SUMMARY OF CHANGES – Protocol

For Protocol Amendment #3 to: A Phase 2 Study of Nivolumab in Advanced Leiomyosarcoma of the Uterus

NCI Protocol #: 9672
Local Protocol #: DFCI- 15-707

NCI Version Date:
Protocol Date: 27 April 2018

Please provide a list of changes from the previous CTEP approved version of the protocol. The list shall identify by page and section each change made to a protocol document with hyperlinks to the section in the protocol document. All changes shall be described in a point-by-point format (i.e., Page 3, section 1.2, replace 'xyz' and insert 'abc'). When appropriate, a brief justification for the change should be included.

#	Section	Page(s)	Change
1.	N/A	1	The protocol version number and date have been updated to Version 3/
2.	5.8 7.2	31 51	Beginning April 1, 2018, the study has converted from the use of CTCAE v4.0 to CTCAE v5.0 for adverse event reporting. The protocol has been updated to reflect this change.

(Please retain the section break below, so that the Title Page is page "1" of the document.)

NCI Protocol #: 9672

Local Protocol #: DFCI- 15-707

ClinicalTrials.gov Identifier: NCT02428192

TITLE: A Phase 2 Study of Nivolumab and Ipilimumab in Advanced Leiomyosarcoma of the Uterus

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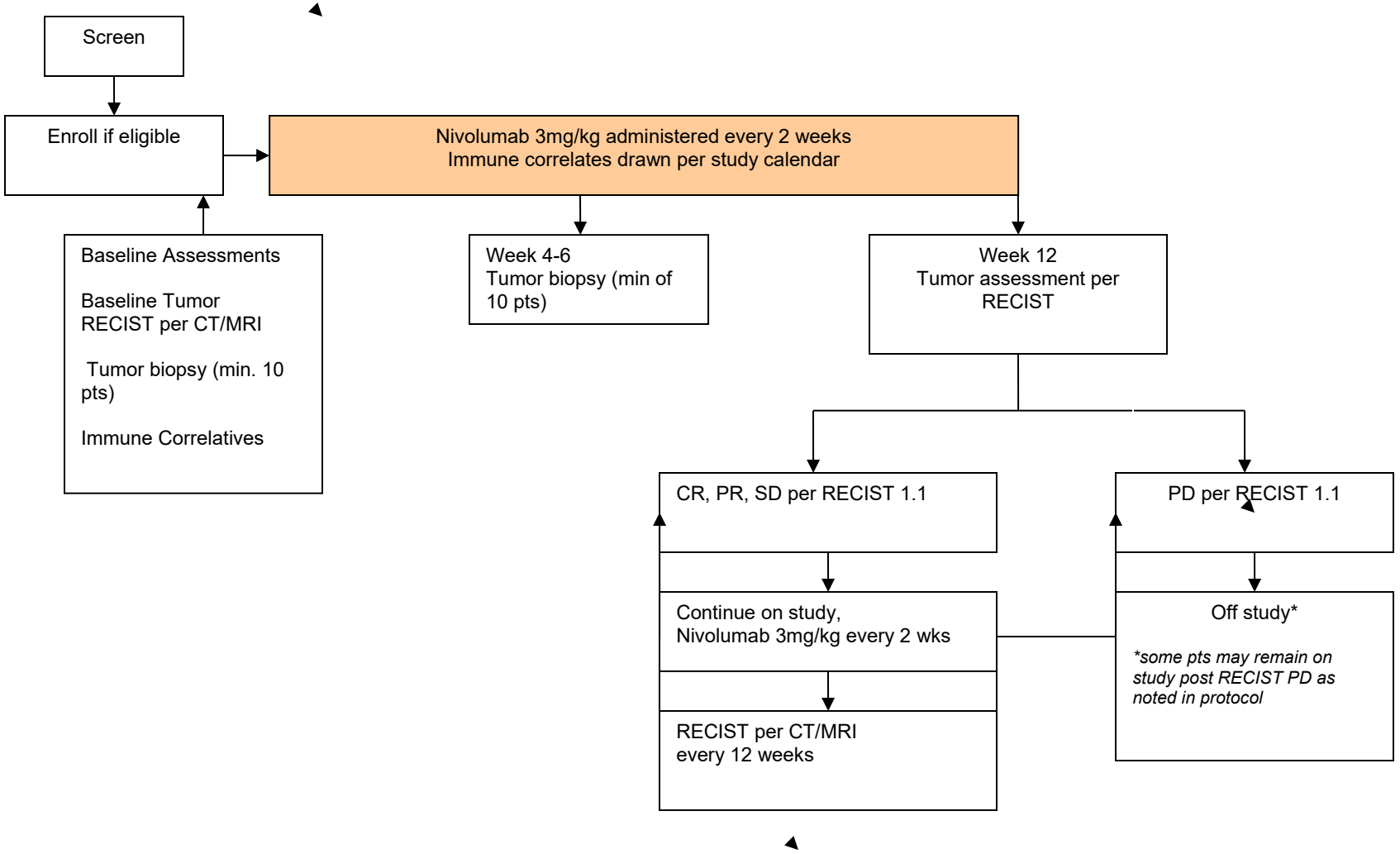
NCI-Supplied Agents: Nivolumab (BMS-936558, MDX-1106, and ONO-4538) NSC #748726; Ipilimumab (BMS-743016; MDX-010 Transfectoma-derived) NSC #732442

IND #: 125336
IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date: Original / Version#3 / 27 April 2018

SCHEMA COHORT A



SCHEMA COHORT B

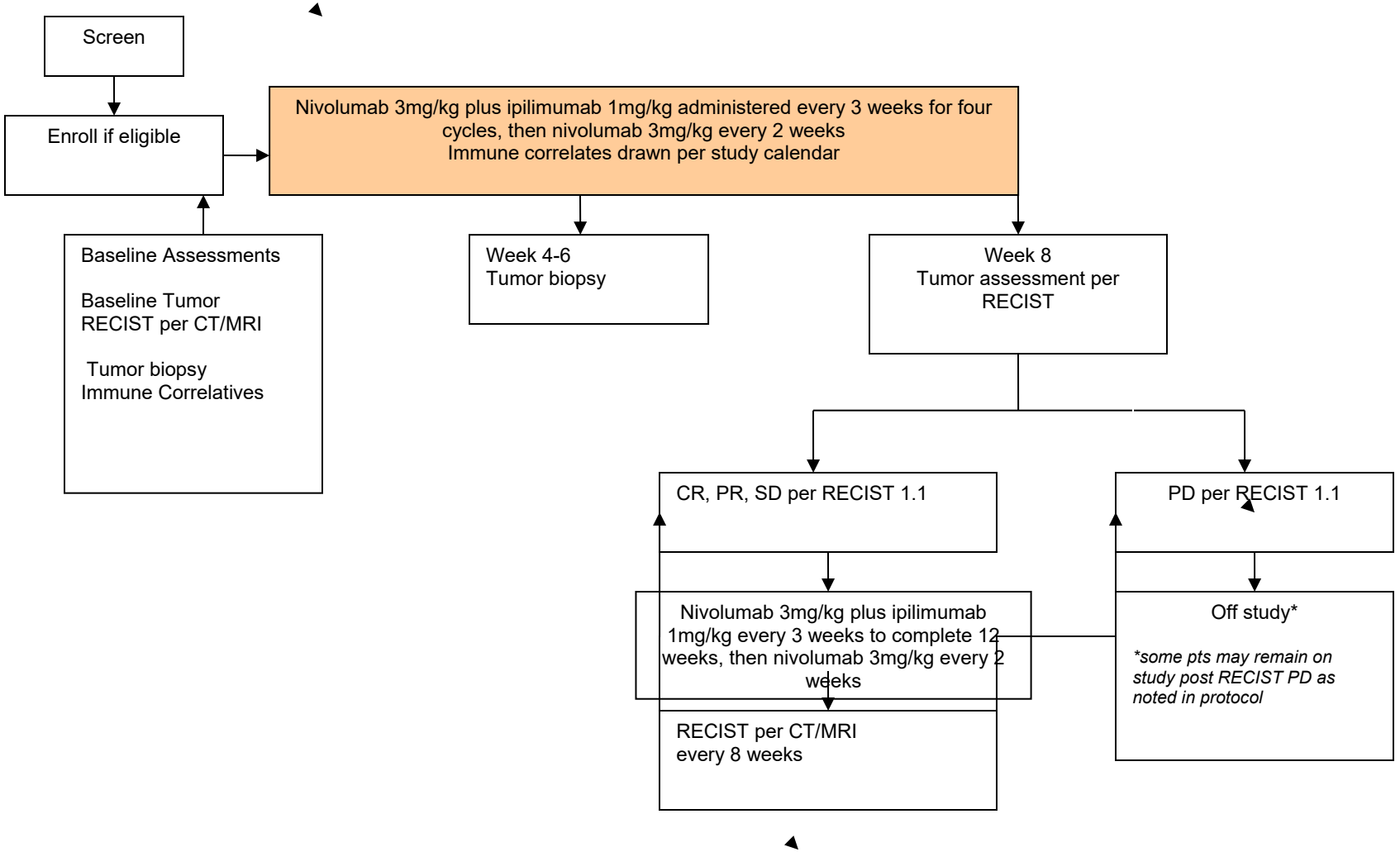

Screen
Enroll if eligible
Nivolumab 3mg/kg plus ipilimumab 1mg/kg administered every 3 weeks for four cycles, then nivolumab 3mg/kg every 2 weeks
Immune correlates drawn per study calendar
Baseline Assessments
Baseline Tumor RECIST per CT/MRI
Tumor biopsy
Immune Correlatives
Week 4-6
Tumor biopsy
Week 8
Tumor assessment per RECIST
CR, PR, SD per RECIST 1.1
PD per RECIST 1.1
Nivolumab 3mg/kg plus ipilimumab 1mg/kg every 3 weeks to complete 12 weeks, then nivolumab 3mg/kg every 2 weeks
RECIST per CT/MRI every 8 weeks
Off study*
*some pts may remain on study post RECIST PD as noted in protocol

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

- To evaluate the objective response rate per RECIST 1.1 of patients with advanced leiomyosarcoma of the uterus (ULMS) treated with nivolumab.
- To evaluate the objective response rate per RECIST 1.1 of patients with advanced (ULMS) treated with nivolumab in combination with ipilimumab.

1.2 Secondary Objectives

Secondary Objectives:

- To evaluate the toxicity of nivolumab in patients with advanced ULMS.
- To evaluate the toxicity of nivolumab in combination with ipilimumab in patients with advanced ULMS.
- To evaluate the progression-free survival of ULMS treated with nivolumab.
- To evaluate the progression-free survival of ULMS treated with nivolumab in combination with ipilimumab.
- To explore the relationship between PDL1, PD1 in infiltrating lymphocytes and PD2 status in archival tumor, and pre/post treatment biopsies in a minimum of 10 patients.

Exploratory Objectives:

- To explore the relationship between general immune response and specific markers of immunomodulation and response to nivolumab.
- To explore the relationship between tumor inflammatory gene signature and response to nivolumab in archival material.

2. BACKGROUND

2.1 Study Disease – Leiomyosarcoma of the uterus

Sarcomas vary widely in anatomic location as well as histologic subtype, with the current WHO classification listing over 50 distinct histologic subtypes. Prognosis and outcomes can vary widely based on histologic subtype and location of origin; because of this, histology-specific clinical trials in soft tissue sarcomas are necessary to evaluate novel therapies in order to optimize the likelihood of identifying both active and inactive agents within specific sarcoma subtypes.

Uterine sarcomas constitute approximately 3% of all uterine malignancies (Harlow *et al*, 1986). With an estimated incidence of 0.64 cases per 100,000 women, leiomyosarcoma is the most common uterine sarcoma and likely accounts for the single largest site-specific group of leiomyosarcomas (Amant *et al*, 2009). Localized disease is treated with hysterectomy, however rates of local and distant failure are high (45 to 80%), with an

estimated median overall survival of two years once disease is disseminated (Raut *et al*, 2009). Management of metastatic disease focuses on disease control and palliation, often with a combination of systemic therapies and local treatments, surgery and radiation, as indicated. Doxorubicin and gemcitabine based therapies are the most active regimens in this disease with estimated response rates of 20% to 40% with median PFS of approximately 5 -8 months (Omura *et al*, 1993, Look *et al* 2004, Hensley *et al*, 2008)). The most recently FDA approved agent for soft tissue sarcomas, including ULMS, is pazopanib a multi-targeted tyrosine kinase inhibitor. In a phase III placebo controlled trial, pazopanib demonstrated an ORR of 6% and a median PFS of 4.6 months in patients with advanced soft tissue sarcomas who had failed standard prior therapies (van der Graaf *et al*, 2012). Therefore, ULMS remains a disease with a dire need for additional effective systemic therapies.

The primary biologic underpinnings of ULMS continue to be elucidated. The exact mechanisms of action of pazopanib leading to benefit in soft tissue sarcomas remain unclear. There are no other successfully "targeted" approaches to the disease. ULMS is cytogenetically complex. Several pathways and signal intermediates have been investigated in leiomyosarcoma, and relevance of PI3K/AKT pathway activation has been consistently demonstrated throughout several studies. Indeed, genomic deletion of chromosome 10q targets PTEN tumor suppressor gene and leads to hyperactivation of PI3K/AKT, which is a common finding in leiomyosarcoma. Somatic TP53 mutations are estimated to be present in 50 -60% of cases, however the primary drivers of the malignant phenotype of the disease remain poorly understood.

Interestingly, a relationship between tumor immune infiltration, specifically macrophages, and outcomes in LMS has been reported (Espinosa *et al*, 2009, Ganjoo *et al* 2011)). To date, this data has been limited to prognostication, such that patients with more extensive tumor macrophage infiltration, and gene signature consistent with CSF1 and related proteins have inferior outcomes (Espinosa *et al*, 2009). The relationship of these findings to underlying tumor biology and response to specific therapies continues to be explored, however, this finding which has been uniquely reported in LMS subtype of soft tissue sarcomas, suggests that immune infiltration and disease control may be relevant in this specific subtype of soft tissue sarcoma. In addition, there has been least one objective PR (duration unknown at this time) observed with an antiPD1 monoclonal antibody in one patient with metastatic ULMS demonstrating that this class of drugs has activity in at least a subset set of patients with advanced ULMS (S. George, personal communication, 27aug2014).

2.2 CTEP IND Agent

2.2.1 Nivolumab

Nivolumab (BMS-936558, MDX-1106, and ONO-4538) is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) that is specific for human programmed

death-1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor (Investigator Brochure, 2013). PD-1 is a negative regulatory molecule that is expressed transiently following T-cell activation and on chronically stimulated T cells characterized by an "exhausted" phenotype. Nivolumab binds to cynomolgus monkey PD-1 but not mouse, rat, or rabbit molecules. Clinical activity of nivolumab has been observed in patients with melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC). The combination of nivolumab and ipilimumab (anti-cytotoxic T lymphocyte associated antigen-4 [anti-CTLA-4]) in a phase 1/2 trial showed markedly enhanced clinical activity with an acceptable safety profile in melanoma patients (Wolchok *et al*., 2013).

The clinical use of monoclonal antibodies to T-cell inhibitory receptors has provided transformative information on the nature of the immune system and cancer. An emerging picture suggests that endogenous immune responses can mediate effective tumor regression and/or improved survival even in patients with large volume tumors resistant to other forms of therapy. Some of the unique features of this type of therapy, based largely on experience in advanced melanoma, include: improved overall survival (OS) with or without radiographic responses or improved progression-free survival (PFS); responses that may be delayed or occur after radiographic disease progression; combinations of immune modulators with enhanced or novel activities (in the example of ipilimumab and nivolumab); and toxicity that is almost exclusively immune or inflammatory in nature. It is not yet clear what factors determine responses and which components of the immune system are needed for this to occur. It seems likely that both memory helper and effector cells would be needed to sustain long-term responses. Increasing emphasis has been placed on understanding the relationships of the tumor, celluar infiltrate, and immunologic milieu surrounding each tumor.

PD-1, a 55-kDa type 1 transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that include Ig super family member CD28, CTLA-4, inducible co-stimulator (ICOS), and B and T lymphocyte attenuator (BTLA) (Investigator Brochure, 2013). PD-1 is transiently but highly expressed on activated T cells functioning to limit immune effectors at the site of activation. Chronic stimulation may prevent the re-methylation of the PD-1 gene leading to continuous expression and characterizes a state of "exhausted" T cells that lose function and proliferative capacity while enhancing a suppressive tumor microenvironment. PD-1 may act together with other T-cell modulating molecules, including CTLA-4, TIM-3, lymphocyte-activation gene 3 (LAG-3) as well as indoleamine-pyrrole 2,3-dioxygenase 1 (IDO-1), cytokines, and transforming growth factor beta (TGF-beta).

Two ligands specific for PD-1 have been identified: PD-ligand 1 (PD-L1, also known as B7-H1 or CD274, expressed on tumor, antigen-presenting cells [APCs], and dendritic cells [DCs]) and PD-L2 (also known as B7-DC or CD273, expressed on endothelial cells). The interaction of PD-1 with PD-L1 and PD-L2 results in negative regulatory stimuli that down-modulate the activated T-cell immune response through SHP-1 phosphastase.

