SWOG CANCER RESEARCH NETWORK

Version Date: June 10, 2021

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Catrina Mireles, Protocol Coordinator (E-mail: cmireles@swog.org)

RE: **S1616**, "A Phase II Randomized Study of Nivolumab (NSC-748726) with Ipilimumab (NSC-732442) or Ipilimumab alone in Advanced Melanoma Patients Refractory to an Anti-PD1 or Anti-PD-L1 Agent" Study Chairs: Drs. A VanderWalde and A. Ribas

REVISION #8

Study Chair: Ari VanderWalde, M.D., M.P.H.
Phone number: 901/683-0055 ext. 63015
E-mail: avanderw@uthsc.edu

IRB Review Requirements
(√) Expedited review allowed

Protocol changes
(√) Other: Request for Amendment (RA) and Additional Translational Medicine
(√) Informed Consent changes
(√) Patient notification not required

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice.

REVISION #8

The above-referenced study has been revised. The purposes of this revision are to add a reference to the Parker Institute for Cancer Immunotherapy in response to the Request for Amendment (RA) received on May 18, 2021 from Dr. Jianqiao Zhang, ACG RAB, and to incorporate additional translational medicine details.

Protocol Changes

1. The Version Date of the protocol has been updated.

2. The Table of Contents has been updated.

3. Section 1.3a & 1.3b: These sections have been updated to include additional translational medicine objectives as outlined in Appendix 18.1.

4. Appendix 18.1: In response to the Request for Amendment referenced above, a description of Parker Institute for Cancer Immunotherapy's (PICI) role in analyzing genomic data generated by UCLA has been added. In addition, details about the additional translational medicine objective have been added throughout this section. In summary, ctDNA profile will be captured and analyzed and the IHC analysis has been clarified to include the various quantitative multiplexed IHC and staining techniques now available to not only achieve the original goals but to exceed the depth of data that can be yielded from the same amount of study samples.

Model Consent Form Changes

1. The version date has been updated. No additional changes were made to the Model Consent Form.

This memorandum serves to notify the NCI, CIRB and SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Jia Chen-UCLA

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

Activation Date July 17, 2017

SWOG

A PHASE II RANDOMIZED STUDY OF NIVOLUMAB (NSC-748726) WITH IPILIMUMAB (NSC-732442) OR IPILIMUMAB ALONE IN ADVANCED MELANOMA PATIENTS REFRACTORY TO AN ANTI-PD1 OR ANTI-PD-L1 AGENT

Partially funded by SU2C Catalyst Grant – SU2C-AACR-CT06-17

NCT #**03033576**

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AGENTS:

NCI Supplied Investigational Agents:
Ipilimumab (BMS-734016, MDX-010, YERVOY®) (NSC-732442)
Nivolumab (BMS-936558, MDX1106, Opdivo®) (NSC-748726)

IND Sponsor: DCTD, NCI

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NRG/NRG Oncology
SWOG/SWOG

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

– CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 866-651-2878 to receive further information and support. Contact the CTSU Regulatory Help Desk at 866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench via the SWOG website (www.swog.org).

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.
Note: Non-lead group institutions will order the following supplies from the CTSU Operations Office:

