue treatment beyond progression, the BOR will be determined based on response designations recorded up to the time of the initial RECIST 1.1-defined progression.

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of >= 4 weeks later.

Further characterization of the response will include time to objective response (time from first dosing date to first CR or PR) and depth of response (maximum tumor shrinkage in target lesions).

The analysis of the primary endpoint ORR will be performed six months after the last subject's first treatment.

12.3.2 Secondary Endpoints

Secondary endpoints include safety and tolerability of study treatment; PFS, DCR, DOR and OS in the all treated subjects population.

Safety and tolerability objectives will be measured by the incidence of adverse events, serious events, deaths, and laboratory abnormalities. Dates and duration of study treatment delays will also be described.

PFS is defined as the time from first dose to the date of the first documented tumor progression (per RECIST 1.1), or death due to any cause. Clinical deterioration in the absence of radiographic evidence is not considered progression for purposes of determining PFS. 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 first dosing date. Subjects who started any palliative local therapy or subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the palliative local therapy or subsequent anti-cancer therapy, whichever procedure occurred first. PFS rate at 6 months is defined as the rate from Kaplan-Meier estimate 6 months after first dosing date.

Disease control rate is defined as the number of subjects with a BOR (per RECIST v1.1 criteria) of confirmed CR or PR or SD (stable disease), divided by the number of treated subjects.

Duration of response will be summarized among subjects with objective response in and is measured from the time at which the criteria for objective response are first met until the date of a progression event (according to the definition of PFS). Subjects with objective response who does not have a progression event will be censored at the same time they were censored under the definition of PFS.

Overall survival is defined as the time from first dosing date to the date of death. A subject who has not died will be censored at last known alive date. The overall

survival rate at 6 months is the rate from Kaplan-Meier estimate 6 months after dosing date.

12.3.3 Exploratory Endpoint(s)

All biomarker measures, T-cell response, immune phenotype and inflammatory response evaluation will be listed, tabulated, and where appropriate plotted. Tumor tissue IHC, functional analysis and genomic analysis will be listed, tabulated and where appropriate plotted. For the continuous data, summary statistics and the corresponding changes (or percent changes) from baseline will be provided at each time-point of assessment as well as for the changes from baseline to the peak value. Categorical data will be summarized as appropriate. Subjects will be grouped by dose level or clinical response. As this is an open-label study without a control treatment, statistical analyses will be done to aid in the understanding of the results. The associations of biomarkers with dose, clinical response, or time-to-event endpoints may be assessed using the appropriate statistical methods (analysis of variance [ANOVA], categorical, or survival model), depending on the endpoint. Correlation of baseline expression levels or changes in expression levels with response or time-to-event endpoints will identify potential responsive (or resistant) subgroups.

The ctDNA and IMG objectives will be measured from serum concentration. Response characteristics will be summarized descriptively and are further described in the statistical analysis plan.

Other exploratory endpoints are discussed in details in the statistical analysis plan.

12.4 Efficacy Analyses

12.4.1 Methods for Primary Endpoints

Among all treated subjects, the ORR will be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using Clopper-Pearson method. The null hypothesis will be rejected if the 2-sided 95% CI lower bound for the ORR radiology assessed estimate is greater than 15%.

To further characterize the response: time to objective response, depth of response and BOR by response category will be summarized using descriptive statistics.

12.4.2 Methods for Secondary Endpoints

Secondary endpoints will be evaluated based on the treated population.

Time to event distribution will be estimated using Kaplan Meier techniques. This will be done for PFS. Median PFS along with 95% CI will be constructed based on a log-log transformed CI for the survivor function. Rates at fixed time points (e.g., PFS at 6 and 12 months) will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function.

The DCR will be summarized for subjects who achieve confirmed PR or CR using the Kaplan-Meier (KM) product-limit method. Median values of DCR, along with

95% CI will be constructed based on a log-log transformed CI for the survivor function.

The DOR will be summarized for subjects who achieve confirmed PR or CR using the Kaplan-Meier (KM) product-limit method. Median values of DOR, along with 95% CI will be constructed based on a log-log transformed CI for the survivor function.