PD-1 knockout mice develop strain-specific lupus-like glomerulonephritis (C57BL/6) and cardiomyopathy (BALB/c). In transplantable tumor models that expressed PD-1 and LAG-3 on tumor-infiltrating $CD4^+$ and $CD8^+$ T cells dual anti-LAG-3/anti-PD-1 antibody treatment cured most mice of established tumors that were largely resistant to single antibody treatment (Woo *et al*., 2012). Despite minimal immunopathologic sequelae in PD-1 and LAG-3 single knockout mice, dual knockout mice abrogated self-tolerance with resultant autoimmune infiltrates in multiple organs, leading to eventual lethality.

PD-L1 expression is found on a number of tumors, and is associated with poor prognoses based on OS in many tumors, including melanoma (Taube *et al*., 2012), renal (Thompson *et al*., 2004; Thompson *et al*., 2005; Thompson *et al*., 2006), esophageal (Ohigashi, *et al.* 2005), gastric (Wu *et al*., 2006), ovarian (Dong *et al*., 2003), pancreatic (Nomi, *et al*., 2007), lung (Zitvogel, *et al*., 2006), and other cancers (Investigator Brochure, 2013).

The PD-1/PD-L1 axis plays a role in human infections, particularly in hepatitis C virus (HCV) and human immunodeficiency virus (HIV). In these cases, high expression levels of PD-1 were found in viral-specific $CD8^+$ T cells that also display a non-responsive or exhausted phenotype. Non-responsive PD-1-high T cells were observed in simian immunodeficiency virus (SIV) infection in rhesus macaques. Treatment of SIV-infected macaques with an anti-PD-1 mAb (3 mg/kg x4) resulted in decreased viral loads and increased survival along with expanded T cells with increased T-cell functionality.

2.2.1.1 Nonclinical Development of Nivolumab

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab alone was well tolerated (Investigator Brochure, 2013). Combination studies have highlighted the potential for toxicity when combined with ipilimumab, MDX-1408, and BMS-986016. Nivolumab bound specifically to PD-1 (and not to related members of the CD28 family such as CD28, ICOS, CTLA-4, and BTLA) with a K_d = 3.06 nM. A surrogate rat anti-mouse PD-1 antibody (4H2) was derived and expressed as chimeric IgG1 murine antibody. Antitumor activity was seen for several tumor models, including colon carcinoma and fibrosarcoma.

2.2.1.2 Clinical Development of Nivolumab

Nivolumab is being evaluated as monotherapy and in combination with cytotoxic chemotherapy, other immunotherapy (such as ipilimumab), anti-angiogenesis therapy, and targeted therapies in completed and ongoing BMS-sponsored clinical trials in NSCLC, melanoma, RCC, hepatocellular carcinoma (HCC), gastrointestinal (GI) malignancies including microsatellite instability (MSI) in colorectal cancer, and triple-negative breast cancer (TNBC) with an expanding group of indications (Investigator Brochure, 2013). In addition, two investigator-sponsored trials (ISTs) of nivolumab in combination with a peptide vaccine in melanoma are being conducted in the adjuvant setting and advanced disease.

Seven nivolumab studies were conducted in Japan, including six studies in advanced solid tumors and recurrent or unresectable stage III/IV melanoma sponsored by Ono Pharmaceuticals Co. Ltd., and one IST in recurrent or advanced platinum-refractory ovarian cancer.

2.2.1.2.1 Pharmacokinetics

Pharmacokinetics (PK) of nivolumab was linear in the range of 0.3 to 10 mg/kg, with dose-proportional increases in maximum serum concentration (C_{max}) and area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), with low to moderate inter-subject variability observed at each dose level (Investigator Brochure, 2013). Clearance of nivolumab is independent of dose in the dose range (0.1 to 10 mg/kg) and tumor types studied. Body weight normalized dosing showed approximately constant trough concentrations over a wide range of body weights. The mean terminal elimination half-life of BMS-936558 is 17 to 25 days consistent with the half-life of endogenous IgG4.

2.2.1.2.2 Efficacy

In a phase 1 (1, 3, and 10 mg/kg nivolumab doses) dose-escalation study the 3 mg/kg dose was chosen for expanded cohorts. Among 236 patients, objective responses (ORs) (complete or partial responses [CR or PR]) were seen in NSCLC, melanoma, and RCC. ORs were observed at all doses (Sznol *et al*., 2013). Median OS was 16.8 months across doses and 20.3 months at the 3 mg/kg dose. Median OS across all dose cohorts was 9.2 months and 9.6 months for squamous and non-squamous NSCLC, respectively (Brahmer *et al*., 2013). In the RCC cohort, median duration of response was 12.9 months for both doses with 5 of the 10 responses lasting ≥1 year (Drake *et al*., 2013).

In an advanced melanoma phase 1 study, nivolumab and ipilimumab were administered IV every 3 weeks for 4 doses followed by nivolumab alone every 3 weeks for 4 doses (concurrent regimen) (Wolchok *et al*., 2013). The combined treatment was subsequently administered every 12 weeks for up to 8 doses. In a sequenced regimen, patients previously treated with ipilimumab received nivolumab every 2 weeks for up to 48 doses. In the concurrent regimen (53 patients), 53% of patients had an OR at doses 1 mg/kg nivolumab and 3 mg/kg ipilimumab, with tumor reduction of 80% or more (modified World Health Organization [mWHO] criteria). In the sequenced-regimen (33 patients), the objective response rate (ORR) was 20%.

In a phase 1 study of nivolumab plus platinum-based doublet chemotherapy (PT-doublet) in chemotherapy-naïve NSCLC patients, 43 patients were treated with nivolumab + PT-doublet (Rizvi *et al*., 2013). No dose-limiting toxicities (DLTs) were reported and total/confirmed ORRs were 43/33%, 40/33%, and 31/31% in nivolumab/gemcitabine/cisplatin, nivolumab/pemetrexed/cisplatin, and nivolumab/carboplatin/paclitaxel arms, respectively.

2.2.1.2.3 Toxicology

A maximum tolerated dose (MTD) of nivolumab was not defined (Topalian *et al*., 2012). Serious adverse events (SAEs) occurred in 32 of 296 patients (11%) similar to the immune-related inflammatory events seen with ipilimumab: pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis (with noted pulmonary toxicity resulting in 3 deaths. Renal failure, symptomatic pancreatic and DM, neurologic events, and vasculitis have also been reported.). In combination with ipilimumab in the concurrent-regimen group (Wolchok *et al*., 2013), grade 3 or 4 treatment-related events were noted in 53% of patients. Skin rash represents the majority of these event.

2.2.1.2.4 Pharmacodynamics/Biomarkers

Tumor-cell expression (melanoma) of PD-L1 was characterized in combination with ipilimumab with the use of IHC staining and pharmacodynamics changes in the peripheral-blood absolute lymphocyte count (Wolchok *et al*., 2013). With PD-L1 positivity defined as expression in at least 5% of tumor cells, biopsy specimens from 21 of 56 patients (38%) were PD-L1–positive. Among patients treated with the concurrent regimen of nivolumab and ipilimumab, ORs were observed in patients with either PD-L1–positive tumor samples (6 of 13 patients) or PD-L1–negative tumor samples (9 of 22). In the sequenced regimen cohorts, a higher number of overall responses was seen among patients with PD-L1–positive tumor samples (4 of 8 patients) than among patients with PD-L1–negative tumor samples (1 of 13) suggesting the possibility that these tumors have higher response rates to the combination. The relationship between PDL-1 expression and responses may not be present in patients treated with the combination. Tissue expression of PDL-2, interferon-γ (IFN- γ), IDO, and T cell $CD8^+$ are of current interest. Until more reliable data based on standardized procedures for tissue collection and assays are available, PD-L1 status cannot be used to select patients for treatment at this time.

2.3 Other Agent(s)

2.3.1 Ipilimumab

Ipilimumab is a fully human anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) IgG1 monoclonal antibody. Following antigen presentation by peptide/major histocompatability complex, full activation of T cell requires co-stimulatory signals provided by binding of CD28 (expressed on T cells) and B7 molecules present on antigen presenting cells. This interaction is crucial for T cell activation and proliferation. CTLA4 antigen is induced on the surgace of T cell upon activation and is a member of the CD28:B7 immunoglobulin superfamily that competes with greater avidity with CD28 for

B7.1 and B7.2 (CD80 and CD86). CTLA4 ligation with B7 molecules down-regulates T-cell response resulting in diminished cytokine production and T cell proliferation. Binding of ipilimumab to CTLA-4 with B7 thereby potentiates antitumor T-cell activation and proliferation (Krummel *et al*., 1995, Kearney *et al*. 1995).

Ipilimumab efficacy as monotherapy was demonstrated in two phase III studies in advanced melanoma, where treatment with ipilimumab resulted in clinically meaningful and statistically significant survival benefit. The MDX10-20 evaluated ipilimumab (3 mg/kg) with or without a melanoma specific vaccine (gp100) compared with gp100 alone in pre-treated advanced melanoma patients. The median overall survival was 10 months with ipilimumab treatment (with or without gp100) versus 6.4 months for gp100 therapy alone (Hodi *et al*., 2010).

The CA184024 trial compared ipilimumab at a higher dose (10 mg/kg) plus dacarbazine versus dacarbazine alone in treatment naive advanced melanoma patients. Overall survival was improved in the ipilimumab plus dacarbazine group compared to the dacarbazine group (11.2 months vs 9.1 months, respectively) (Robert *et al*., 2011). Both trials demonstrated objective responses of 10-15% with ipilimumab treatment and grade 3 or 4 immune-related toxicities or colitis (5.3%), diarrhea (4.6%), endocrinopathies (3.8%) and rash (0.8%).

A pooled overall survival analysis based on studies with more than 1800 ipilimumab treated patients with advanced melanoma showed a plateau of overall survival at 3-years confirming durability of response and long term survival in ipilimumab treated patients (Schadendorf *et a*l., 2015).

2.4 Summary of Nivolumab and ipilimumab combination data

The combination of nivolumab and ipilimumab in untreated advanced melanoma patients was evaluated in a phase III trial (CheckMate-067) and demonstrated significant improvement in objective response rate and progression free survival with the combination therapy compared with either nivolumab or ipilimumab as monotherapy. In this trial, ipilimumab was given at 3 mg/kg every 3-weeks for four cycles and nivolumab was given at 1 mg/kg every 3 weeks for four cycles, and then escalated to 3mg/kg every 2-weeks until disease progression or unacceptable toxicity (Larkin et al., 2015).

The median progression-free survival was 11.5 months with nivolumab plus ipilimumab, as compared with 2.9 months with ipilimumab and 6.9 months with nivolumab. The rates of investigator-assessed objective response were 43.7% in the nivolumab group, 57.6% in the nivolumab-plus-ipilimumab group, and 19.0% in the ipilimumab group. Grade 3 or 4 treatment related adverse events were more common in the combination arm (55%) than with nivolumab (16.3%) or ipilimumab (27.3%) arms, with diarrhea (9.3%), colitis (7.7%) and rash (4.8%) the most clinically common, and elevation of ALT (8.3%) and

AST (6.1%) levels the most common laboratory abnormalities in the nivolumab plus ipilimumab arm. Treatment related adverse events leading to discontinuation were observed in 36.4% of patients in the combination arm. Ipilimumab and nivolumab combination therapy has also been tested in the CheckMate-012 trial which evaluated different doses and schedules for the combination in 148 previously untreated advanced non-small cell lung cancer patients (Rizvi *et al*., 2015).

Four administration/dosing schedules for the combination of nivolumab and ipilimumab were evaluated. In arm A, both agents were administered at a dose of 1 mg/kg every 3 weeks (Q3W, N = 31). In arm B nivolumab was administered at 1 mg/kg every 2 weeks (Q2W) plus ipilimumab 1 mg/kg every 6 weeks (Q6W; N = 40). Arm C and D dosed nivolumab at 3 mg/kg Q2W and ipilimumab 1 mg/kg every 12 weeks (Q12W; N = 38) or Q6W (N = 39). Activity was observed in all arms with arms containing nivolumab at 3 mg/kg showing the best objective response rate (39% in arm C and 31% in arm D) and arms B and A demonstrating 25% and 13% response rates respectively, whereasPFS correlated less with nivolumab dose with median PFS of 10.6 months, 4.9 months, 8 and 8.3 months for arms A, B, C, and D respectively).

Treatment- emergent grade 3 or 4 adverse events occurred in 28% to 35% of patients in each group but led to discontinuation in just 3% to 10% of cases. All grade treatment-related AEs occurred in 77%, &3%, 74%, and 69% of patients in groups A, B, C, and D, respectively. The safety profile was consistent with previous studies of the combination, and the discontinuation rate associated with AEs was similar to rates observed with nivolumab alone. The only grade 3/4 adverse events that occurred in as many as 10% of patients were hepatic in arm B (10%) and skin-related in arm C and D (13%). Grade 3/4 pulmonary AEs occurred in no more than 3% of patients in any of the groups. There were no treatment-related deaths in the trial.

2.5 Rationale

ULMS is a complex karyotype malignancy without a clear oncogenic driver, and although cytotoxic chemotherapy may lead to disease control in a subset of patients for some number of months, it is a disease with a median overall survival of 2 years following the development of metastatic disease. Effective therapies are desperately needed.

The rationale underlying synergistic immunotherapeutic effects is that each dysfunctional antitumor T cell could be kept unresponsive by more than one repressor and could only be fully capable to exert its functions when completly released from checkpoint inhibition. Combining immune checkpoint inhibitors to block more than one immunomodulatory pathway thereby may further enhance the antitumor efficacy of each individual treatment. Although PD-1 and CTLA-4 are both coinhibitory mechanisms to limit T cell activation, evidence suggests that they use distinct mechanisms to limit T cell activation, and preclinical and clinical evidence suggest that the combination of nivolumab and ipilimumab may be synergistic.

Preclinical data have shown that ipilimumab treatment may lead to broadening of specific killer T cell response in melanoma, pointing towards a role in the priming of cancer-specific T cell immunity. In addition, evidence is emerging that CTLA4-specific antibodies can promote the depletion of regulatory T cells specifically in tumors, and increase PD-1+, PDL1+ and CTLA-4+ tumor infiltrating T cells. Conversely, nivolumab has been shown to increase peripheral CTLA-4+ and regulatory T cells in subjects without clinical response. There is growing evidence of benefit of nivolumab in solid tumors, even those without a clear immunologic driver, and the FDA approval for nivolumab in 2015 for non-small cell lung cancer is expected to be followed in other solid tumors as well, Furthermore, combination therapy with nivolumab and ipilimumab has shown superior efficacy over nivolumab monotherapy in melanoma and was granted FDA approval. Advanced clinical trials in other solid tumors (non-small cell lung cancer, renal cell carcinoma) are currently ongoing with encouraging preliminary results. Most interestingly, results of subgroup analyses in the Checkmate-067 suggest that the greatest benefit with the combination of nivolumab and ipilimumab versus nivolumab alone may occur in the context of negative PD-L1 tumor expression. In this trial, in the subgroup of patients with PD-L1 positive tumors, both nivolumab alone and nivolumab plus ipilimumab resulted in a similar prolongation of progression-free survival as compared with ipilimumab alone, although objective response rates were numerically higher in the combination group than in either monotherapy group. However, among patients with a negative PD-L1 tumor status, the median progression-free survival was 11.2 months for nivolumab plus ipilimumab compared with 5.3 months with nivolumab, and 2.8 months ipilimumab monotherapy. This observation of at least additive activity of the combination of nivolumab plus ipilimumab in the context of negative PD-L1 expression may be of particular interst in uterine leiomyosarcoma. A profound and durable response observed in one patient with metastatic ULMS (S. George, personal communication, 27Aug2014) should serve as a proof for anti PD-1 drug class activity in at least a subset of patients with advanced ULMS. Cohort A of the current protocol (nivolumab as a single agent in advanced ULMS) has been completed with no responses observed; therefore, the protocol has been amended to include Cohort B, defined as the combination of nivolumab plus ipilimumab, with the rationale that this combination may provide enhanced immune response and increased tumor response rate.

2.6 Correlative Studies Background

Nivolumab was initially thought to be most effective in tumors which express PDL1, a marker that may vary in a variety of tumor samples over time, however, with increased experience with this agent, it appears that both PDL1 and nonPDL1 expressing tumors may benefit from nivolumab, either as a single agent or in combination with ipilmumab. Development of biomarkers for response to nivolumab remain under active investigation and are a critical aspect to study design.

We aim to explore the relationship between ORR and PFS to general immune response (CD3, CD4, CD8, FOX-P3, CD68, CD63) as well as more specific markers of immunomodulation including PD-1, PDL-1, PDL-2. We hypothesize that the expression of these markers, either alone or in combination, may lead to the identification of a subset

of patients with ULMS who are more likely to respond to nivolumab. This evaluation will be performed on archival tumor material for all participants when available, and in paired pre/post-treatment biopsies in up to10 participants. In addition, we have extensive experience using digital scanning of pathology slides and using image analysis to quantify immune infiltrates which will be applied to this cohort and related to response (14) . This work will be performed under the direction of Scott Rodig, MD, PhD and at the Center for Immuno-oncology Pathology Core at Dana Farber–Harvard Cancer Center housed in the Specialized Histopathology Core at the Brigham and Women's Hospital. The immuno-onology core at Dana-Farber Harvard Cancer Center (DFHCC) has optimized IHC for these markers (Chen *et al*, 2013) and is actively developing IHC for IDO.