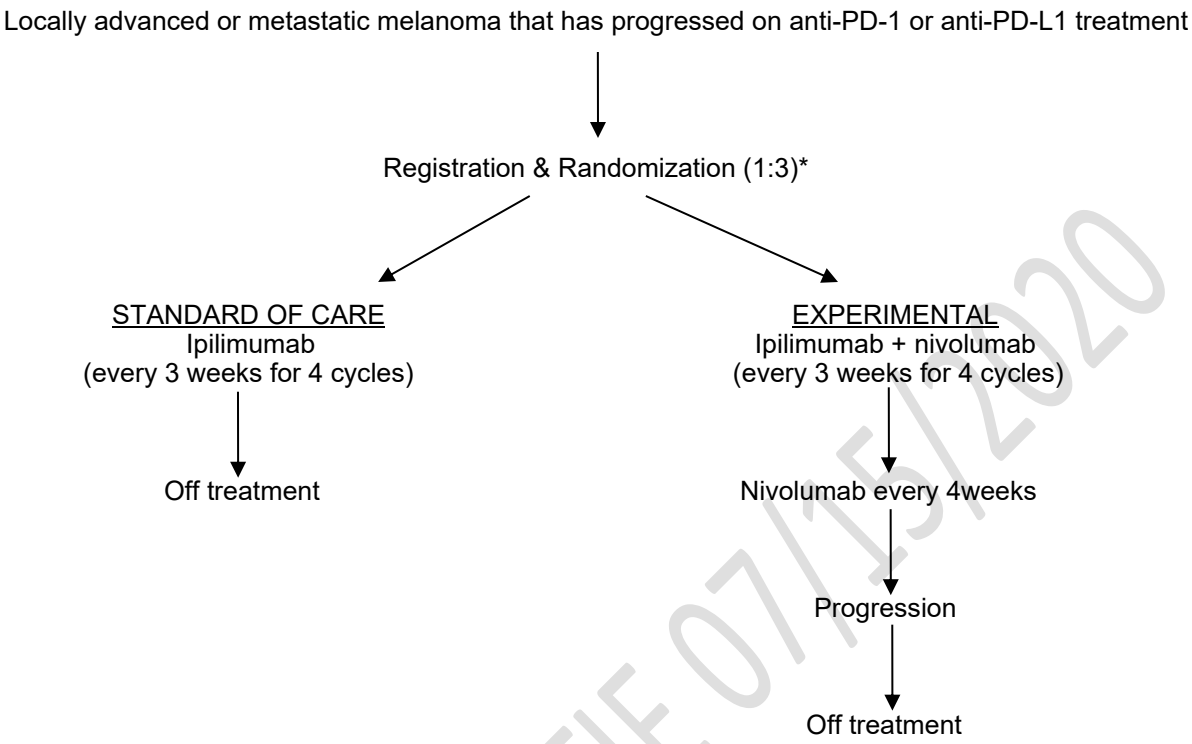
For patient eligibility or data submission questions contact the SWOG Data Operations Center by phone or email:
206/652-2267
melanomaquestion@crab.org

For treatment or toxicity related questions contact the Study Chair by phone or email:
Ari VanderWalde, M.D., M.P.H
Phone: 901-683-0055
avanderw@uthsc.edu

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Website is located at https://www.ctsu.org.

SCHEMA



NOTE: This study includes mandatory specimen submission. See Section 15.0 for details.

* For every patient randomized to receive standard of care, there will be three randomized to receive the experimental regimen (see Section 11.0).

1.0 OBJECTIVES

1.1 Primary Objective(s)

To compare progression free survival (PFS) of patients with advanced melanoma refractory to an anti-PD-1 or anti-PD-L1 agent, treated with combination therapy ipilimumab plus nivolumab versus ipilimumab alone.

1.2 Secondary Objective(s)

a. To estimate difference in T-cell infiltrate between on-study biopsy samples of patients who respond to combination therapy (including confirmed and unconfirmed, complete and partial response per RECIST 1.1, in each treatment arm).

b. To evaluate the objective response rate (ORR), defined as confirmed complete or partial response per RECIST 1.1, in each treatment arm.

c. To evaluate the overall survival (OS) of patients in each treatment arm.

d. To evaluate the toxicity profile of patients in each treatment arm.

1.3 Translational Objectives

a. To assess the marginal prognostic value of baseline T-cell density, T-cell receptor (TCR) clonality, mutational load, mRNA and other phenotypical expression levels, and circulating tumor DNA in terms of response.

b. To assess the joint prognostic value of T-cell density, TCR clonality, and mutational load, mRNA and other phenotypical expression levels, and circulating tumor DNA in terms of response.

c. To identify T-cell poor subtype(s) that are associated with response.

2.0 BACKGROUND

The landscape of treatment for metastatic melanoma continues to rapidly change with the continued emergence of effective immunotherapeutic agents. Response to PD-1 inhibitors in front-line metastatic melanoma has been demonstrated to be approximately 30-40% and can produce both durable remissions and prolong survival. *(1,2)* T-cell inflamed tumors show remarkable sensitivity to this therapeutic class while T-cell poor tumors are generally non-responsive. *(3)*

Response to the front-line combination of the CTLA-4 inhibitor ipilimumab and the PD-1 inhibitor nivolumab is approximately 60% but with substantial toxicity. *(4,5)* Additionally, the added benefit of the combination over single-agent PD-1 inhibitors may be limited to those without high PD-L1 expression. *(6)* Adding ipilimumab to PD-1 therapy, therefore, might be capturing additional responders by influencing the peri-tumoral milieu such that the cancer becomes more responsive to immune manipulation, while avoiding the added toxicity of the combination in patients who were poised to respond to anti-PD-1 therapy alone.