12.4.3 Safety Analyses

Safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All on-study AEs, drug-related AEs, SAEs and drug-related SAEs, AEs and drug-related AEs leading to drug discontinuation will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term, based on MedDRA terminology. On-study lab parameters including hematology, coagulation, chemistry, liver function and renal function will be summarized using worst grade per NCI CTCAE v 4.0 criteria.

Frequency, management and resolution of IMAEs will be analyzed. A tabular summary of the incidence of overall IMAEs (by preferred term) and serious IMAEs will be performed. A descriptive analysis of IMAEs including time-to-onset, severity, duration, action taken with the study drug, dosing delays of the study drug, corticosteroid details, re-challenge information and outcome of the AE will be individually characterized by IMAE category (**Section 6.6.1**).

REFERENCES

1. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26:3063-72.
2. Rinke A, Muller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol. 2009;27:4656-63.
3. Caplin ME, Pavel M, Cwikla JB, Phan AT, Raderer M, Sedlackova E, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014;371:224-33.
4. Oberg KE. Gastrointestinal neuroendocrine tumors. Ann Oncol. 2010;21 Suppl 7:vii72-80.
5. Modlin IM, Moss SF, Chung DC, Jensen RT, Snyderwine E. Priorities for improving the management of gastroenteropancreatic neuroendocrine tumors. J Natl Cancer Inst. 2008;100:1282-9.
6. Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD. Current status of gastrointestinal carcinoids. Gastroenterology. 2005;128:1717-51.
7. Wolin EM. Challenges in the Diagnosis and Management of Well-Differentiated Neuroendocrine Tumors of the Lung (Typical and Atypical Carcinoid): Current Status and Future Considerations. The oncologist. 2015;20:1123-31.
8. Yao JC, Lombard-Bohas C, Baudin E, Kvols LK, Rougier P, Ruszniewski P, et al. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. J Clin Oncol. 2010;28:69-76.
9. Pavel ME, Hainsworth JD, Baudin E, Peeters M, Horsch D, Winkler RE, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet. 2011;378:2005-12.
10. Yao JC, Pavel M, Phan AT, Kulke MH, Hoosen S, St Peter J, et al. Chromogranin A and neuron-specific enolase as prognostic markers in patients with advanced pNET treated with everolimus. The Journal of clinical endocrinology and metabolism. 2011;96:3741-9.
11. Yao JC, Pavel M, Lombard-Bohas C, Van Cutsem E, Voi M, Brandt U, et al. Everolimus for the Treatment of Advanced Pancreatic Neuroendocrine Tumors: Overall Survival and Circulating Biomarkers From the Randomized, Phase III RADIANT-3 Study. J Clin Oncol. 2016.
12. Hendifar AE, Marchevsky AM, Tuli R. Neuroendocrine Tumors of the Lung: Current Challenges and Advances in the Diagnosis and Management of Well-Differentiated Disease. J Thorac Oncol. 2016.
13. Hendifar AE, Marchevsky AM, Tuli R. Neuroendocrine Tumors of the Lung: Current Challenges and Advances in the Diagnosis and Management of Well-Differentiated Disease. J Thorac Oncol. 2017;12:425-36.
14. Forde PM, Hooker CM, Boikos SA, Petrini I, Giaccone G, Rudin CM, et al. Systemic therapy, clinical outcomes, and overall survival in locally advanced or metastatic pulmonary carcinoid: a brief report. J Thorac Oncol. 2014;9:414-8.
15. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67:7-30.
16. Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011;364:501-13.
17. Kim ST, Ha SY, Lee S, Ahn S, Lee J, Park SH, et al. The Impact of PD-L1 Expression in