The immuno-oncology core lab at DFHCC evaluation of gene expression profiling with the aim of identification of an immune gene signature with the goal of identify patients more likely to respond to therapy with immune checkpoint inhibitors. Therefore, when material is available, we plan to evaluate targeted expression profiling for immune response signature on FFPE using nanostring platform at the immuno-onolocogy core at DFHCC (Scott *et al*, 2014).

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed advanced leiomyosarcoma of the uterus (ULMS). Advanced ULMS is defined as metastatic ULMS or unresectable primary ULMS.

3.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm (≥2 cm) with conventional techniques or as ≥10 mm (≥1 cm) with spiral CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease

3.1.3 Patients must have received at least one prior line of chemotherapy, for ULMS (either in the adjuvant or metastatic setting).

3.1.4 Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of nivolumab and ipilimumab in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.5 ECOG performance status of 0 or 1 (see Appendix A).

3.1.6 Life expectancy of greater than 9 months.

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

- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL
- total bilirubin ≤1.5× institutional upper limit of normal (ULN) (except patients with Gilbert Syndrome, who can have total bilirubin <3.0 mg/dL)

- AST(SGOT)/ALT(SGPT) ≤2.5× ULN/ ≤5xULN for subjects with liver metastases

- Serum creatinine ≤1.5× ULN

OR

- creatinine clearance (CrCl) ≥50 mL/min (if using the Cockcroft-Gault formula below):

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

3.1.8 Patients with a requirement for steroid treatment or other immunosuppressive treatment: Patients should be excluded if they have a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

3.1.9 The effects of nivolumab on the developing human fetus are unknown. For this reason women of child-bearing potential (WOCBP) must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. WOCBP should use an adequate method to avoid pregnancy for 31weeks after the last dose of investigational drug. Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of nivolumab. Women must not be breastfeeding. Women who are not of childbearing potential (*i.e.*, who are postmenopausal or surgically sterile) do not require contraception.

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

WOCBP receiving nivolumab will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product. These durations have been calculated using the upper limit of the half-life for nivolumab (25 days) and are based on the protocol requirement that WOCBP use contraception for 5 half-lives plus 30 days.

Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform the treating physician immediately.

The effects of nivolumab on the developing human fetus are unknown.

3.1.10 Ability to understand and the willingness to sign a written informed consent document.

3.1.11 For enrollment in the first stage of Cohort B, patients must have accessible pre-treatment and post-treatment (4-6 weeks) tumor for biopsy.

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events (AEs) due to agents administered more than 3 weeks earlier. Patients who have had prior pelvic radiation may be at increased risk for bowel perforation, and therefore may not have residual inflammatory disease of the bowel or residual bowel toxicity based on baseline imaging and clinical assessment. Palliative (limited-field) radiation therapy is permitted, if all of the following criteria are met:

1) Repeat imaging demonstrates no new sites of bone metastases.
2) The lesion being considered for palliative radiation is not a target lesion.
3) Bowel toxicity is not expected from the target field due to increased risk of perforation

3.2.2 Patients who are receiving any other investigational agents.

3.2.3 Patients are excluded if they have had 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 immune checkpoint pathways.

3.2.4 Active brain metastasis or leptomeningeal disease. Patients with known brain metastases are allowed if metastases have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 12 weeks after treatment is complete and within 28 days prior to the first dose of nivolumab administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (>10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

3.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to nivolumab.

3.2.6 History of severe hypersensitivity reaction to any monoclonal antibody.

3.2.7 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 Pregnant women are excluded from this study because the effects of nivolumab on the developing fetus are unknown. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with nivolumab, breastfeeding should be discontinued if the mother is treated with nivolumab.

3.2.9 Because the effects of nivolumab on chronic viral infection are not well known, patients should be excluded if they have known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) or if they have a positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection.

3.2.10 Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids, are excluded. These include but are not limited to patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, connective tissue diseases, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome should be excluded because of the risk of recurrence or exacerbation of disease. Patients with vitiligo, endocrine deficiencies including thyroiditis managed with replacement hormones including physiologic corticosteroids are eligible. Patients with rheumatoid arthritis and other arthropathies, Sjögren's syndrome and psoriasis controlled with topical medication and patients with positive serology, such as antinuclear antibodies (ANA), anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.

3.2.11 Patients are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger (precipitating event).

3.2.12 Patients should be excluded if they have a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses ≤10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if ≤10 mg/day prednisone equivalents. A brief 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 contact allergen) is permitted.

3.2.13 Patients who have had evidence of active or acute diverticulitis, intra-abdominal abscess, GI obstruction, fistula and abdominal carcinomatosis which are known risk factors for bowel perforation should be evaluated for the potential need for additional treatment before coming on study.

3.3 Inclusion of Women and Minorities

Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the population of women with advanced leiomyosarcoma of the uterus treated by participating institutions.

Please see the Planned Enrollment Report (table in Section 13.2).

4 REGISTRATION PROCEDURES (ROSTERED PROTOCOL MODEL)

4.1 Investigator and Research Associate Registration with CTEP

4.1.1 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at http://ctep.cancer.gov/investigatorResources/investigator_registration.htm. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at pmbregpend@ctep.nci.nih.gov.

4.1.2 CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account is needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, and is critical to the conduct of this study, including document access, patient enrollment, and clinical data submission.

Additional information can be found on the CTEP website at http://ctep.cancer.gov/branches/pmb/associate_registration.htm. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at ctepreghelp@ctep.nci.nih.gov.

4.1.3 For Questions and Support

For questions about Investigator Registration, please contact the CTEP Investigator Registration Help Desk: pmbregpend@ctep.nci.nih.gov.

For questions about Associate Registration or CTEP-IAM Account Creation, please contact the CTEP Registration Help Desk: ctepreghelp@ctep.nci.nih.gov.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Each investigator or group of investigators at a clinical site must obtain Institutional Review Board (IRB) approval for this protocol and submit all required regulatory documents (including any protocol specific documents) to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to: an active Federal Wide Assurance (FWA) number, an active

roster affiliation with the Lead Network or a participating organization, a valid IRB approval, and compliance with all protocol specific requirements.

Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the 9672 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder, then select LAO-MA036 and protocol #9672
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Requirements For 9672 Site Registration:

- CTSU Transmittal Sheet (optional)
- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.4 Checking **Site** Registration Status

Sites can verify their site registration status on the members' section of the CTSU website:

- Go to https://www.ctsu.org and log in to the members' area using your CTEP IAM username and password.
- Click on the Regulatory tab at the top of your screen.
- Click on the Site Registration subtab.
- Enter your 5-character CTEP Institution Code and click on Go.

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or other affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

For trials with slot reservation requirements, OPEN will connect to IWRS at enrollment initiation to check slot availability. Registration staff should ensure that a slot is available and secured for the patient before completing an enrollment.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar.
- To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN/IWRS, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the CTSU web site as a tool to verify eligibility.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

4.3.3 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://theradex.com/CTMS/Downloads.aspx. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk: 609-619-7802 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 21 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5 TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.1.1 COHORT A (nivolumab alone)- Closed to Accrual

Cohort A opened for accrual on 13-May-2015; accrual to this cohort was completed on 21-Oct-2015. All participants in Cohort A received Nivolumab monotherapy as per the below dosing instructions.

Nivolumab will be given every two weeks (±2 days) at a dose of 3 mg/kg. Patients may be dosed no less than 12 days from the previous dose of drug.
The dosing calculations should be based on the actual body weight. If the patient's weight on the day of dosing differs by >10% from the weight used to calculate the original dose, the dose must be recalculated. Actual body weight at each visit may be used to calculate dose, as per institutional standard. All doses should be rounded as per institutional standard. There will be no dose modifications allowed.

Nivolumab is to be administered over an approximately 60-minute IV infusion, using a volumetric pump with a 0.2-1.2 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution cannot be below 0.35 mg/mL. 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. .

5.1.2 COHORT B (nivolumab and ipilimumab)

Cohort B explores combination therapy with nivolumab and ipilimumab. All participants enrolled to this cohort will receive nivolumab in combination with ipilimumab as per the dosing instructions below.

Nivolumab will be given every three weeks (±2 days) at a dose of 3 mg/kg together with ipilimumab at a dose of 1 mg/kg for 4-cycles. Starting at cycle 5, nivolumab will be given as a monotherapy every two weeks at a dose of 3 mg/kg. Patients may be dosed no less than 12 days from the previous dose of drug. The dosing calculations should be based on the actual body weight. If the patient's weight on the day of dosing differs by >10% from the weight used to calculate the original dose, the dose must be recalculated. Actual body weight at each visit may be used to calculate dose, as per institutional standard. All doses should be rounded as per institutional standard. There will be no dose modifications allowed.

Nivolumab is to be administered over an approximately 60-minute IV infusion, using a volumetric pump with a 0.2-1.2 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution cannot be below 0.35 mg/mL. 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.

Ipilimumab injection can be used for IV administration without dilution after transferring to a PVC (polyvinyl chloride), non-PVC/non-DEHP (di-(2-ethylhexyl)phthalate) or glass containers and is stable for 24 hours at 2-8°C or room temperature/room light (RT/RL). Ipilimumab is to be administered as a 90-minute IV infusion, using a volumetric pump with a 0.2 to 1.2 micron in-line filter at the protocol-specified dose. 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. At the end of the infusion, flush the line with a sufficient quantity of normal saline or 5% dextrose solution.

Separate infusion bags and filters must be used for each infusion of nivolumab and ipilimumab. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion.

5.1.3 Other Modality(ies) or Procedures

Not applicable

5.1.4 Investigational Imaging Agent Administration

Not applicable

5.2 Definition of Dose-Limiting Toxicity

Not applicable

5.3 General Concomitant Medication and Supportive Care Guidelines

Nivolumab is a human monoclonal antibody and as such is not expected to be metabolized by cytochrome P450 (CYP) enzymes or other typical drug metabolizing enzymes. Thus, it is not expected to have any effect on CYP or other drug metabolizing enzymes in terms of inhibition or induction, and is, therefore, not expected to induce this type of PK-based drug interactions.

5.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for up to 46 doses in Cohort A or until one of the following criteria applies. In Cohort B, treatment may continue for up to 4 doses of combination therapy (nivolumab + ipilimumab), and up to 46 doses of nivolumab monotherapy after the combination therapy, or until one of the following criteria applies:

- Disease progression, as per section 5.9
- Intercurrent illness that prevents further administration of treatment,
- Any patients who require additional immune suppressive treatment beyond steroids should go off study treatment

- Unacceptable adverse event(s) which include the following (see also section 6 and

specific algorithms in Appendix E):

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

- Patients requiring > two dose delays for the same type of event should go off protocol therapy.

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

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

- Patients being tapered after high dose corticosteroids over one month followed by a two-week observation period will be allowed an additional two weeks to restart treatment (a maximum eight week interruption).

- Dosing interruptions >6 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting >6 weeks, the Principal Investigator must be consulted.

- Grade 3 drug-related autoimmune or inflammatory events including uveitis, pneumonitis, diarrhea, colitis, neurologic adverse events, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation except as noted below:

- Any other grade 3 non-skin, drug-related AE lasting >7 days including fatigue.

- Any grade 3 or 4 drug-related laboratory abnormality or electrolyte abnormality, <u>not associated with underlying organ pathology</u>, that does not require treatment except for electrolyte replacements **does not** require treatment discontinuation.

- Grade 3 amylase or lipase abnormalities that are not associated with diabetes mellitus (DM), associated liver or gall bladder inflammation clinical manifestations of pancreatitis and which decrease to <u>≤</u> Grade 2 within 1 week of onset **may** resume study treatment when resolved.

- Any grade 4 events except as noted above.

- Patient decides to withdraw from the study, or

- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.5 Duration of Follow Up

Patients will be followed for 100 days based on 5 half lives after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Patients who complete all protocol therapy (46 doses), without disease progression or unacceptable toxicity will continue to be followed until disease progression or the initiation of a new anticancer therapy.

5.6 Criteria for Removal from Study

Patients will be removed from study when any of the applicable criteria, including progressive disease as per section 5.9, adverse events, patient withdrawal or inability to follow study protocol as listed in Section 5.4. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

5.7 Criteria to Resume Treatment

Management of adverse events is summarized in section 6 and may include holding of nivolumab and ipilimumab, and/or the use of steroids for the management of immune related AEs.

If drug administration is held until the next scheduled time point, please continue to count weeks/doses. If patients must be delayed due to toxicity, all assessments can be obtained with the modified treatment dose schedule as noted in this section.

Some patients may continue to benefit from treatment, maintaining or improving responses after progression including those treated with steroids.

Restarting nivolumab may be considered in patients who experience grade 2 events and some grade 3 events (skin rash and thyroiditis). Because of this, stopping treatment and starting steroids earlier, as per section 6, to obtain resolution with the possibility for restarting rather than waiting for higher grade events is encouraged.

For non-autoimmune or non-inflammatory events patients may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤1 or baseline value, with the following exceptions:

- Evaluation to exclude any additional immune mediated events endocrine, GI, and liver / pancreas function as clinically indicated must be made prior to restarting.
- Non-drug-related toxicity including hepatic, pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed.

If the criteria to resume treatment are met, the patient should restart treatment no sooner than the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol the treatment should resume at the earliest convenient point that is within the six week delay period.

For protocols using combination nivolumab/ipilimumab for the initial induction period patients with grade 2 or 3 events requiring discontinuation of treatment with the combination, the PI may consider continuing treatment with single agent nivolumab at the same dose when the event resolves to baseline. However, patients with renal, CNS, or pulmonary toxicity must be removed from study.

For patients treated with corticosteroids:

For patients treated with high dose steroids with nivolumab/ipilimumab, toxicity must resolve to baseline within 8 weeks of treatment.

Patients should be off steroids for at least 2 weeks with no recurrence or new events. New immune related events or exacerbation of existing events during steroid treatment or taper suggest the presence of ongoing immune activation and should require permanent discontinuation of nivolumab.

Grade 2 events must resolve to grade $\leq$ 1 before considering retreatment.

All patients treated with steroids for grade $\geq$2 events should have nivolumab held until resolution to grade $\leq$ 1 for at least 2 weeks following complete removal from steroid treatment except for maintenance replacement doses for adrenal insufficiency (preferably no greater than 10mg prednisone equivalent daily).

All patients treated with steroids for grade $\geq$3 events should have nivolumab discontinued. Patients with grade 3 thyroiditis and skin rash may continue therapy as for grade 2 events with resolution and stable replacement treatment.

Patients with hepatitis, pancreatitis, pneumonitis, and colitis are at risk for exacerbation with retreatment if there is residual inflammation and should resolve to Grade 0 or baseline before retreatment. Baseline can mean the initial grade *i.e.* grade <1 where permitted on study.

Patients with thyroiditis or hypopituitarism who are stable as above may be restarted with replacement hormones including thyroid hormone and physiologic doses only of corticosteroids. Please note that grading and for hypophysitis with symptoms of headache, visual or neurologic changes or radiologic evidence of pituitary enlargement and other CNS events such as aseptic meningitis or encephalitis should be considered grade 3 events.

New immune related events or exacerbation of existing events during steroid treatment or taper suggest the presence of ongoing immune activation and should require permanent discontinuation of nivolumab.

A patient who is treated with steroids, evaluated, and found to not have an autoimmune or inflammatory event requiring steroid treatment, may be restarted if asymptomatic off steroids for 2 weeks and other restarting criteria are met.

Prior to starting corticosteroids or hormone replacement for any reason, appropriate endocrine

testing including cortisol, ACTH, TSH and T4 must be drawn if clinically feasible to document baseline function and distinguish the pituitary from peripheral organ dysfunction and later from steroid (or thyroid) treatment associated ACTH (or TSH) suppression. Steroids should be started prior to obtaining results based on clinical indications.

5.8 Treatment of Nivolumab or Ipilimumab Related Infusion Reactions

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

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE version 5.0 guidelines.

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

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

Remain at bedside and monitor subject until recovery from symptoms. Infusion rate may be slowed. 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 patient closely.

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations, slowing infusion rate as above.

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]; close observation for recurrence and treatment medications may need to be continued for 24-48 hours).

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor patient until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur, then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the patient until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications

are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and (acetaminophen) (or paracetamol) 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction), Grade 3 symptoms: 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 symptoms: (life threatening; pressor or ventilatory support indicated).

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

Please note that late occurring events including isolated fever and fatigue may represent the presentation of systemic inflammation. Please evaluate accordingly.

5.9 Treatment Beyond Progression

A minority of subjects treated with immunotherapy may derive clinical benefit either delayed responses, stable disease, or increased overall survival despite initial evidence of progressive disease (PD) with nivolumab or combination treatment.