The rapid pace of changing paradigms for first-line treatment has left little room for elucidation of later-line choices. Little data exist on appropriate sequencing of immune therapy following PD-1 therapy. Given the possible synergistic effects of the combination, and given the possibility that the addition of ipilimumab may work by making the tumor more sensitive to PD-1 inhibition, it is rational to conclude that ipilimumab may be added as salvage therapy for patients whose tumors have progressed on single-agent PD-1 therapy. The effects of combining therapy in the second line

following failure of first-line anti-PD-1 treatment could be hypothesized to result in more responders than would be expected if patients received ipilimumab alone as salvage. This study will attempt to provide evidence of the utility of combining ipilimumab, a CTLA-4 antagonist, with the PD-1 inhibitor nivolumab even after primary progression on a PD-1 inhibitor. Progression free survival on the combination will be compared to rates seen with ipilimumab as a single agent. If the study reveals a longer progression-free survival with a high response rate in patients who receive the combination, this could provide preliminary evidence to potentially limit a toxic combination to salvage use only. On the other hand, if the study reveals equivalent PFS with a low response rate it could provide evidence that combination immunotherapy is most useful in front-line use. Additionally, key translational components will work to identify subsets of patients that are more or less likely to respond to the combination if exhibiting primary refractoriness to PD-1 antibodies alone.

The combination of ipilimumab and nivolumab in the treatment of previously untreated advanced melanoma was approved by the U.S. Food and Drug Administration based on the results of the Phase II Checkmate 069 trial, which compared this combination to ipilimumab alone and demonstrated an improved objective response rate among patients with BRAF wild type tumors (61% for the combination as compared to 11% for ipilimumab alone) and improved progression free survival with a hazard ratio of 0.4 ($p<0.001$). *(7)* The combination was also compared to ipilimumab alone and nivolumab alone in a Phase III study. The combination showed improved progression free survival as compared to ipilimumab and thus met its primary endpoint (HR 0.42, $p<0.01$). *(8)* The combination also showed improved progression-free survival as compared to nivolumab alone (HR 0.57, $p<0.001$). This benefit, however, may have been limited to patients with tumors negative for the PD-1 ligand, though objective response rates were numerically higher in the combination arm than in the nivolumab arm. Overall survival data have not yet been reported. *(9)*

PD-1 inhibitors as single agents in the first-line setting have been shown to consistently result in response rates of 33-44%. *(10,11,12)* Both pembrolizumab and nivolumab have been shown superior to ipilimumab in the front-line setting in advanced melanoma. *(13,14)* As such, PD-1 inhibitors have become standard of care in the first-line setting, either alone or in combination with ipilimumab. Data for second-line use of any therapy after PD-1 inhibitors is lacking. While ipilimumab was initially approved based on a study of patients who received the drug after failure of prior therapy, no studies of ipilimumab following failure on a PD-1 inhibitor have been reported. *(15)* As such, there are no data that guide the appropriate management of patients who have progressed on first-line immune-checkpoint therapy with BRAF wild-type mutations.

Further elucidation of patients who are more likely to benefit from combination checkpoint inhibition versus single agent PD-1s are also somewhat immature. While Phase III data point toward PD-L1 overexpression as a marker that may distinguish between patients who benefit from combination therapy versus single-agent, translational data present a more complicated picture. *(16)* PD-L1 expression may confer different levels of susceptibility dependent on whether overexpressed by tumor cells, tumor-infiltrating immune cells, or expression at the invasive tumor margin. *(17)* Additionally, investigations of T-cell repertoire, whole exome modalities, and mutational load have shown preliminary predictive potential of response to checkpoint inhibitors in various tumor types. *(18,19,20)*

The current standard of care in patients who progress on PD-1 therapy alone is single-agent CTLA-4 inhibitor therapy (e.g. ipilimumab), despite lack of currently available prospective data in this setting. Historical response rates to ipilimumab as a single agent have been approximately 10%, and this includes first-line studies with ipilimumab, which could be expected to have a higher response rate than in the second line after failure of immunotherapy. (21,22,23) Additionally, one retrospective case series has reported a response to single-agent ipilimumab of 10% following single-agent nivolumab (PD-1 inhibitor) among 40 patients. *(24)* A clear benefit over the expected background rate of 10% response to ipilimumab alone would provide important preliminary data in the development of a synergistic effect between the combination even after failure of PD-1 therapy alone, and would have potential clinical utility in guidance of physicians and patients in choice of

upfront combinatorial approaches versus combination immunotherapy after failure of single-agent immunotherapy.