Patients with Metastatic GEP-NETs. Journal of Cancer. 2016;7:484-9.
18. Pinato D, Brown M, White S, Zhang H, Toloue S, Dina R, et al. Programmed cell death (PD-1) ligands expression in gastro-entero-pancreatic neuroendocrine tumours (GEP-NETs): relationship with angiogenesis and clinical outcome. ASCO Annual Meeting; 20162016.
19. Fan Y, Ma K, Wang C, Ning J, Hu Y, Dong D, et al. Prognostic value of PD-L1 and PD-1 expression in pulmonary neuroendocrine tumors. OncoTargets and therapy. 2016;9:6075-82.
20. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature. 2011;480:480-9.
21. Postow MA, Harding J, Wolchok JD. Targeting immune checkpoints: releasing the restraints on anti-tumor immunity for patients with melanoma. Cancer journal. 2012;18:153-9.
22. Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol. 2010;28:3167-75.
23. Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med. 2015;372:2006-17.
24. Larkin J, Hodi FS, Wolchok JD. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015;373:1270-1.
25. Hellmann MD, Rizvi NA, Goldman JW, Gettinger SN, Borghaei H, Brahmer JR, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. The lancet oncology. 2017;18:31-41.
26. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009;15:7412-20.
27. Shankaran S, Muro K, Bang Y-J, Geva R, Catenacci D, Gupta S, et al. Correlation of gene expression signatures and clinical outcomes in patients with advanced gastric cancer treated with pembrolizumab (MK-3475). J Clin Oncol 33, 2015 (suppl; abstr 3026). 2015:Abstract 3026.
28. Simon R. Optimal two-stage designs for phase II clinical trials. Controlled clinical trials. 1989;10:1-10.

APPENDIX 1 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS [a]	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g.,, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

[a] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649-655.

APPENDIX 2 MANAGEMENT ALGORITHMS FOR IMMUNO-ONCOLOGY AGENTS

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

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

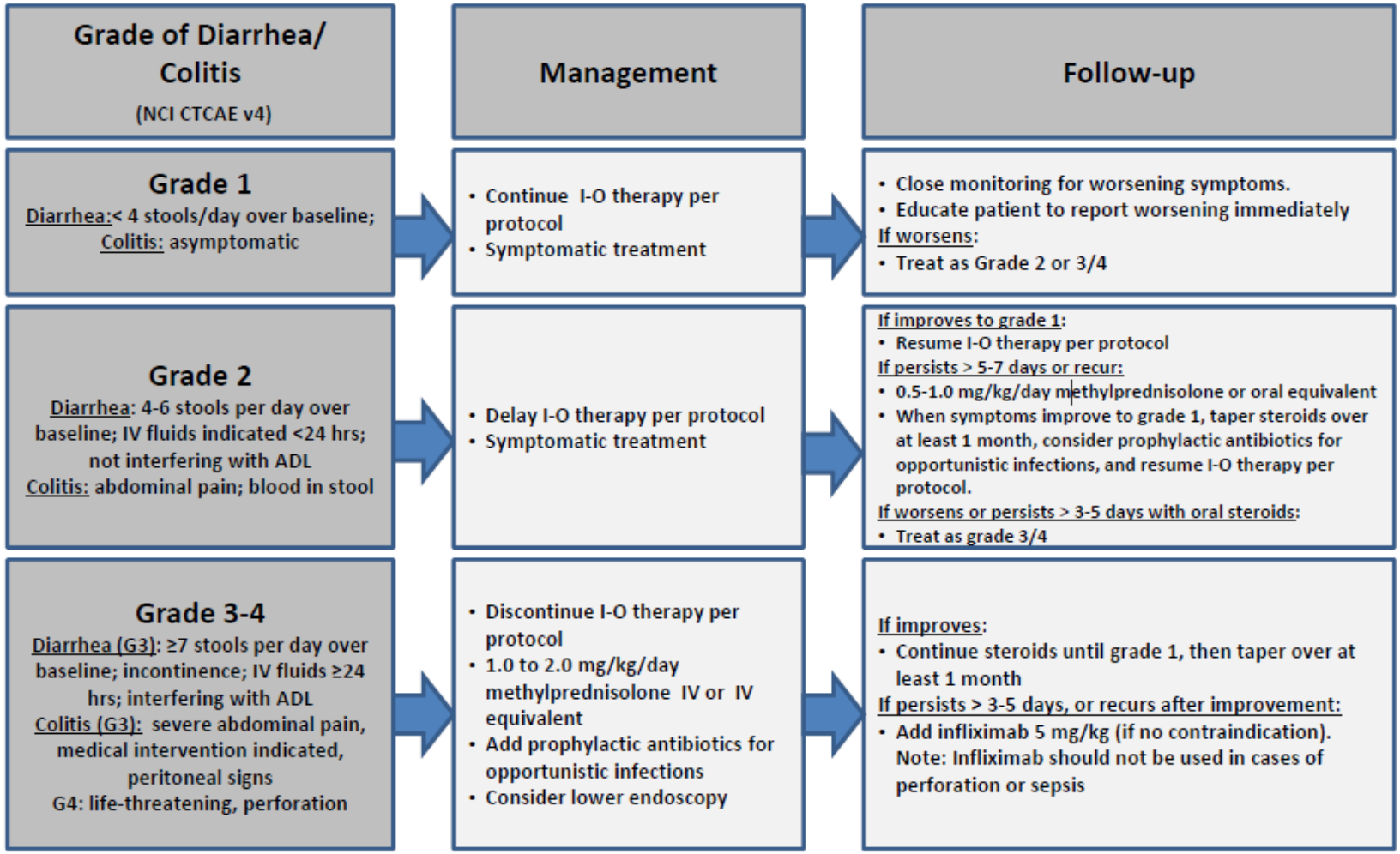
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