Patients may be permitted to continue treatment beyond initial RECIST 1.1-defined PD that occurs during the initial (24 weeks) of treatment as long as they meet the following criteria:

- No more than 4 new lesions total sum of the longest diameter (SHORT diameter for LN) cannot exceed 40% of the initial sum including new lesions
- Patients must be clinically stable with no change in performance status due to disease progression
- No indication for immediate alternative treatment
- Patient [assessed by the investigator] is showing clinical benefit and tolerates study drug. The assessment of clinical benefit should take into account whether the subject is clinically stable or deteriorating and likely or unlikely to receive further benefit from continued treatment.

- The time of progression is noted from the first assessment that exceeds standard criteria

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

6 DOSING DELAYS/DOSE MODIFICATIONS

Dose delays for nivolumab and ipilimumab for adverse events are described below. There are no dose reductions of nivolumab or ipilimumab allowed. See section 5.6 for guidelines regarding resumption of nivolumab and ipilimumab following dose delays.

Please refer to the Nivolumab Investigator Brochure, Ipilimumab Investigator Brochure or Appendix B to the protocol for toxicity management algorithms which include specific treatment guidelines. These algorithms should be followed unless there are specific clinical circumstances which the treating physician indicates variations or alternative treatment is needed.

Evaluation of possible AEs should occur early, with early withholding of drug, and appropriate treatment as indicated in the management tables and following event specific guidelines. In some cases, nivolumab and ipilimumab may be resumed as per section 5.6

ALL OTHER EVENTS*	**Management/Next Dose for Nivolumab and combination Nivolumab/ipilimumab**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below); Evaluate and continue at investigator discretion
Grade 3	Off protocol therapy (exceptions as noted below)
Grade 4	Off protocol therapy
* **Not agent related**, or agent related non-immunologically mediated	
Recommended management: As clinically indicated	
ALL OTHER EVENTS**	**Management/Next Dose for Nivolumab and combination Nivolumab/ipilimumab**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1 OR baseline* When resolved < or following steroids resume at same dose level .
Grade 3	Off protocol therapy (exceptions noted in 5.4)

ALL OTHER EVENTS*	**Management/Next Dose for Nivolumab and combination Nivolumab/ipilimumab**
Grade 4	Off protocol therapy
** immunologically mediated	
Recommended management: As clinically indicated	

- Any grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment should go off protocol treatment.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued study drug dosing should go off protocol treatment.
- Tumor pain or associated tumor flare does not require permanent discontinuation.
- Any grade < 2 laboratory only abnormality may continue study treatment at the discretion of the investigator. Any grade 3 or 4 drug-related laboratory abnormality or electrolyte abnormality, that can be managed independently from underlying organ pathology with electrolyte replacement, hormone replacement, insulin, or that does not require treatment **does not** require discontinuation.

Skin Rash and Oral Lesions	**Management/Next Dose for Nivolumab and combination Nivolumab/ipilimumab**
≤ Grade 1	No change in dose;* evaluate and continue at investigator discretion
Grade 2	Hold* until 1≤ Grade resolved^. Evaluate and continue at investigator discretion.
Grade 3	Hold* until ≤ Grade 1; evaluate and resume at investigator discretion same dose level.
Grade 4	Off protocol therapy
*Patients with purpuric or bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome, TEN, and autoimmune bullous disease including oral lesions of bullous pemphigus/pemphagoid. Pruritus may occur with or without skin rash and should be treated symptomatically if there is no associated liver or GI toxicity. Note skin rash typically occurs early and may be followed by additional events particularly during steroids tapering.	
Recommended management: AE management guidelines – Appendix B	

Liver Function AST, ALT, and Bilirubin (total)	**Management/Next Dose for Nivolumab and combination Nivolumab/ipilimumab**
≤ Grade 1	Hold pending evaluation. Continue treatment at same level at investigator decision.
Grade 2	Hold until UNL or baseline. Evaluate and resume at investigator discretion same dose level.
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
Continued treatment of active immune mediated heapatitis may exacerbate ongoing inflammation. Holding drug to evaluate LFT changes and early treatment are recommended.	

Liver Function AST, ALT, and Bilirubin (total)	**Management/Next Dose for Nivolumab and combination Nivolumab/ipilimumab**
LFT changes may occur during steroid tapers from other events and may occur together with other GI events including cholecystitis/pancreatitis.	
Recommended management: see Hepatitic AE management algorithm	

Diarrhea/ Colitis	**Management/Next Dose for Nivolumab and combination Nivolumab/ipilimumab**
≤ Grade 1	Evaluate and continue treatment at same level at investigator discretion.
Grade 2	Hold until Grade ≤1 or baseline following treatment algorithm; evaluate and resume at investigator discretion if additional therapy is not required.
Grade 3	Hold until Grade ≤1 or baseline following treatment algorithm; evaluate and resume at investigator discretion.
Grade 4	Off protocol therapy
See GI AE Algorithm for management of symptomatic colitis. Patients with grade 2 symptoms but normal colonoscopy and biopsies may be retreated after resolution. Please evaluate pituitary function prior to starting steroids if possible without compromising acute care. Evaluation for all patients for additional causes includes *C. diff*, acute and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD.	
Recommended management: see GI AE management Algorithm	

Pancreatitis Amylapse/Lipase	**Management/Next Dose for Nivolumab and combination Nivolumab/ipilimumab**
≤ Grade 1	Continue treatment at same level at investigator discretion.
Grade 2	Continue treatment at same level at investigator discretion if asymptomatic.
Grade 3	Hold until Grade≤ 2. Resume at same dose level if asymptomatic. Patients who develop symptomatic pancreatitis or DM should be taken off treatment.
Grade 4	Hold until Grade≤ 2. Resume at same dose level if asymptomatic. Patients who develop symptomatic pancreatitis or DM should be taken off treatment.
Patients may develop symptomatic and radiologic evidence of pancreatitis as well as DM and DKA. Lipase elevation may occur during the period of steroid withdrawal and with other immune mediated events or associated with colitis, hepatitis, and patients who have asymptomatic lipase elevation typically have self-limited course and may be retreated. For treatment management of symptomatic pancreatitis please follow the Hepatic Adverse Event Management Algorithm.	

Pneumonitis	**Management/Next Dose for Nivolumab and combination Nivolumab/ipilimumab**
≤ Grade 1	Hold dose pending evaluation and resolution to baseline including baseline pO2. Resume no change in dose after pulmonary and/or ID consultation excludes agent associated lymphocytic pneumonitis.
Grade 2	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes nivolumab/ipilimumab associated lymphocytic pneumonitis As the cause of the pneumonitis. Off study if steroids are required.
Grade 3	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes nivolumab/ipilimumab associated lymphocytic pneumonitis as the cause of the penumonitis. Off study if steroids are required.
Grade 4	Off protocol therapy
Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Patients with new lung nodules should be evaluated for sarcoid like granuloma. Please consider recommending seasonal influenza killed vaccine for all patients.	
Recommended management: See Pulmonary Adverse Event Management Algorithm	

Other GI N-V	**Management/Next Dose for Nivolumab and combination Nivolumab/ipilimumab**
≤ Grade 1	No change in dose.
Grade 2	Hold pending evaluation for gastritis duodenitis and other immune adverse events or other causes. Resume at investigator discretion.
Grade 3	Hold pending evaluation until ≤ Grade 2. Resume at same dose level. If symptoms do not resolve within 7 days with symptomatic treatment patients should go off protocol therapy
Grade 4	Off protocol therapy
Patients with grade 2 or 3 N-V should be evaluated for upper GI inflammation and other immune related events.	

Fatigue	**Management/Next Dose for Nivolumab and combination Nivolumab/ipilimumab**
≤ Grade 1	No change in dose.
Grade 2	No change in dose
Grade 3	Hold until ≤ Grade 2. Resume at same dose level at investigator discretion.
Grade 4	Off protocol therapy
Fatigue is the most common adverse event associated with immune checkpoint therapy. Grade 2 or greater fatigue should be evaluated for associated or underlying organ involvement including pituitary, thyroid, and hepatic, or muscle (CPK) inflammation	

Cardiac *	Management/Next Dose for BMS-936558 (Nivolumab) + Ipilimumab Cardiac Toxicities
≤ Grade 1	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize may resume therapy. If labs worsen or symptoms develop then treat as below. Hold pending evaluation.
Grade ≥2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone. If no improvement within 24 hours, add either infliximab, ATG or tacrolimus. Consult algorithm for more details. Resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone. Add ATG or tacrolimus if no improvement. Off treatment.

**Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin*
***Patients with evidence of myositis without myocarditis may be treated according as "other event"*
Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.

Neurologic events	**Management/Next Dose for Nivolumab and combination Nivolumab/ipilimumab**
≤ Grade 1	Hold dose pending evaluation and observation. Resume with no change in dose when resolved to baseline at investigator dicrestion
Grade 2	Hold dose pending evaluation and observation. Hold until ≤ Grade 1.Off protocol therapy if treatment with steroids is required. Resume at same dose level for peripheral isolated n. VII (Bell's palsy)
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
*Patients with any CNS events including aseptic meningitis, encephalitis, symptomatic hypophysitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, myasthenia gravis should be off study.	
Recommended management: See Neurologic Adverse Event Management Algorithm	

Endocrine Hypophysitis Adrenal Insufficiency	**Management/Next Dose for Nivolumab and combination Nivolumab/ipilimumab**
≤ Grade 1	Asymptomatic TSH elevation*; continue at investigator discretion with evaluation of thyroid function.
Grade 2	Hold until patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable off steroids for two weeks. Resume at same dose level.
Grade 3	Off protocol therapy.
Grade 4	Off protocol therapy
Note all patients with symptomatic pituitary enlargement, exclusive of hormone deficiency, but including severe headache or enlarged pituitary on MRI should be considered grade 3 events. Isolated thyroid or testosterone deficiency may be treated as grade 2 if there are no other associated deficiencies and adrenal function is monitored. Please evaluate pituitary function before beginning steroid therapy or replacement therapy of any kind. *Note patients with thyroiditis may be retreated on replacement therapy. Patients must be evaluated to rule out pituitary disease prior to initiating thyroid replacement.	
Recommended management: TSH, T3, and T4 will be collected at baseline. After baseline, TSH will be collected every 6 weeks; T3/T4 will be collected when indicated. See Endocrine Management Algorithm	

Renal	**Management/Next Dose for Nivolumab and combination Nivolumab/ipilimumab**
≤ Grade 1	Continue at same dose at investigator discretion
Grade 2	Hold pending evaluatio. Resume at same dose level at investigator discretion.
Grade 3	Off study treatment
Grade 4	Off study treatment
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever	
Infusion reaction	**Management/Next Dose for Nivolumab and combination Nivolumab/ipilimumab**
≤ Grade 1	Continue at slower rate at investigator discretion
Grade 2	Hold until ≤ Grade 1. Resume at same dose level
Grade 3	Hold until ≤ Grade 1. Resume at same dose level
Grade 4	Off protocol therapy
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever *See section 5.8- Treatment of Nivolumab or Ipilimumab Infusion reactions*	

Fever	**Management/Next Dose for Nivolumab**
≤ Grade 1	Evaluate and continue at same dose level

Fever	**Management/Next Dose for Nivolumab**
Grade 2	Continue at investigator discretion
Grade 3	Hold until ≤ Grade 1. Resume at same dose level at investigator discretion.
Grade 4	Off protocol therapy
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever	
See section 5.8: Treatment of Nivolumab or Ipilimumab Infusion reactions	

If treatment is delayed >8 weeks for an adverse event, the patient must be permanently discontinued from study therapy.

Patients requiring high dose steroid treatment for autoimmune or inflammatory events should be managed as described in section 5.7, except for a short course of tapering steroids for infusion reaction, skin rash, or endocrine events.

Patients with grade 3 thyroiditis and skin rash may continue therapy as for grade 2 events with resolution and stable replacement treatment.

Patients with thyroiditis or hypopituitarism who are stable as above may be restarted with replacement hormones including thyroid hormone and physiologic doses of corticosteroids. Please note that grade for hypophysitis with symptoms of headache, visual, or neurologic changes or radiologic evidence of pituitary enlargement and other CNS events such as aseptic meningitis or encephalitis should be considered grade 3 events.

Any patient who requires additional immune suppressive treatment beyond steroids should go off protocol therapy.

Patients requiring > two dose delays, other than for evaluation for the same event, should go off protocol therapy. Patients may be dose-delayed for evaluation and restarted depending on results.

Prior to starting corticosteroids or hormone replacement for any reason, appropriate endocrine testing including cortisol, ACTH, TSH and T4 must be obtained to document baseline.

Please note that in some cases the treatment algorithms recommend steroids if symptoms do not resolve in 7 days. However, this recommendation is not meant to delay steroid treatment at any time it is clinically indicated.

Any patient started on corticosteroids initially who is determined to not require steroids treatment for an autoimmune adverse event may resume therapy after a 2 week observation period without further symptoms at the discretion of the PI or investigator.

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The

following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

7.1.2 CAEPRs for CTEP IND Agent

7.1.2.1 CAEPR for Nivolumab

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
BMS-936558 (Nivolumab, MDX-1106, NSC 748726)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2069 patients.* Below is the CAEPR for BMS-936558 (Nivolumab, MDX-1106).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.2, November 15, 2016[1]

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 4.0 Term) [n= 782]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
CARDIAC DISORDERS			
		Cardiac disorders-other (cardiomyopathy)	
		Myocarditis	
		Pericardial tamponade[2]	

		Pericarditis	
ENDOCRINE DISORDERS			
	Adrenal insufficiency		
	Endocrine disorders - Other (hypophysitis)		
	Hyperthyroidism		
	Hypothyroidism		
EYE DISORDERS			
		Eye disorders - Other (diplopia)	
		Eye disorders – Other (Graves ophthalmopathy)	
		Eye disorders - Other (optic neuritis retrobulbar)	
	Uveitis		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis		
		Colonic perforation	
	Diarrhea		***Diarrhea (Gr 2)***
	Dry mouth		***Dry mouth (Gr 2)***
		Gastritis	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[3]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
	Infusion related reaction[4]		
	Injection site reaction		***Injection site reaction (Gr 2)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
		Autoimmune disorder[5]	
		Cytokine release syndrome[6]	
		Immune system disorders - Other (GVHD in the setting of autotransplant)[7]	

		Immune system disorders – Other (sarcoid granuloma)[5]	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Creatinine increased		
	Lipase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		
	Platelet count decreased		
	Serum amylase increased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Hyperglycemia	***Hyperglycemia (Gr 2)***
		Metabolism and nutritional disorders - Other (diabetes mellitus with ketoacidosis)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue disorder- Other (polymyositis)	
		Musculoskeletal and connective tissue disorder- Other (rhabdomyolysis)	
		Myositis	
NERVOUS SYSTEM DISORDERS			
		Encephalopathy	
		Facial nerve disorder[5]	

		Nervous system disorders – Other (demyelination myasthenic syndrome)	
		Nervous system disorders – Other (encephalitis)	
		Nervous system disorders – Other (Guillain-Barre syndrome)[5]	
		Nervous system disorders - Other (meningoencephalitis)	
		Nervous system disorders - Other (meningoradiculitis)	
		Nervous system disorders – Other (myasthenia gravis)[5]	
		Nervous system disorders - Other (myasthenic syndrome)	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleural effusion		
	Pneumonitis		
		Respiratory, thoracic and mediastinal disorders – Other (brochiolitis obliterans with organizing pneumonia)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***

	Skin hypopigmentation		
	Skin and subcutaneous disorders – Other (Sweet's Syndrome)		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Pericardial tamponade may be related to possible inflammatory reaction at tumor site.

[3]Pancreatitis may result in increased serum amylase and/or more frequently lipase.

[4]Infusion reactions, including high-grade hypersensitivity reactions which have been observed following administration of nivolumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of nivolumab.

[5]BMS-936558 (Nivolumab, MDX-1106) being a member of class of agents involved in the inhibition of "immune checkpoints", may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous pemphigoid; exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia, systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome.

[6]Cytokine release syndrome may manifest as hemophagocytic lymphohistiocytosis with accompanying fever and pancytopenia.

[7]Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell transplant (SCT) after receiving BMS-936558 (Nivolumab, MDX-1106). These complications may occur despite intervening therapy between receiving BMS-936558 (Nivolumab, MDX-1106) and allo-SCT.