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

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

GI Adverse Event Management Algorithm

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

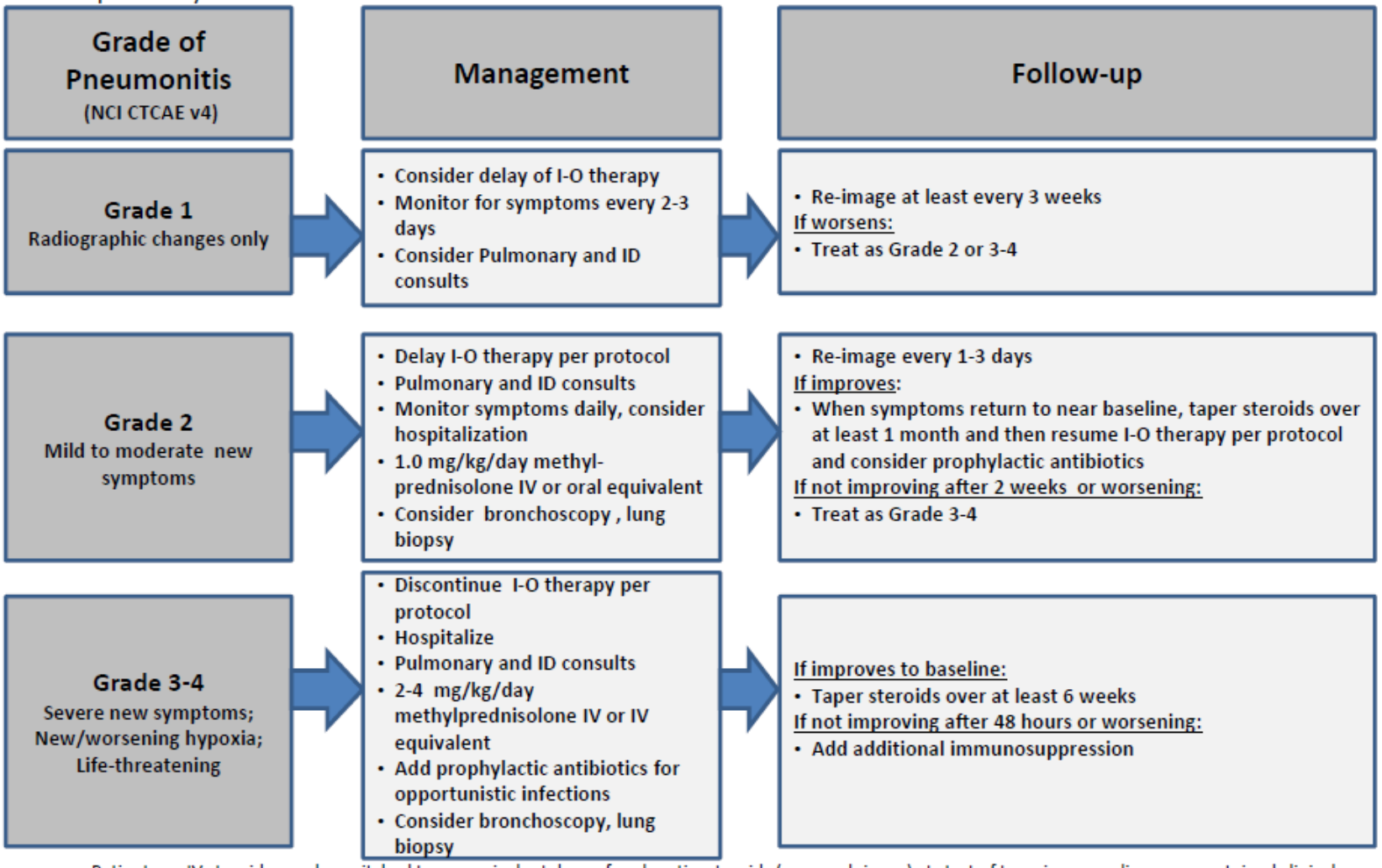


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

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.

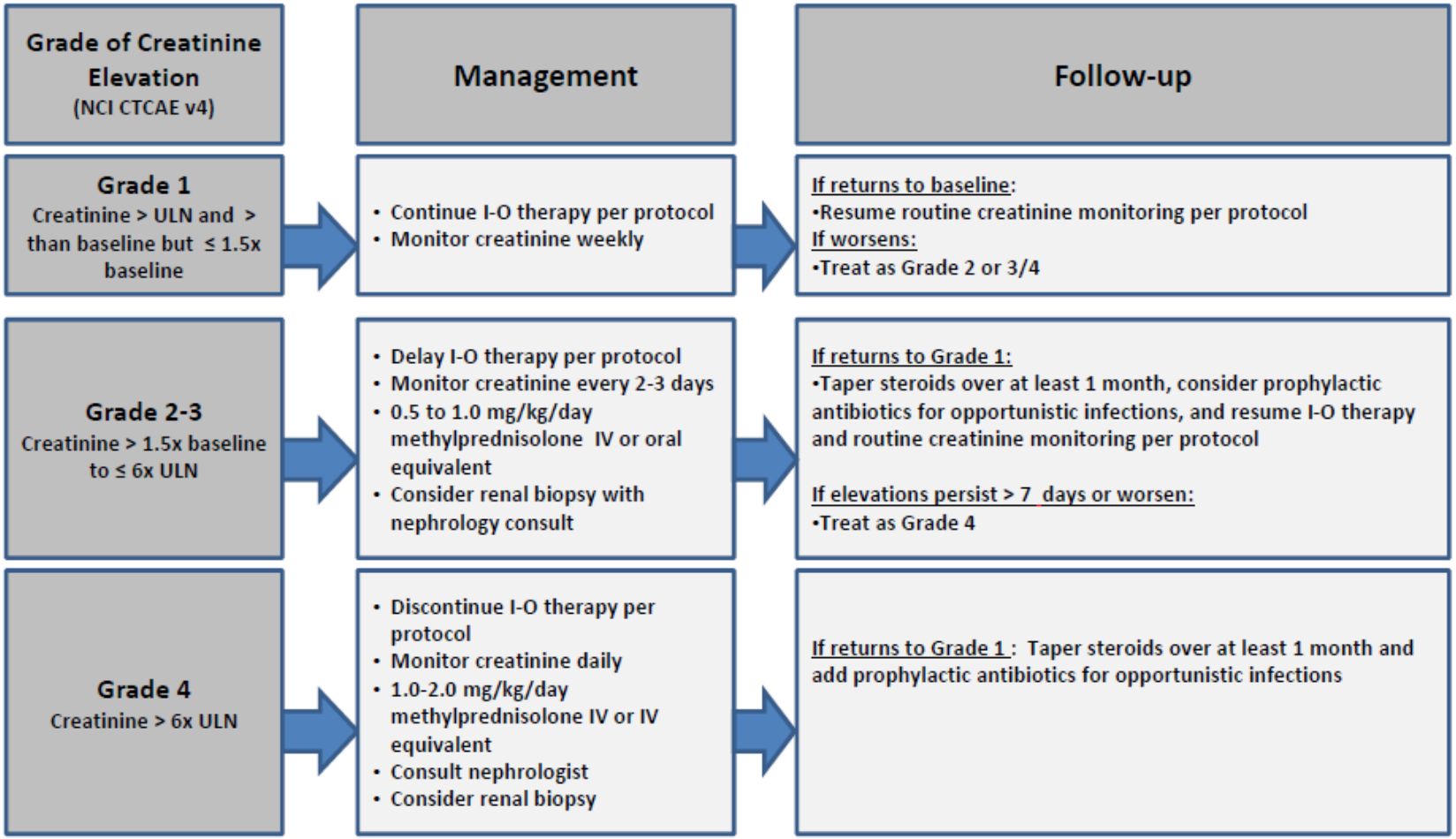


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

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