Also reported on BMS-936558 (Nivolumab, MDX-1106) trials but for which there is insufficient evidence to suggest that there was a reasonable possibility that BMS-936558 caused the adverse event:

CARDIAC DISORDERS – Atrial fibrillation; Atrioventricular block complete; Heart failure; Pericarditis; Ventricular arrhythmia

EAR AND LABYRINTH DISORDERS – Vestibular disorder
EYE DISORDERS - Eye disorders – Other (iridocyclitis); Optic nerve disorder
GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Flatulence; Gastrointestinal disorders - Other (mouth sores); Mucositis oral; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS – Chills; Edema limbs; Malaise; Pain
HEPATOBILIARY DISORDERS – Bile duct stenosis
IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic microangiopathy); Immune system disorders – Other (limbic encephalitis)
INFECTIONS AND INFESTATIONS – Bronchial infection; Lung infection; Sepsis; Upper respiratory infection
INVESTIGATIONS - GGT increased; Investigations - Other (blood LDH increased); Investigations - Other (protein total decreased); Investigations - Other (WBC count increased); Lymphocyte count increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia, Hypocalcemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (histiocytic necrotizing lymphadenitis)
NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Intracranial hemorrhage
PSYCHIATRIC DISORDERS - Insomnia
RENAL AND URINARY DISORDERS – Hematuria; Renal and urinary disorders - Other (tubulointerstitial nephritis)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS – Bronchospasm; Cough; Dyspnea; Hypoxia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS – Alopecia; Dry skin; Hyperhidrosis; Pain of skin; Periorbital edema; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea); Toxic epidermal necrolysis
VASCULAR DISORDERS – Flushing; Hypertension; Hypotension; Vasculitis

Note: BMS-936558 (Nivolumab, MDX-1106) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.2.2 CAEPR for Ipilimumab

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Ipilimumab (MDX-010, NSCs 732442 and 720801)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform

presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2678 patients.* Below is the CAEPR for Ipilimumab (MDX-010).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.8, December 21, 2016[1]

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 4.0 Term) [n= 2678]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Blood and lymphatic system disorders - Other (acquired hemophilia)	
CARDIAC DISORDERS			
	Atrial fibrillation		
		Myocarditis[2]	
EAR AND LABYRINTH DISORDERS			
	Hearing impaired		
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (hypopituitarism/hypophysitis)[2]		
	Endocrine disorders - Other (testosterone deficiency)[2]		
	Hyperthyroidism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
	Eye disorders - Other (episcleritis)[2]		
	Uveitis[2]		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 4.0 Term) [n= 2678]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		***Colitis (Gr 3)***
		Colonic perforation[3]	
	Constipation		
Diarrhea			***Diarrhea (Gr 3)***
	Enterocolitis		
	Esophagitis		
		Ileus	
Nausea			***Nausea (Gr 3)***
	Pancreatitis[2]		
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Infusion related reaction		
		Multi-organ failure	
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
	Autoimmune disorder[2]		
		Immune system disorders - Other (GVHD in the setting of allotransplant)[4]	
INFECTIONS AND INFESTATIONS			
		Infections and infestations - Other (aseptic meningitis)[2]	
INVESTIGATIONS			
	Alanine aminotransferase increased		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 4.0 Term) [n= 2678]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Aspartate aminotransferase increased		
	Neutrophil count decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		
	Hyperglycemia		
		Metabolism and nutrition disorders – Other (exacerbation of pre-existing diabetes mellitus)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Arthritis		
	Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]		
NERVOUS SYSTEM DISORDERS			
	Facial nerve disorder		
	Headache		
	Nervous system disorders - Other (Guillain-Barre syndrome)[2]		
	Nervous system disorders - Other (myasthenia gravis)[2]		
	Trigeminal nerve disorder		
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
	Renal and urinary disorders - Other (granulomatous tubulointerstitial nephritis)		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 4.0 Term) [n= 2678]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Respiratory, thoracic and mediastinal disorders – Other (bronchiolitis obliterans with organizing pneumonia)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Pruritus		***Pruritus (Gr 3)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
	Skin and subcutaneous disorders - Other (Sweet's Syndrome)		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
	Urticaria		
VASCULAR DISORDERS			
	Hypotension		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Ipilimumab can result in severe and fatal immune-mediated adverse events probably due to T-cell activation and proliferation. These can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune thyroiditis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, and adrenal insufficiency), ocular manifestations (e.g., uveitis, iritis, conjunctivitis, blepharitis, and episcleritis), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome. The majority of these reactions manifested early during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab especially with the initiation of additional

treatments.

[3]Late bowel perforations have been noted in patients receiving MDX-010 (ipilimumab) in association with subsequent IL-2 therapy.

[4]Complications including hyperacute graft-versus-host disease (GVHD), may occur in patients receiving allo stem cell transplant (SCT) after receiving Ipilimumab (MDX-010). These complications may occur despite intervening therapy between receiving Ipilimumab (MDX-010) and allo-SCT.

[5]In rare cases diplopia (double vision) has occurred as a result of muscle weakness (Myasthenia gravis).

[6]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC

[7]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on Ipilimumab (MDX-010) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Ipilimumab (MDX-010) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (pure red cell aplasia)[2]; Febrile neutropenia
CARDIAC DISORDERS - Conduction disorder; Restrictive cardiomyopathy
EYE DISORDERS - Extraocular muscle paresis[5]; Eye disorders - Other (retinal pigment changes)
GASTROINTESTINAL DISORDERS - Dyspepsia; Dysphagia; Gastrointestinal hemorrhage[5]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure[2]
IMMUNE SYSTEM DISORDERS - Allergic reaction
INFECTIONS AND INFESTATIONS - Infection[7]
INVESTIGATIONS - Creatinine increased; Investigations - Other (rheumatoid factor); Lipase increased; Platelet count decreased; Serum amylase increased; Weight loss; White blood cell decreased
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Joint range of motion decreased; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Dizziness; Dysphasia; Ischemia cerebrovascular;

Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia
RENAL AND URINARY DISORDERS - Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Cough; Dyspnea; Laryngospasm
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia, Dry skin; Hyperhidrosis; Skin hypopigmentation
VASCULAR DISORDERS - Flushing; Hypertension; Vascular disorders - Other (temporal arteritis)

Note: Ipilimumab (MDX-010) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.3 Adverse Event List(s) for *[Other Investigational Agent(s)]*

Not Applicable

7.1.4 Adverse Event List(s) for Commercial Agent(s)

Not Applicable

7.1.5 CAEPR for *[CIP IND Agent #1)]*

Not Applicable

7.1.6 Adverse Event List(s) for CIP (*e.g.* Study-Specific) Commercial Imaging Agents

Not Applicable

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.2 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.3 CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

The Coordinating Center of the Corresponding Organization is responsible for submitting to the CTSU documentation of AEs that they deem reportable for posting on the CTSU protocol web page and inclusion on the CTSU bi-monthly broadcast.

7.3.4 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign,**

malignant and unspecified (including cysts and polyps) - Other (Progressive Disease)" under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.5 Secondary Malignancy

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

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.6 Second Malignancy

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

8 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent(s)

8.1.1 Nivolumab

Amino Acid Sequence: 4 polypeptide chains, which include 2 identical heavy chains with 440 amino acids and 2 identical light chains.

Other Names: BMS-936558, MDX1106

Classification: Anti-PD-1MAb

M.W.: 146,221 daltons

Mode of Action: Nivolumab targets the programmed death–1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor. PD-1 is a negative regulatory receptor expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligand 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Nivolumab inhibits the binding of PD-1 to PD-L1 and PD-L2. 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.

Description: Nivolumab Injection 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 in sodium citrate, sodium chloride, mannitol, diethylenetriamine pentacetic acid (pentetic acid) and polysorbate 80 (Tween® 80), pH 6.0.

How Supplied: Nivolumab is supplied by Bristol-Myers Squibb and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as 100 mg vials (10 mg/mL) with a 0.7 mL overfill. It is supplied in 10 mL type I flint glass vials, with butyl rubber stoppers and aluminum seals.

Preparation: Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose, USP to concentrations no less than 0.35 mg/mL.

Storage: Vials of Nivolumab injection must be stored at 2°-8°C (36°-46°F) and protected from light, freezing, and shaking.

Stability: Shelf-life surveillance of the intact vials is ongoing.

The administration of undiluted and diluted solutions of Nivolumab must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 24 hours in a refrigerator at 2°-8°C (36°-46°F) and a maximum of 4 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and room light. The maximum 4-hour period under room temperature and room light conditions includes the product administration period.

CAUTION: The single-use dosage form contains no antibacterial preservative or bacteriostatic agent. Therefore, it is advised that the product be discarded 8 hours after initial entry.

Route of Administration: Intravenous infusion. Do not administer as an IV push or bolus injection.

Method of Administration: Administer through a 0.2 micron to 1.2 micron pore size, low-protein binding polyethersulfone membrane in-line filter.

Potential Drug Interactions: No incompatibilities between Nivolumab injection and polyvinyl chloride (PVC), non-PVC/non-DEHP (di[2-ethylhexyl]phthalate) IV components, or glass bottles have been observed.

Availability

Nivolumab is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Nivolumab is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.2 Ipilimumab (NSC 732442)

Chemical Name or Amino Acid Sequence: 4 polypeptide chains, 2 identical heavy chains with 447 amino acids and 2 identical light chains consisting of 215 amino acids.

Other Names: Anti-CTLA-4 monoclonal antibody, MDX-010, Yervoy™

Classification: Human monoclonal antibody

M.W.: 147,991 Daltons

Mode of Action: Ipilimumab is specific for the CTLA4 antigen expressed on a subset of activated T-cells. CTLA4 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 CTLA4 with the B7 ligand, resulting in a blockade of the inhibitory effect of T-cell activation. The CTLA4/B7 creates the interaction.

Description: Ipilimumab is a fully human immunoglobulin ($IgG_1\kappa$) with two manufacturing processes – ongoing trials have been using substances manufactured using Process B. New clinical trials will be using ipilimumab that is manufactured by Process C. The Process C has been developed using a higher producing sub-clone of the current Master Cell Bank, and modified cell culture and purification steps.

How Supplied: Bristol-Myers-Squibb (BMS) supplies Ipilimumab to the DCTD/NCI. 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.

Each vial is a Type I flint glass vial with gray butyl stoppers and sealed with aluminum seals.

	Process C
Component	**200 mg/ vial**[a]
Ipilimumab	213 mg
Sodium Chloride, USP	249 mg
TRIS-hydrochloride	134.3 mg
Diethylenetriamine pentacetic acid	1.67 mg
Mannitol, USP	426 mg
Polysorbate 80 (plant-derived)	4.69 mg
Sodium Hydroxide	QS to pH 7
Hydrochloric acid	QS to pH 7
Water for Injection	QS: 42.6 mL
Nitrogen[b]	Processing agent

[a]Includes 2.6 mL overfill.
[b]Nitrogen is used to transfer the bulk solution through the pre-filled and sterilizing filters into the aseptic area.

Preparation: Ipilimumab is given undiluted or further diluted in 0.9% NaCl Injection, USP or 5% Dextrose Injection, USP in concentrations between 1 mg/mL and 4 mg/mL. Ipilimumab is stable in a polyvinyl chloride (PVC), non-PVC/non DEHP (di-(2-ethylhexyl) phthalate) IV bag or glass container up to 24 hours refrigerated at (2^0 to 8^0 C) or at room temperature/ room light.

Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.

Storage: Store intact vials refrigerated at (2^0 to 8^0 C), protected from light. Do not freeze.

Stability: Shelf-life surveillance of the intact vials is ongoing. Solution as described above is stable up to 24 hours refrigerated at (2^0 to 8^0 C) or at room temperature/ room light.

CAUTION: Ipilimumab does not contain antibacterial preservatives. Use prepared IV solution immediately. Discard partially used vials.

Route*(s)* **of Administration:** Intravenous infusion. Do not administer ipilimumab as an IV push or bolus injection.

Method of Administration: Can use a volumetric pump to infuse ipilimumab at the protocol-specific dose(s) and rate(s) via a PVC IV infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (0.2 micron to 1.2 micron).

Patient Care Implications: Monitor patients for immune-related adverse events, e.g., rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis and hypothyroidism. If you suspect toxicity, refer to

the protocol guidelines for ruling out other causes.

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.1.3.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.3.3 Investigator Brochure Availability – The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

8.1.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci,nih.gov

- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://eapps-ctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- IB coordinator: IBCoordinator@mail.nih.gov
- PMB phone and hours of services: (240)276-6575 Monday through Friday between 8:30AM and 4:30PM (ET)

9 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Integrated Laboratory or Imaging Studies

9.1.1 Immunohistochemical Staining for PDL1 (CD274), PDL2 (CD273) and PD1 (CD279)

We hypothesize that CD274, CD273 and CD279 protein expression in tumor tissues might be associated with favorable clinical response to immune checkpoint inhibition, and might serve as biomarkers for patient selection for CD279 blockade in clinical treatment. PDL1 assessment by BMS DAKO kit will be considered an integrated biomarker for this study because PDL1 assessment by this method has been used across multiple studies evaluating nivolumab and therefore will support standardization, reproducibility, and comparison across studies. Additional staining for PDL1 by the antibody method noted below will occur in parallel for exploratory comparison of these two techniques.

9.1.1.1 Collection of Specimen(s)

Assay, patient and specimen information

Immunohistochemical (IHC) staining of CD274 will be used as an integrated biomarker in this clinical trial, and to identify a group of patients most likely to respond to the immune checkpoint inhibition with nivolumab or nivolumab and ipilimumab. This information may be used in the future phase II trials as a stratification variable. IHC staining of CD273, CD279 will also be performed as exploratory biomarkers to explore a possible relationship between expression and response to nivolumab or nivoluamb and ipilimumab in this population. Pre-treatment archival tumor material will be collected for all eligible patients. In addition, because expression of these markers may change over time, paired immediate pre-treatment and post- treatment biopsies will be obtained in all patients enrolled to Cohort B. In Cohort A, pre-treatment archival tumor material was collected for ten out of the twelve patients treated. In Cohort A, paired biopsies were not required for all participants; one set of paired biopsies was conducted. These paired biopsies will

be collected and fixed by 10% neutral buffered formalin overnight, dehydrated and paraffin embedded. Four-micrometer-thick sections will be cut. The paraffin blocks and unstained slides will be stored at room temperature. All IHC staining will be performed in the Center for Immuno-Oncology Pathology Core at Dana-Farber/Harvard Cancer Center Specialized Histopathology Core, which will be a central research laboratory for this multiple-center clinical trial. Unstained slides from other two centers will be shipped to Dr Xiaoyun Liao, Thorn building 603B, Brigham and Women Hospital, 75 Francis Street, Boston, MA, 02215.

Primary antibody characteristics

Mouse monoclonal anti-CD279, anti-CD274 and anti-CD273 antibodies were generated in the laboratory of Dr. Gordon Freeman (Dana-Farber Cancer Institute). The antibodies are human gene product and can recognize all isoforms. The specificity of these antibodies was confirmed by western blotting in human cancer cell lines and bands were at expected mass. The IHC staining was abolished in knock-down cancer cells. CD279 is expressed on the surface of activated T cells. CD274 is present in macrophages, dendritic cells, T cells, B cells and in multiple cancers (Sznol M, 2013). CD273 is expressed on dendritic cells, macrophages and bone marrow-derived mast cells whereas its expression on cancers is under exploration (Rozali EN, 2012). No cross-reactive proteins that may confound interpretation of IHC staining were identified. The antigens are stable when the period between tissue sectioning and staining is more than 30 days.

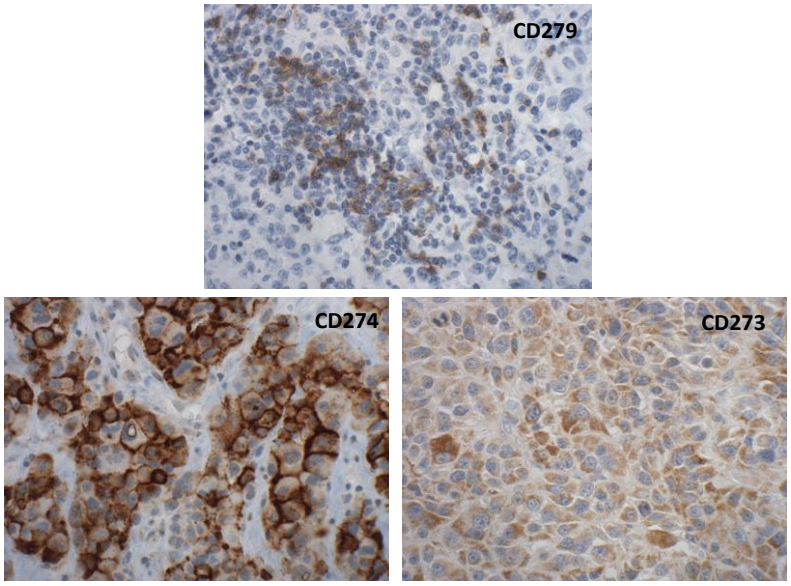
Design of immunohistochemical assay

The IHC assay for CD274, CD273 is semi-quantitative while CD279 stained slides will be scanned by an automated scanning microscope and quantitatively analyzed by Aperio image analysis system (Leica Biosystems) after they are evaluated and positive cells are manually counted by a pathologist.

Standard EnVision two-step (indirect) staining method will be utilized. Four-micrometer-thick sections will be cut, deparaffinized, rehydrated and subjected to heat mediated antigen retrieval in citrate buffer (pH 6) (Invitrogen) by steaming for 30 minutes. After cooling, tissue sections will be incubated with peroxidase block (DAKO, Carpinteria, CA) for five minutes, then serum free protein block (DAKO) for 20 minutes. Slides will be incubated at room temperature for one hour with a primary antibody. Antibodies will be diluted in Da Vinci Green Diluent (Biocare Medical, Concord, CA). Envision^{TM} anti-mouse HRP-labeled polymer (DAKO) will be applied to the sections for 30 minutes, followed by visualization by using the chromogen 3, 3-diaminobenzidine (DAKO). All the sections will then be counterstained with haematoxylin, dehydrated, mounted and coverslipped. Positive and negative controls shall be included in each staining. Known positive stained Hodgkin lymphoma (CD274), tonsil (CD279) and melanoma (CD273) slides will be used as external control (separate slides). Stained slides will be stored at room temperature.