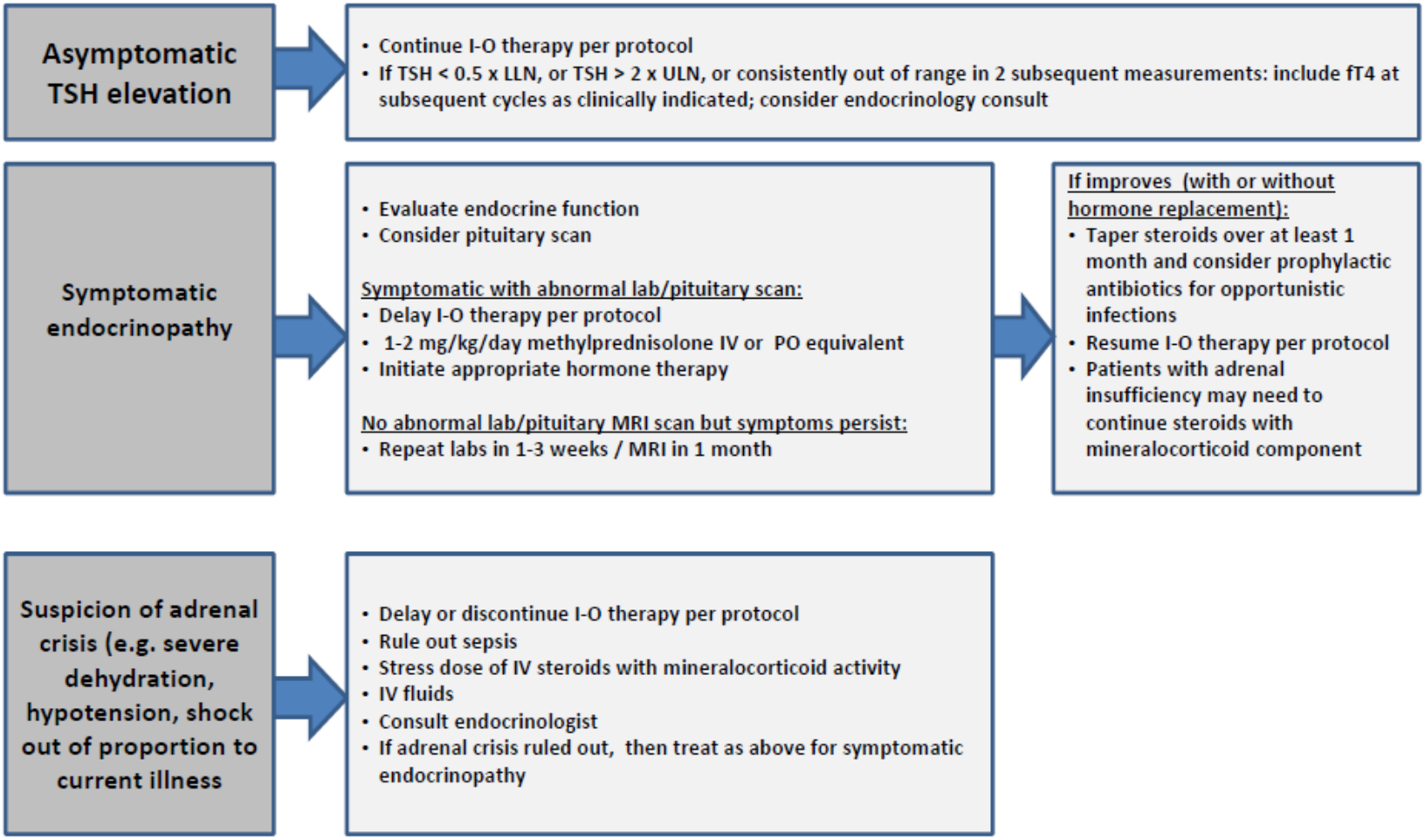


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

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.