In our pilot study, immunoreactivity for CD274 was detected in the cytoplasm and cell membrane while CD273 and CD279 expression was observed in the cytoplasm. Scoring for CD274, CD273 will be semi-quantitative/ordered categorical. The percentage of the tumor cells staining positive for CD274, CD273 and the intensity of the tumor cells will be recorded as 0 (no staining), 1 (weak staining), 2 (moderate staining) and 3 (intense staining). Absolute CD279 positive cells will be counted under microscope lens x 20 power field. Representative 5 areas will be chosen to count. The average number from 5 areas will be recorded and be compared with data from image analysis.

Figure shows the immunohistochemical staining of CD279, CD274 and CD273 in advanced melanoma.



Assay performance

The results will be obtained on retrospective data sets. Protocols of these three antibodies have been optimized, standardized to minimize staining variance. Positive control and negative controls were used and stained separately with each batch of slides. The IHC staining of three markers (CD274, CD273 and CD279) has been performed in two different labs by three different technicians on whole tissue sections of Hodgkin lymphomas, melanomas, lung cancers and renal cell carcinomas. Three readers were involved, confirming the good reproducibility of the assay. Tumor will be considered positive if >5% (CD274) (Topalian S, 2012) or 10% (CD273) of the tumor cell population demonstrates unequivocally staining, respectively. CD279 positivity was defined as >3% positive cells/HPF (Bachireddy P, 2013). Statistically, Fisher's Exact Test will be used to measure the association between CD274, CD273, CD27 expression and objective response

of patients. All p values will be two sided, and statistical significance will be set at $p<0.05$.
All IHC stained slides will be evaluated and scored by a pathologist (Dr Xiaoyun Liao). A subset of slides will be reviewed by a second pathologist (Dr Scott Rodig) to ensure concordance of interpretation.
For CD279 staining, slides will be scanned by an automated scanning microscope and analyzed by Aperio image analysis system (Leica Biosystems). Tumor areas will be marked by a pathologist to exclude non-neoplastic areas, such as stroma, normal epithelial and necrotic regions. The software will be used to count the number of positive cells in each tissue. The percentage of CD279 positive cells will be calculated. Data will be compared with that of manual counting by a pathologist to exclude tissue artifacts that cannot be recognized by computer image software.

9.1.1.2 Site Performing Correlative Study

Laboratory information
The IHC staining, including the CD274 by BMS DAKO kit, will be conducted in a research laboratory with GLP standard by Dr. Xiaoyun Liao. Dr. Liao received her medical degree and anatomical pathology training from Peking University Health Science Center, Beijing, China, and obtained her PhD degree from the University of Hong Kong Faculty of Medicine, Hong Kong, China. Before she joined Dana-Farber Cancer Institute in 2010, she served Peking University as a general pathologist for over 15 years. She completed her postdoctoral research fellow training at Dana-Farber Cancer Institute in 2013 and joined Center for Immuno-Oncology Pathology Core. Dr. Liao has extensive experience in tumor pathology and immunohistochemistry (Liao X, 2012). Dr. Scott Rodig is a hematopathologist at the Brigham and Women's hospital with prior expertise evaluating PD1, PDL1 and other immunologic markers in paraffin embedded tumor samples (Chen BJ, 2013).

9.2 Exploratory/Ancillary Correlative Studies

9.2.1 Monitoring Peripheral Blood for Changes in Immune Function

Subpopulations of PBMCs will be isolated, including but not limited to dendritic cells, T cells, and B cells. Phenotype changes in these cell populations by flow cytometry will be determined as a function of treatment. These include regulatory and effector immune panels, naïve and memory CD4, CD8 and NK lymphocyte populations. Both humoral and cellular immune responses will be investigated by ELISAs, ELISPOTs, and cytotoxic T cell chromium release assays.

IHC staining of PDL2 (CD273) and PD1 (CD279) will be performed as exploratory assays as noted above in section 9.1.

9.2.1.2 Handling of Specimens(s)
Peripheral blood:
In Cohort A, serial blood/serum samples was collected every 2 weeks prior to each nivolumab

administration starting on day 1 (pre-treatment), through week 12, and then with decreased frequency as per section 10. In Cohort B, serial blood/serum samples will be collected at week 1 of each cycle prior to study drug infusion starting on day 1 (pre-treatment), through cycle 4. A panel of cytokines and chemokines will be tested in serum using Luminex cytokine assay. Changes in cytokine production in immune cell subsets as a function of treatment will be determined by ELISA and intracellular cytokine staining. Absolute lymphocyte count (ALC) will be monitored.

Peripheral blood mononuclear cells (PBMCs) will be collected from whole blood to assess immune cell populations. Surface staining with a panel of antibodies (CD3, CD4, CD8, CD25, FoxP3, CD11c, CD83, CD86, CD56) and intracytoplasmatic cytokine staining, followed by flow cytometry will be performed in order to identify different T cell populations, their activation status, and the production of different cytokines as well as other immune cell populations as described below.

		FITC	PE	ECD	PE-Cy5	PE-Cy7
1	**Treg (1); intracellular**	FoxP3	CTLA-4	CD3	CD25	CD4
2	**T, B, monocyte, NK,NKT**	CD19	CD56	CD14	CD45	CD3
3	**T cell subset**	CD8	TCRγδ	CD4	TCRαβ	CD3
4	**CD4 T cell naïve memory**	CCR7	CD57	CD45RO	CD28	CD4
5	**CD8 T cell naïve memory**	CCR7	CD57	CD45RO	CD28	CD8
6	**Myeloid DC**	Lineage (CD3,CD14, CD16,CD19,CD56)	CD86	HLA-DR	CD11c	CD45
7	**Plasmacytoid DC**	Lineage (CD3,CD14, CD16,CD19,CD56)	CD86	HLA-DR	CD45	CD123
8	**PD1-ICOS**	ICOS	PD-1	CD3	CD8	CD4
9	**41BB-OX40**	CD3	4-1BB	CD8	OX-40	CD4
10	**CD127 Treg**	CD3	CD127	CD25	CD27	CD4
11	**NK,NKT**	CD16	NKG2D	CD3	CD56	CD8
12	**BDCA.DC**	BDCA-2	BDCA-1	CD14,CD19	BDCA-3	CD45

Serum marker levels will be summarized descriptively and graphically for the patient population. The time course of expression levels will also be summarized graphically by patient, noting times of disease response and disease progression.

9.2.1.3 Sites Performing Correlative Study

The Center for Immuno-oncology Immune Assessment core facilitates the collection, processing, and trafficking of patient blood samples on CIO clinical trials. The Immune Assessment Core has standardized multi-color flow assays for phenotying immune cells as well as standardized ELISA and Luminex platform analyses. Studies will be performed in the Center for Immuno-oncology Immune Assessment core facilitates at Dana-Farber Cancer Institute

9.2.2 **Targeted gene-expression profiling.**

As an exploratory end-point, targeted gene expression profiling will be performed on biopsy samples, when sufficient material is available, to determine the relative expression of a comprehensive set of gene products (161) involved in all aspects of immuno-regulation. The Nanostring nCounter platform will be used for this analysis as it has proven effective for targeted gene expression profiling using RNA isolated from formalin-fixed, paraffin embedded tissues (Scott DW et al., 2014, PMID:24398326). The nCounter platform is located at the Center for Advanced Molecular Diagnostics (CAMD), a CLIA-certified laboratory in the Department of Pathology at BWH. Dr. Rodig's laboratory has extensive experience with the operation of the analytical platform and the analysis of the resulting data (Carey CD et al., J. Mol. Diagn., 2014, *in press*).

RNA will be isolated from 3 X 10um sections of formalin-fixed, paraffin embedded material. The resulting RNA will be quantified using a bioanalyzer and 250ng used for targeted gene expression analysis following manufacturer's protocols. The resulting data will be interrogated to establish whether a limited and defined gene-expression signature is predictive of clinical responses to therapy.

9.3 Integral Correlative Studies

Not applicable

10 STUDY CALENDAR

Cohort A- Nivolumab Monotherapy

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy. Baseline assessments include: hematology panel, serum chemistry panel, pregnancy test, physical examination, medical history, concurrent medications evaluations, and vital signs Scans and x-rays must be done ≤4 weeks prior to the start of therapy. CBC and serum chemistries must be obtained on Week 1 Day 1 and reconfirm eligibility criteria. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next dose of therapy.

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12[d]	Off Study[c]
Nivolumab		A		A		A		A		A		A		
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds	X	X----------											X	
Physical exam	X	X		X		X		X		X		X		X
Vital signs	X	X		X		X		X		X		X		X
Height	X													
Weight	X	X		X		X		X		X		X		X
Performance status	X	X		X		X		X		X		X		X
CBC w/diff, plts[a]	X	X		X		X		X		X		X		X
Serum chemistry[a]	X	X		X		X		X		X		X		X
HIV, Hep B, Hep C screen[J]	X													
EKG (as indicated)	X													
Adverse event evaluation		X----------											X	X
Tumor measurements	X	Tumor measurements are repeated every 12 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X
B-HCG	X[b]													
Tumor [E]	X[F]				X[H]									
Immune correlatives[G]		X		X		X		X		X		X		X
Archival Tumor Tissue[I]	X													

A: Nivolumab: 3mg/kg IV administered over 60 minutes, every two weeks (+/- 2days)

a: Laboratory testing prior to each dose: Within 72 hrs prior to re-dosing to include CBC w/ differential, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, and lipase. TSH will be collected at screening and repeated every 6 weeks unless clinically indicated. Reflexive Free T4 and Free T3 will be collected at screening and repeated when clinically indicated.

b: A serum or urine pregnancy test is required at baseline for women of childbearing potential.

c: Off-study evaluation. AE assessment will be performed at 100 days following last dose of study drug. This

may be done by phone. Patients who complete all planned protocol therapy (46 doses), will continue to be monitored for tumor measurements beyond completion of treatment until disease progression or the initiation of a new anticancer therapy.

d: Schedule post week 12 will repeat as per weeks 1 -12, with the exception of pre/post tumor biopsy and correlative studies

E: Pre/post tumor biopsies will be performed whenever possible, and in a minimum of 10 patients

F: Pre-study tumor biopsy to be performed after eligibility is confirmed and patient is registered on study and prior to first dose of nivolumab.

G: Peripheral blood will be drawn prior to each dose of nivolumab for the first 12 weeks to assess changes in immune function as per section 9.2. After week 12, this will be drawn every 6 weeks prior to dosing for the next 12 weeks, then every 3 months. Samples will also be drawn within 7 days of an objective response, and at off-study.

H: Post-treatment biopsy will be performed at approximately week 4-6 (+/- 7 days)

I: Archival tissue specimen will be collected if available. This is not required prior to study drug dosing.

J: Testing for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS), hepatitis B virus surface antigen (HBV sAg) and hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection.

K. Tumor assessments are repeated every 12 weeks (+/- 2 days) and should continue as per protocol even if dosing is interrupted.

Cohort B: Nivolumab + Ipilimumab

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy. Baseline assessments include: hematology panel, serum chemistry panel, pregnancy test, physical examination, medical history, concurrent medications evaluations, and vital signs. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. CBC and serum chemistries must be obtained on Week 1 Day 1 and reconfirm eligibility criteria. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next dose of therapy.

	Pre-Study	Part I: Nivolumab + Ipilimumab Cycles 1-4 1 cycle = 3 weeks			Part II: Nivolumab Monotherapy Cycles 5+ 1 cycle = 2 weeks		Off Study[c]
		Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	
Nivolumab		A			A		
Ipilimumab		B					
Informed consent	X						
Demographics	X						
Medical history	X						
Concurrent meds	X	X----------X					
Physical exam	X	X			X		X
Vital signs	X	X			X		X
Height	X						
Weight	X	X			X		X
Performance status	X	X			X		X
CBC w/diff, plts[a]	X	X			X		X
Serum chemistry[a]	X	X			X		X
HIV, Hep B, Hep C screen[i]	X						
EKG (as indicated)	X						
ECHO (as indicated)[k]	X	X----------X					
Cardiac evaluations[l]	X	X----------X					
Adverse event evaluation		X----------X					X
Tumor measurements[j]	X	Tumor measurements are repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.					X
B-HCG	X[b]						
Tumor[d]	X[e]						
Immune correlatives[f]		X					X
Archival Tumor Tissue[h]	X						

A: Nivolumab: 3mg/kg IV administered over 60 minutes, every three weeks (+/- 2 days) for the first four cycles. Starting cycle 5, nivolumab will be given as monotherapy every two weeks (+/- 2 days) at a dose of 3 mg/kg.

B: Ipilimumab: 1mg/kg IV administered over 90 minutes, every three weeks (+/- 2 days) for cycles 1-4.

a: Laboratory testing prior to each dose: Within 72 hrs prior to re-dosing to include CBC w/ differential, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, and lipase. TSH will be collected at screening and repeated every 6 weeks unless clinically indicated. Reflexive Free T4 and Free T3 will be collected at screening and repeated when clinically indicated.

b: A serum or urine pregnancy test is required at baseline for women of childbearing potential.

c: Off-study evaluation. AE assessment will be performed at 100 days following last dose of study drug. This may be done by phone. Patients who complete all planned protocol therapy (46 doses), will continue to be monitored for tumor measurements beyond completion of treatment until disease progression or the initiation of a new anticancer therapy.

d: Pre/post tumor biopsies will be required for all participants.

e: Pre-study tumor biopsy to be performed after eligibility is confirmed and patient is registered on study and prior to first dose of combination therapy with nivolumab + ipilimumab .

f: Peripheral blood will be drawn prior to study drug infusion for the first 4 cycles to assess changes in immune function as per section 9.2. Samples will also be drawn within 7 days of an objective response, and at off-study.

g: Post-treatment biopsy will be performed at approximately week 4-6 (+/- 7 days)

h: Archival tissue specimen will be collected if available. This is not required prior to study drug dosing.

i: Testing for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS), hepatitis B virus surface antigen (HBV sAg) and hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection. These viral serologies may be performed within 28 days of registration.

j. Tumor assessments are repeated every 8 weeks (+/- 2 days) and should continue as per protocol regardless of dosing interruptions.

k. For patients with a history of congestive heart failure (CHF) or at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs, EKG and ECHO will be collected as clinically indicated.

l. For patients with evidence of CHF, myocardial infarction (MI), cardiomyopathy, or myositis, cardiac evaluation including lab tests and cardiology consultation (EKG, CPK, troponin levels, ECHO) will be conducted as clinically indicated.

11 MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks (+/- 2 days). In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of 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) [*Eur J Ca* 45:228-247, 2009]. 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.

All patients who receive at least one dose of nivolumab and ipilimumab each will be included in the toxicity analysis. This includes participants who receive study drug and are ultimately deemed ineligible.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with nivolumab and ipilimumab.

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).

Note: Tumor lesions that are situated in a previously irradiated area will not be

considered measurable, unless there is clear evidence of progression of the lesion since completion of radiation and prior to enrollment on study.

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.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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.

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

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.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

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

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

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria: RECIST version 1.1.

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.

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/Non-PD/not evaluated	No	SD	Documented at least once ≥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.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may beaccepted 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

Progression-Free Survival will be evaluated as a secondary objective. 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

At study completion, all objective responses (RECIST PR or CR) will be reviewed by the tumor imaging metrics core (TIMC) at the Dana-Farber Harvard Cancer Center. Patient files will be availble to the readers for concurrent review.

11.2 Antitumor Effect – Hematologic Tumors

Not Applicable

11.3 Other Response Parameters

Not Applicable

12 STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

During the Phase 2 portion of the study, the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

12.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (https://eapps-ctep.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, or Site Investigator) on either the Corresponding Organization or Participating Organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.1.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/CTMS. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at ctms@theradex.com for additional support with Rave and completion of CRFs.

12.1.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include the recommended

phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

12.2 CTEP Multicenter Guidelines

N/A

12.3 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with

(an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release.

Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13 STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

COHORT A - Study Design and Endpoints
This is a phase II two-stage clinical trial with a primary endpoint of objective response per RECISTS 1.1 among patients with advanced ULMS treated with nivolumab.
For the primary endpoint of overall response with a null hypothesis of 5% and an alternative hypothesis of 20% we would need 37 patients in a two-stage design with 12 patients in the first stage and 25 patients in the second stage. At the first stage analysis we will assess overall response, we will need to observe at least 1 response out of 12 patients to continue through the second stage. At the second stage we will assess overall response rate again, and we will need to observe at least 4 responses out of 37 patients to accept the treatment. The overall power for overall response rate is 90%. The overall type I error, the chance of incorrectly rejecting the null hypothesis is 9%. The probability of stopping at the first stage under the null hypothesis is 54%. The operating characteristics of this design are calculated using the exact binomial distribution. Subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-definedthe initial progression event but may be designated as delayed responses for purposes of determining ORR and counted as responses for two stage designs.
Paired immediate pre-treatment and post- treatment biopsies will be obtained whenever possible in consenting patients, and in a minimum of 10 patients. If less than 10 patients have provided paired tumor biopsies, the remaining slots will give priority to obtain biopsies in the last group of 10 patients prior to completion of accrual. For the primary endpoint of overall response rate with the parameters as noted in section 13.1, a total sample size of 37 patients is needed in a two-stage design with 12 patients in the first stage and 25 patients in the second stage. A minimum accrual rate is expected to be 3 subjects per month. With a minimal accrual rate of 3 subjects per month, we expect the study enrollment tolast approximately 13 months.

For Cohort A, 12 participants were accrued to the first stage. Since an objective response was not seen in the first stage of Cohort A, enrollment to the second stage did not begin.

COHORT B – Study Design and Endpoints
This phase II two-stage clinical trial will include patients with advanced ULMS treated with

nivolumab and ipilimumab with a primary endpoint of objective response per RECISTS 1.1 among

For the primary endpoint of overall response with a null hypothesis of 5% and an alternative hypothesis of 30% we would need 25 patients in a two-stage design with 8 patients in the first stage and 17 patients in the second stage. At the first stage analysis we will assess overall response, we will need to observe at least 1 response out of 8 patients to continue through the second stage. At the second stage, we will assess overall response rate again, and we will need to observe at least 3 responses out of 25 patients to accept the treatment. The overall power for overall response rate is 94%. The overall type I error, the chance of incorrectly rejecting the null hypothesis is 9%. The probability of stopping at the first stage under the null hypothesis is 66%. The operating characteristics of this design are calculated using the exact binomial distribution.

Subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event but may be designated as delayed responses for purposes of determining ORR and counted as responses for two stage designs.

In order to assess the impact of immune checkpoint inhibition in this population, tissue will be acquired to analyze the integrated biomarkers and determine the potential drug effect in this disease. Biomarkers will be assessed from pre-treatment and post-treatment biopsies collected in a minimum of 10 patients on this study. During enrollment to Cohort A, one set of pre-treatment and post-treatment biopsies was collected; the additional 9 were not performed because the study did not progress to Stage II. In Cohort B, paired immediate pre-treatment and post- treatment biopsies will be collected in the first eight participants who enroll to the study (stage 1-Cohort B). For this cohort, participants are required to have disease that can be biopsied safely, as discussed in Section 3.1.11. Biopsies will be optional among participants enrolled in the second stage of cohort B.

13.2 Sample Size/Accrual Rate

For the primary endpoint of overall response rate with the parameters as noted in section 13.1, a total sample size of 37 patients is needed in a two-stage design with 12 patients in the first stage and 25 patients in the second stage for Cohort A. For Cohort B, a total sample size of 25 patients is needed in a two-stage design with 8 patients in the first stage and 17 patients in the second stage. A minimum accrual rate is expected to be 3 subjects per month. With a minimal accrual rate of 3 subjects per month, we expect the study enrollment to last approximately 9 months.

PLANNED ENROLLMENT REPORT- COHORT A (Closed to Accrual)

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	1	NA	_	NA	**1**
Asian	1	NA	_	NA	**1**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
Native Hawaiian or Other Pacific Islander	1	NA	_	NA	**1**
Black or African American	1	NA	1	NA	**2**
White	31	NA	1	NA	**32**
More Than One Race	-	NA	-	NA	**-**
Total	**35**	**_**	**2**	**_**	**37**

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PLANNED ENROLLMENT REPORT- COHORT B

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	1	NA	_	NA	**1**
Asian	1	NA	_	NA	**1**
Native Hawaiian or Other Pacific Islander	1	NA	_	NA	**1**
Black or African American	1	NA	1	NA	**2**
White	19	NA	1	NA	**20**
More Than One Race	-	NA	-	NA	**-**
Total	**23**	**_**	**2**	**_**	**25**

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13.3 Stratification Factors

There are no planned stratification factors in this study.

13.4 Analysis of Secondary Endpoints

COHORT A – SECONDARY ENDPOINTS

We will also assess toxicity in patients with ULMS treated with nivolumab. Among the first phase of 12 patients, there is at least 58% probability of observing one or more rare (7% true probability) events, and 83% probability of observing toxicities that have a true occurrence of at least 15%. Among the total cohort of 37 patients, there is at least 85% probability of observing one or more rare (5% true probability) events, and 95% probability of observing toxicities that have a true occurrence of at least 8%. With 37 treated patients, the maximum width of a 90% two-sided exact binomial confidence interval for any estimated adverse event proportion will be no wider than ± 14%.

Rate of Progression-free survival at 12 weeks with a null hypothesis of 20% and an alternative hypothesis of 40% at 12 weeks will be investigated. Patients lost to follow-up or deaths within 12 weeks will be counted as failures. The overall power for overall progression-free rate at 12 weeks is 87%, using the exact binomial distribution. The

operating characteristics of this design are calculated using a one-sided exact test with 10% type I error.

COHORT B – SECONDARY ENDPOINTS

Toxicity: Among the first phase of 8 patients, there is at least 57% probability of observing one or more rare (10% true probability) events, and 73% probability of observing one or more toxicities that have a true occurrence rate as low as15%. Among the total cohort of 25 patients, there is at least 84% probability of observing one or more rare (7% true probability) events, and 93% probability of observing toxicities that have a true occurrence of at least 10%. With 25 treated patients, the maximum width of a 90% two-sided exact binomial confidence interval for any estimated adverse event proportion will be no wider than ± 18%.

Rate of Progression-free survival at 6 months with a null hypothesis of 18% and an alternative hypothesis of 40% at 6 months will be investigated. Patients lost to follow-up or deaths within 6 months will be counted as failures. The overall power for overall progression-free rate at 6 months is 85%, using the exact binomial distribution. The operating characteristics of this design are calculated using a one-sided exact test with 10% type I error.

In addition, we will explore the relationship between integrated biomarkers PDL1/PD1/PD2 status (PDL1 status, PDL1 in infiltrating lymphocytes, PD2 status in archival tumor) and response to combination treatment of nivolumab and ipilimumab. We will use Fisher's Exact Test to assess the relationship between each biomarker and response to combination treatment of nivolumab and ipilimumab. Each is expected to have similar characteristics. For example, with this design, assuming tissue is available on 90% of the sample, the probability of concluding combination treatment of nivolumab and ipilimumab response is related to the exploratory biomarker is 80%; given the unknown true response is 55% and 4% in positive marker versus negative marker patients, respectively, assuming 33% of the population is over-expressed for PDL1. The power to detect the relationship of interest increases as the prevalence of the biomarker increases. The operating characteristics of this design are calculated using a two-sided exact test with 10% type I error.

13.5 Analysis of Exploratory Objectives

COHORT A AND B

- Explore the relationship between tumor CSF1 gene signature by RNA analysis and response to combination treatment of nivolumab and ipilimumab.

- Explore the relationship of potential biomarkers associated with disease control of ULMS treated with combination treatment of nivolumab and ipilimumab by evaluating biomarkers within the tumor microenvironment and the periphery.

We will use non-parametric tests to assess the relationships listed above and response to combination treatment of nivolumab and ipilimumab. Logistic regression will be used for response measured outcomes. Outcome relationships will be largely explorative and descriptive.

13.6 Reporting and Exclusions

13.6.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with nivolumab and ipilimumab. All patients who receive at least one dose of nivolumab and ipilimumab will be included in the toxicity analysis. This includes participants who receive study drug and are ultimately deemed ineligible.

13.6.2 Evaluation of Response

All eligible patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

14 STUDY STATUS UPDATES AND STUDY CLOSURE

14.1 Definitions of Study Status Changes

14.1.1 Temporarily Closed to Accrual

The study status is Temporarily Closed to Accrual when no patient slots are currently available, but there is the possibility that the trial will re-open for accrual (patient slots become available). Sites are not permitted to accrue additional patients until CTEP is notified of Re-Activation.

Study status will need to be changed to Temporarily Closed to Accrual when any of the following criteria are met:

- Sites are notified by CTEP (via Request for Rapid Amendment [RRA]) of changes in the risk/benefit ratio that necessitate changes to the patient Informed Consent document. Requested changes will be specified in the RRA and must be reviewed by the study's IRB.
- CTEP and the lead investigator agree that unacceptable toxicities necessitate a discussion to change the dosing/regimen.
- A protocol-defined benchmark has been achieved (such as an interim analysis before proceeding to the next stage).

14.1.2 Closed to Accrual

The study status is (permanently) Closed to Accrual when no more patient enrollment slots are available, and at least one patient is still actively receiving the study treatment. Sites are no longer permitted to enroll additional patients.

Patient slots are no longer available when the following criteria are met:

- The pre-specified number of evaluable patients has been successfully enrolled, treated, and evaluated.
- The study treatment has failed to meet the pre-specified efficacy goal at the stage 1 interim analysis.
- CTEP and the investigators agree that unacceptable toxicities preclude further enrollment.

14.1.3 Closed to Accrual and Treatment

The study status is Closed to Accrual and Treatment when no more patient enrollment slots are available and no patients are currently receiving the study treatment. Patients may still be enrolled on the protocol only for the purposes of follow-up.

Patient accrual and treatment will be permanently halted when any of the following criteria are met:

- Enrollment was previously closed (study status of "Closed to Accrual"), and no patients are receiving the study treatment.
- CTEP and the investigators agree that unacceptable toxicities preclude further enrollment. In this case, CTEP and the investigators must collaborate to alter the regimen or to halt the study treatment altogether as soon as it can be safely done for patients currently receiving treatment.

CTEP and Theradex **must be notified** when patients are no longer receiving treatment [*i.e.*, when the last patient(s) to be receiving treatment is/are no longer receiving the study regimen for any reason].

14.1.4 Closed to Follow-Up

The study is considered Closed to Follow-Up when all protocol-defined follow-up procedures have been completed for all patients who have not been removed from the study for other reasons. That is, there are no outstanding follow-up procedures to be performed as mandated by the protocol.

CTEP does **not** need to be notified of a status change to "Closed to Follow Up."

14.1.5 Complete

Study is considered Complete if it has been at least thirty (30) days since the last patient follow-up evaluation.

A citation to a final study report (manuscript, meeting abstract, etc.) is required with the submission of the Protocol Status Update Form to CTEP PIO.

14.2 Responsibility for Filing Protocol Status Update Forms

CTEP must be notified of all study status changes in Section 14.1 (except for Closed to Follow-Up) by the Corresponding Organization via Protocol Status Update Form, available from the CTEP website at http://ctep.cancer.gov/protocolDevelopment/default.htm#amendments.

Theradex must be notified as soon as all patients are off treatment (*i.e.*, when study status changes to Closed to Accrual and Treatment). Theradex will produce a report within 90 days of this notification.

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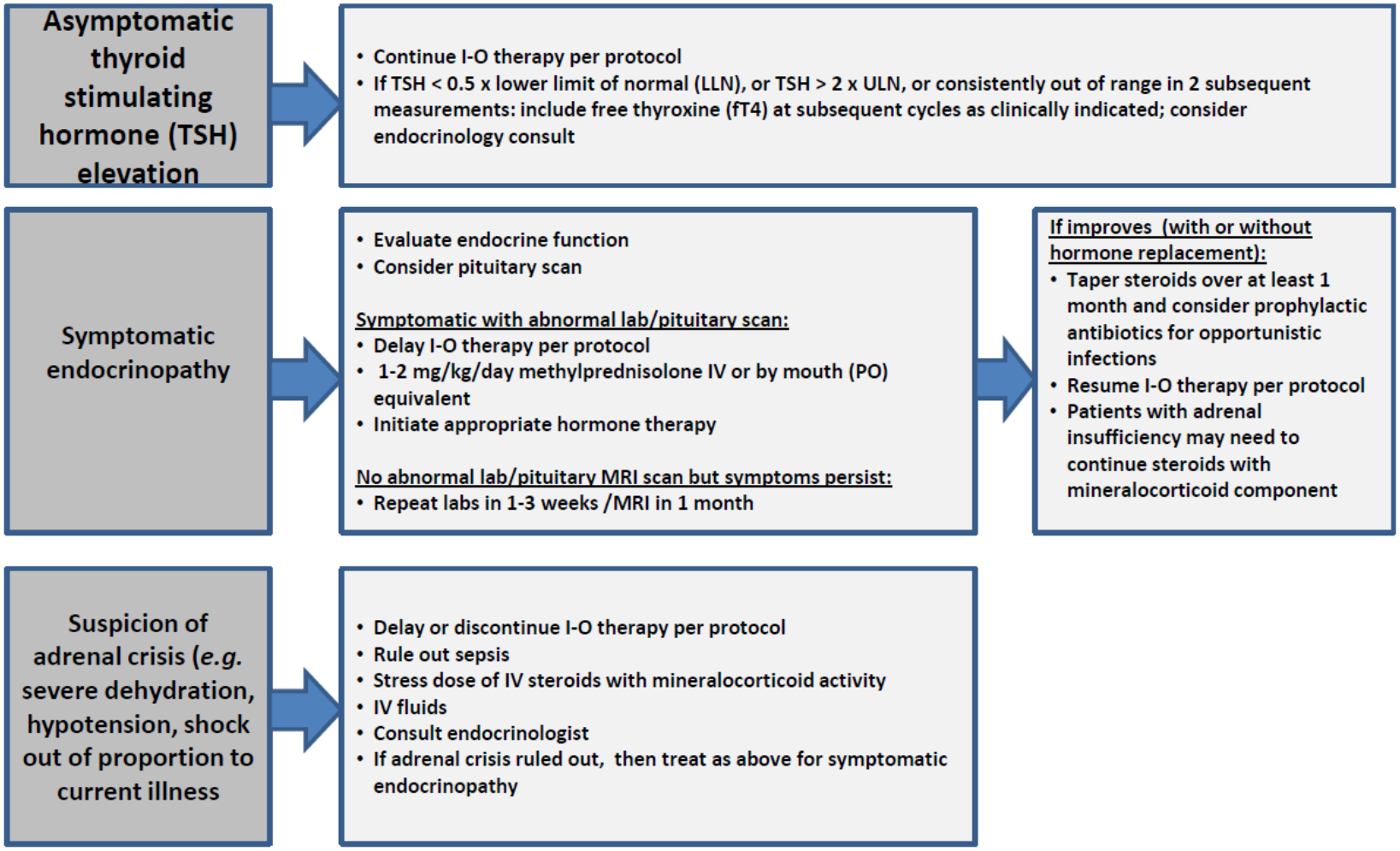
APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B MANAGEMENT ALGORITHMS FOR ENDOCRINOPATHY, GASTROINTESTINAL, HEPATIC, NEUROLOGICAL, PULMONARY, RENAL, AND SKIN ADVERSE EVENTS

Endocrinopathy Management Algorithm

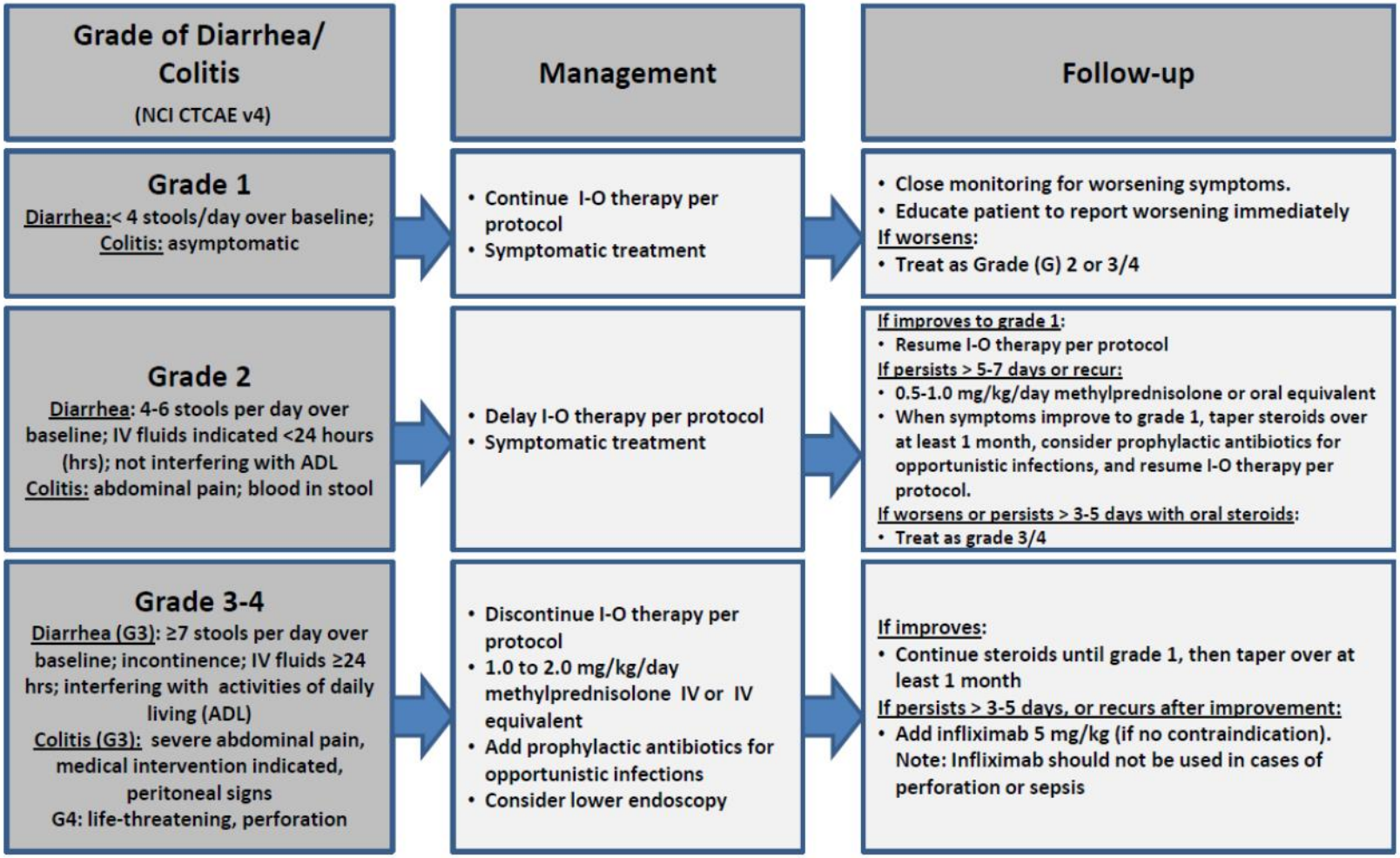
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue immuno-oncology (I-O) therapy.
Consider visual field testing, endocrinology consultation, and imaging.