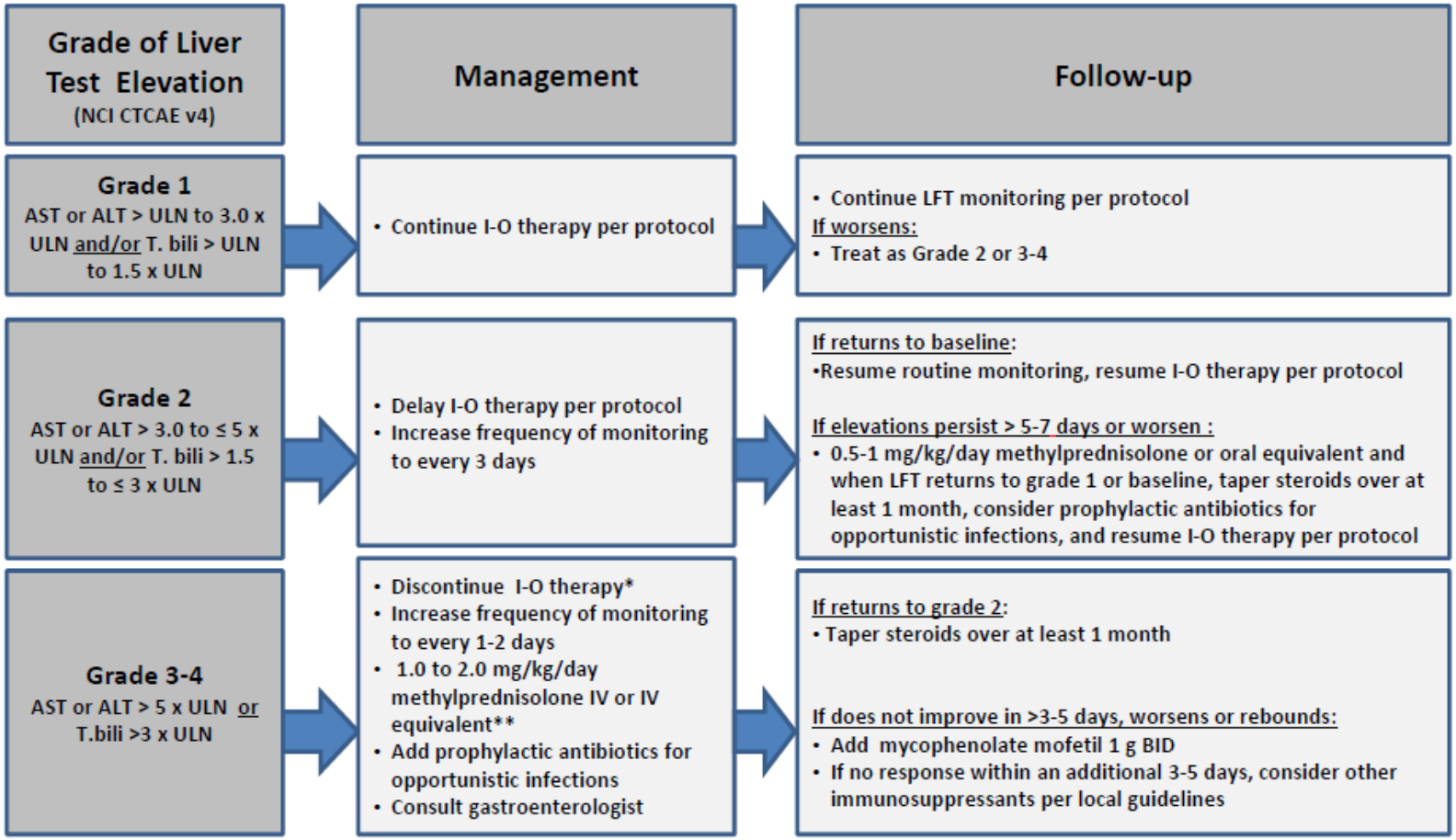


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

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.