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.

GI Adverse Event Management Algorithm

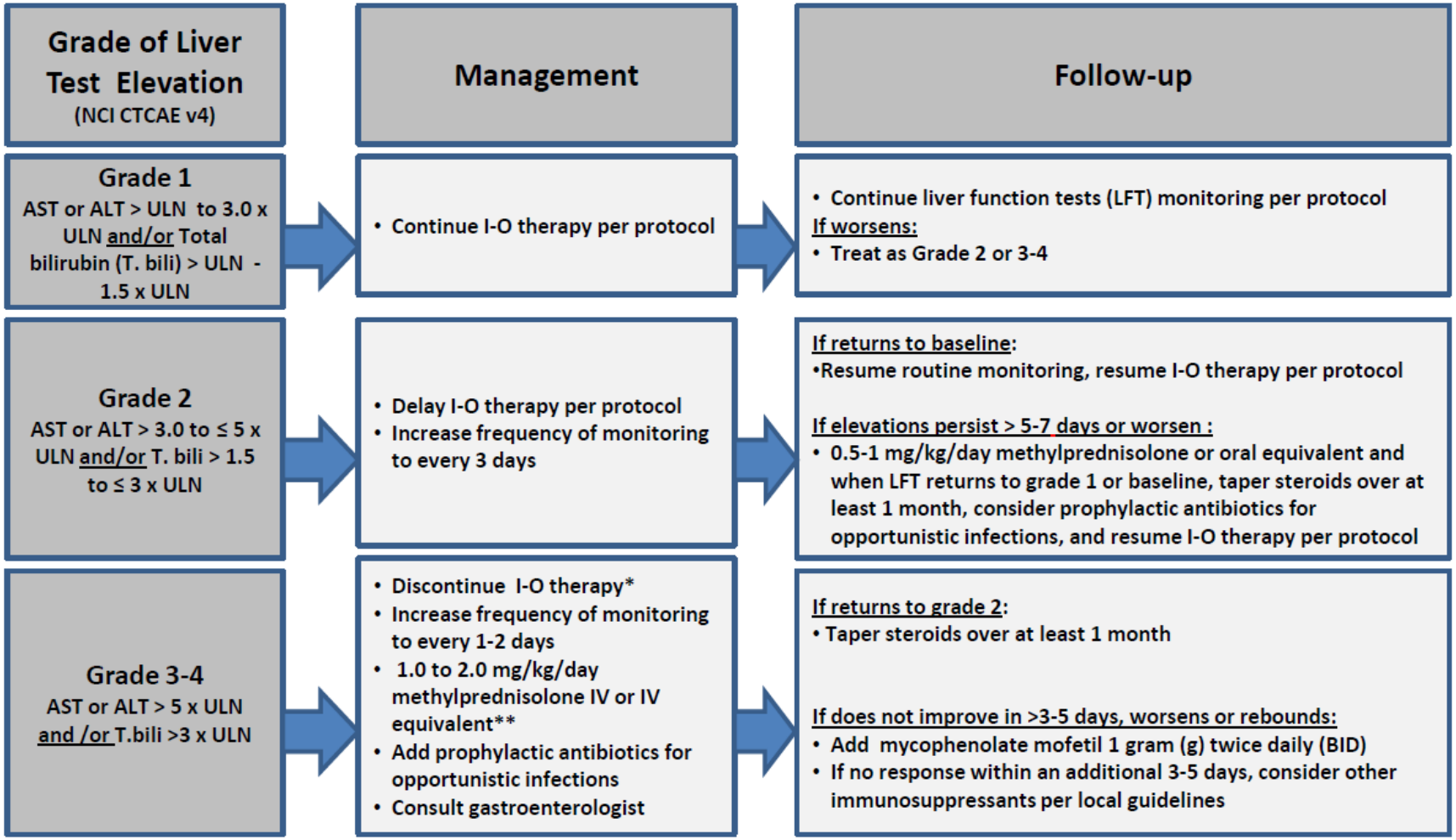
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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.

Hepatic Adverse Event Management Algorithm

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



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

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

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

Neurological Adverse Event Management Algorithm

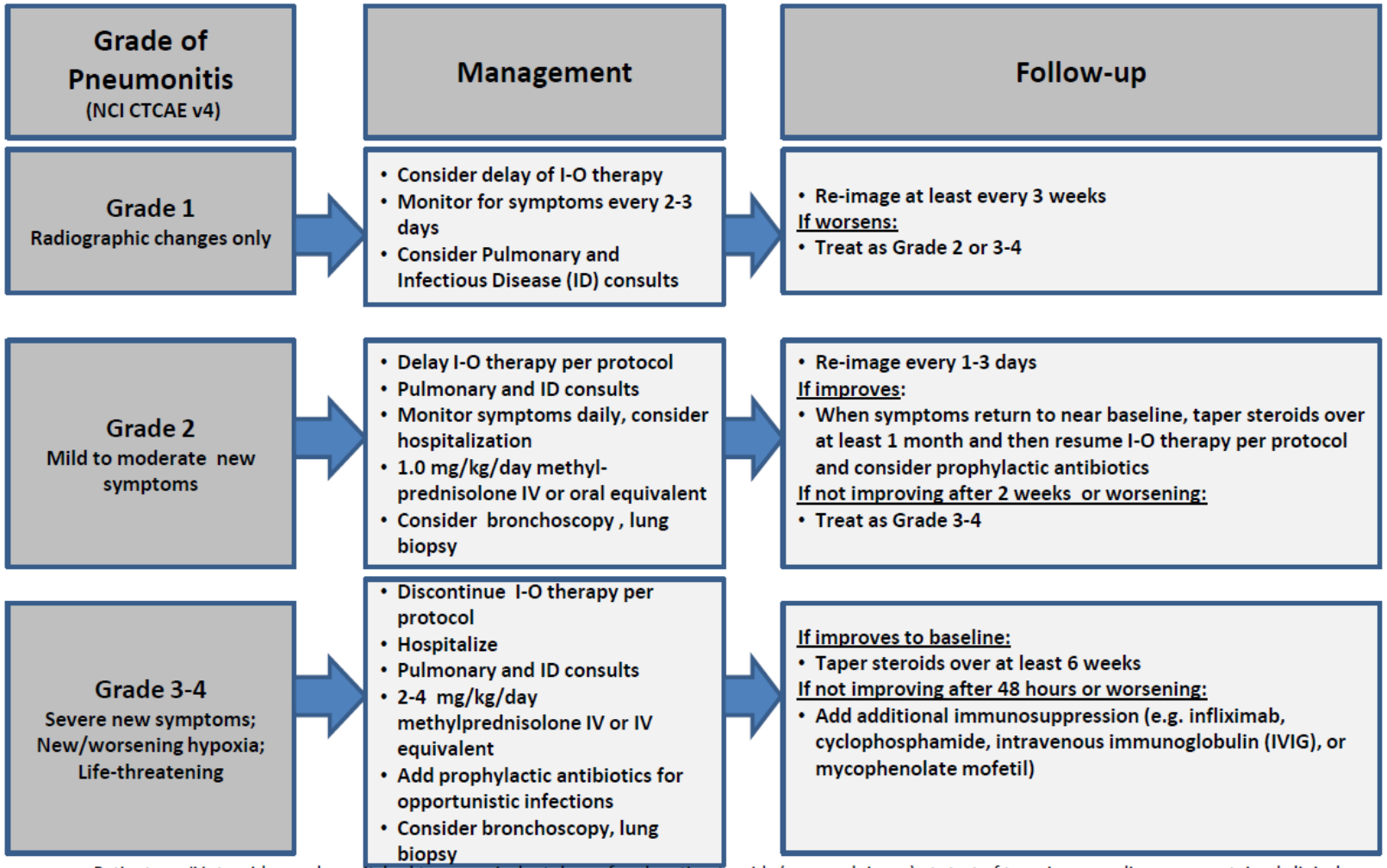
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

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

Pulmonary Adverse Event Management Algorithm

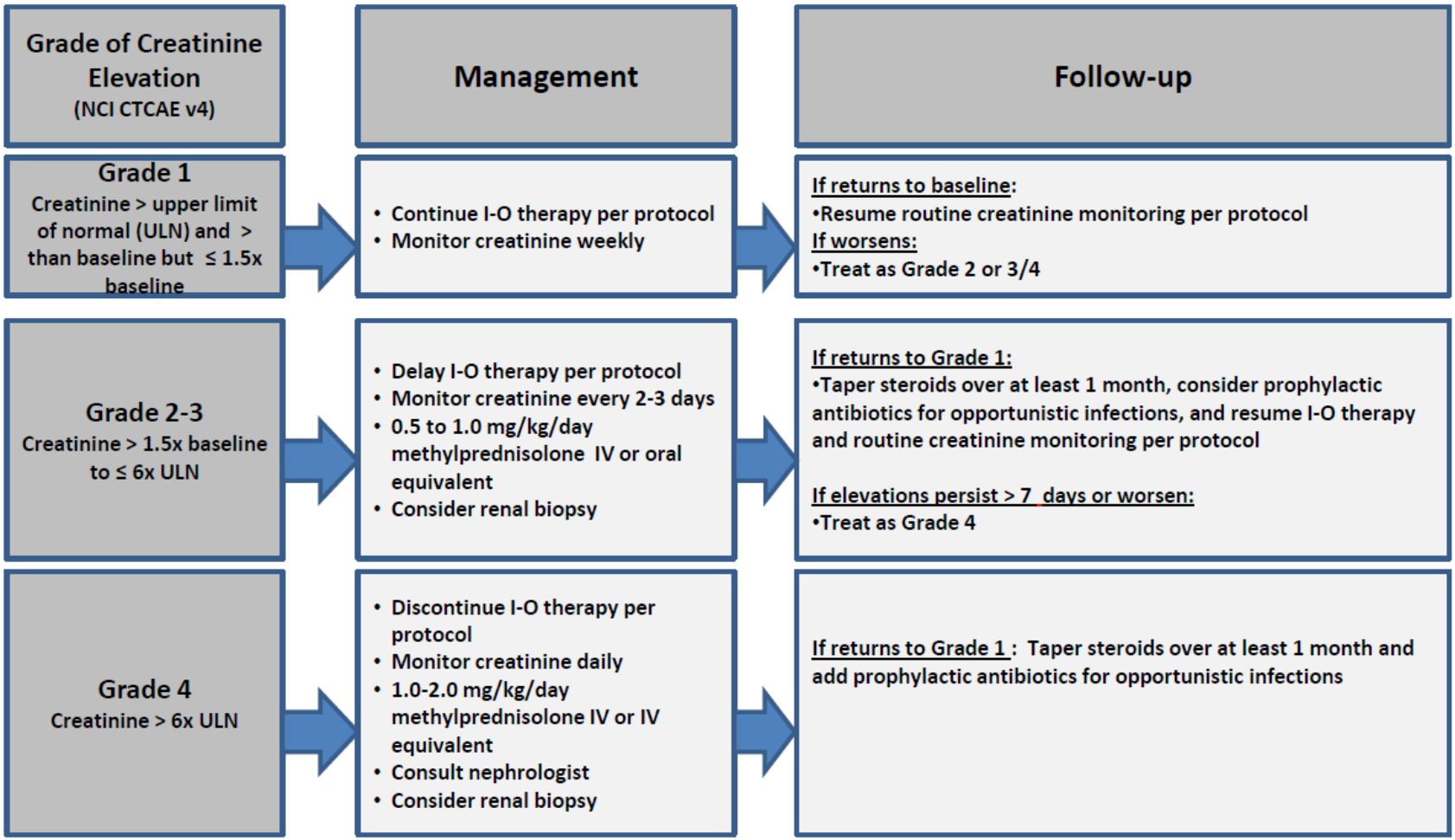
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

Renal Adverse Event Management Algorithm

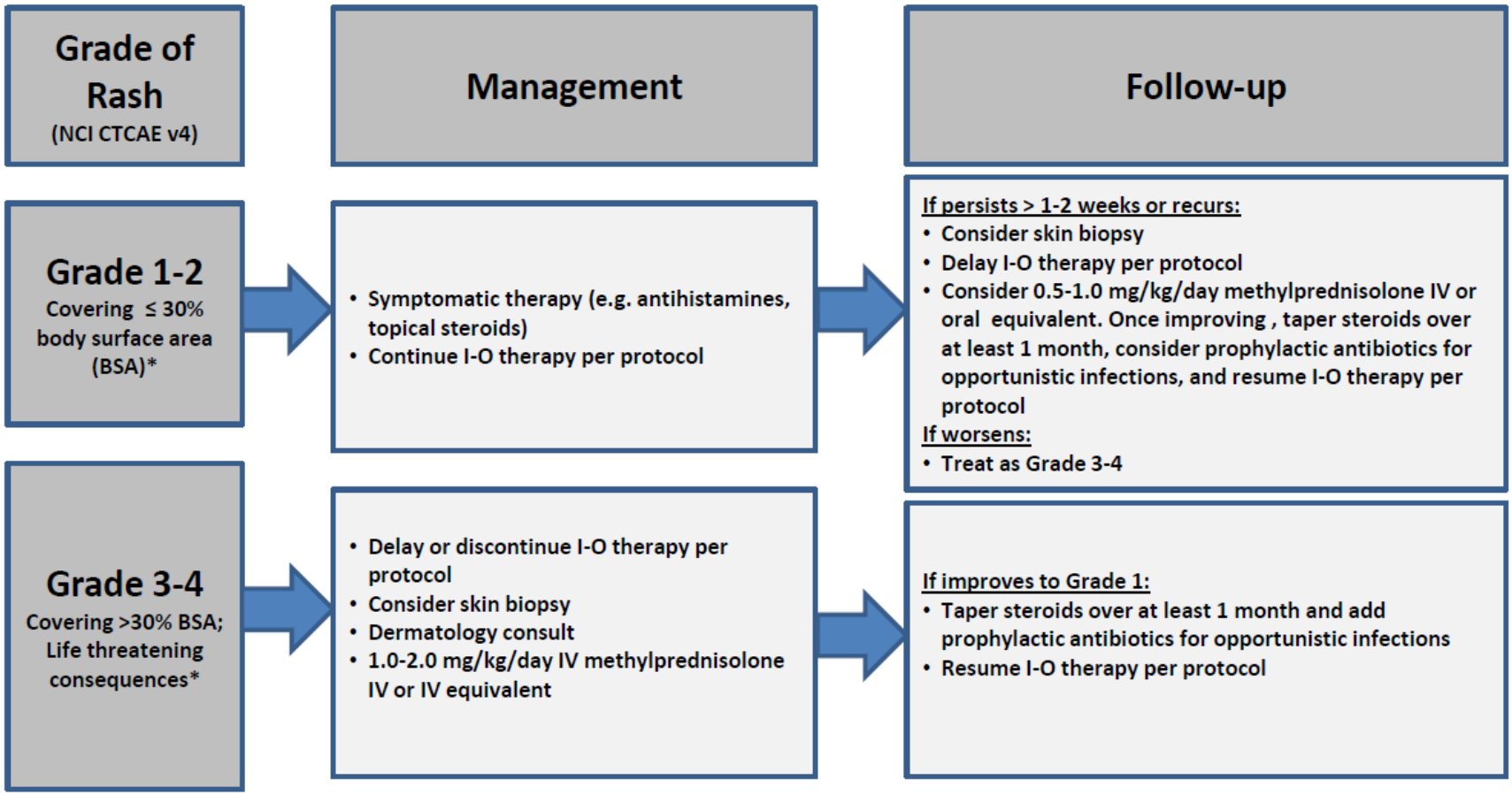
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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.

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.