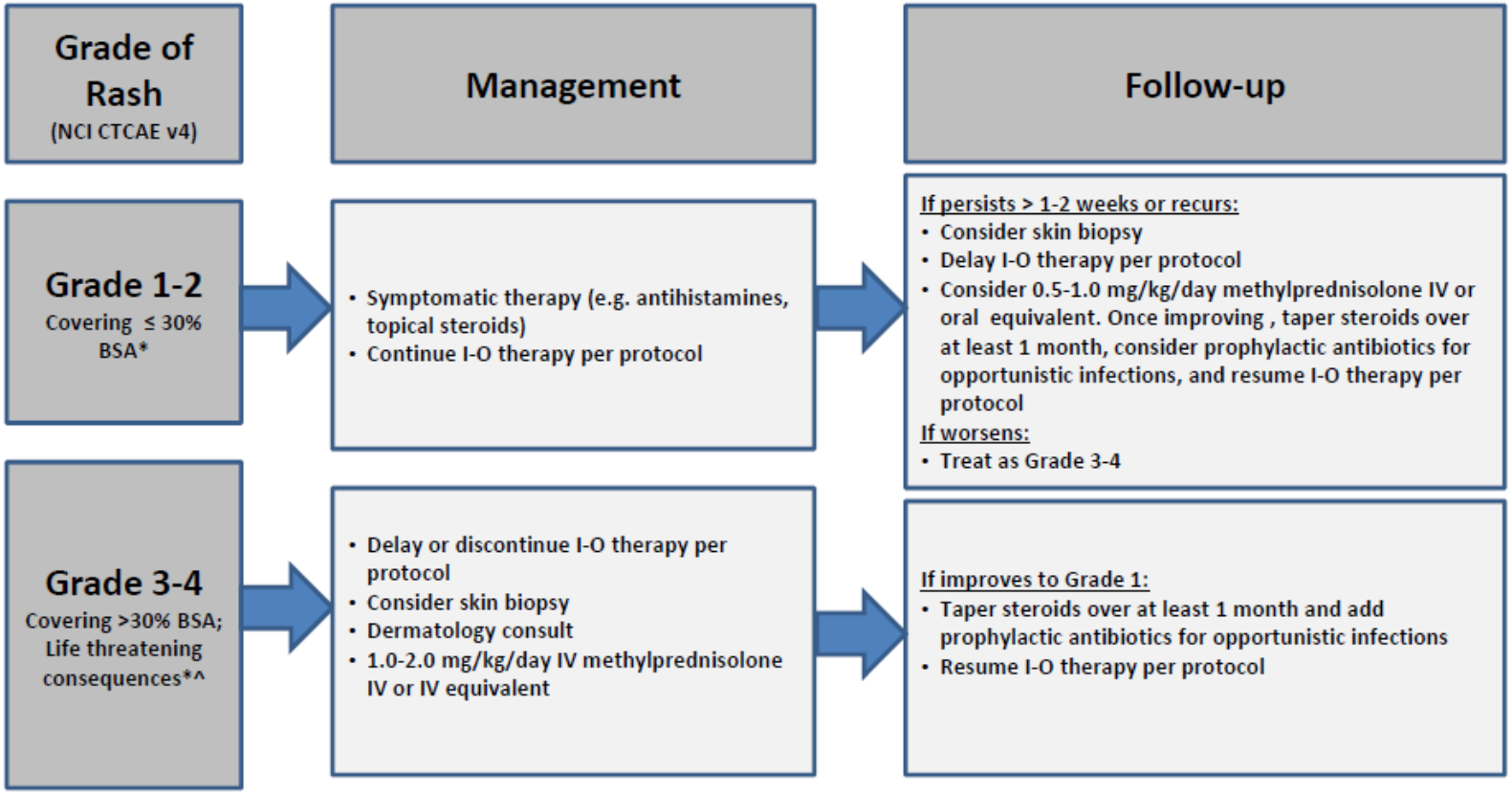
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

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

Updated 05-Jul-2016

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.

Updated 05-Jul-2016