Our main hypothesis, therefore, is that patients with advanced melanoma who progress on anti-PD-1 therapy upfront may ultimately respond to the addition of the CTLA-4 inhibitor ipilimumab to continued PD-1 inhibition (with nivolumab), and that disease control (as measured using PFS) would be longer than that seen with switching to ipilimumab alone. We surmise that this would occur because melanomas primarily refractory to PD-1 antibodies may not have a preexisting T cell infiltrate, which can be corrected by adding treatment with the anti-CTLA-4 antibody ipilimumab. CTLA-4 blockade therapy acts at the activation step of an immune response and allows T cells to expand, circulate and infiltrate tumors, where they become negatively regulated by anti-PD-1. By adding CTLA-4 blockade to continued PD-1 blockade we hypothesize that T cells will infiltrate metastatic lesions and be able to induce their specific antitumor cytotoxic response by having released these two major immune checkpoints.

Translational Medicine

The guiding hypothesis of the translational medicine portion of the study is that patients who progress on single agent PD-1 blockade therapy have “cold” tumors, which lack a pre-existing or induced antitumor immune response, but that they can be turned into “hot” tumors by adding an anti-CTLA-4 blocking antibody. CTLA-4 blockade releases an early activation immune checkpoint, allowing antitumor-T cells to proceed through cell cycle after initial activation, resulting in a remarkable diversification of the peripheral T cell pool and increased T cell infiltration in tumors. *(25,26)* This hypothesis will be tested clinically with the primary endpoint of progression-free survival when adding ipilimumab to continued anti-PD-1 therapy when compared to rates seen with ipilimumab alone and experimentally by analyzing paired tumor biopsies testing for changes in the tumor micro-environment between responders and non-responders, and between those who receive combination therapy and single-agent ipilimumab.

Mechanisms of acquired resistance to anti-PD-1 following initial response appear to be related to acquired mutations. *(27)* However, primary resistance is likely due to the immunologic milieu of the cancer and its environs itself, the presence of tumor infiltrating lymphocytes, and expression of various immune markers. *(28*) Studies have shown that anti-CTLA-4 antibodies are very effective in bringing T-cells into tumors. *(29)* Though direct evidence that this results in inducing PD-1 responsiveness in patients who were previously PD-1 refractory is lacking. We hypothesize that this T-cell recruitment, along with other immune-stimulating effects of anti-CTLA-4 agents will allow the combination to induce responses to overcome prior resistance to PD-1 blockade. To test this hypothesis, we aim to collect blood and tissue both prior to and on-study in patients who were resistant to anti-PD-1 therapy and now receive anti-CTLA-4 in combination with anti-PD-1 therapy or anti-PD-1 therapy alone.

To date, no immune assay has been adopted in the clinic to assist with clinical decision-making. We propose to systematically investigate the predictive utility of three immunodiagnostic approaches that measure distinct parameters within tumors: i) quantitative multiplexed immunohistochemistry (qmIHC) which provides spatially resolved, multiparametric information and measures the density, location and phenotype of immune cell types; ii) immunosequencing of the T-cell receptor (TCR) repertoire which is based on bulk reads and measures the clonality and repertoire of TCRs; and iii) whole exome sequencing which generates signal based on bulk measurements and identifies all non-synonymous mutations, as well as information on potential loss of function mutations in the interferon and antigen presentation pathways that may lead to genetic mechanisms of resistance to PD-1 blockade therapy. *(30)* These approaches have shown preliminary predictive potential by independent groups across different cancer types. No study to date, however, has investigated the relationship between these factors or their predictive value when interrogating the same tumor. By defining the relationships between these three factors in terms of response, we anticipate that our approach will lead to clinically actionable information as well as key insights into why certain tumors are immunogenic and others are not.

We hypothesize that the integration of all three approaches into a predictive model will show incremental predictive value over any single parameter. Additionally, we will be able to determine the relationships between immune cell types, density and location, TCR clonality and mutation load and/or type. Our study objectives will be as follows: to assess the independent prognostic value of baseline T-cell density, T-cell receptor (TCR) clonality, and mutational load in terms of response; to assess the incremental prognostic value of T-cell density, TCR clonality and mutational load in terms of response; and to identify T-cell poor subtype(s) that are associated with response.

Additionally, we will incorporate genomic and transcriptomic evaluation of single-gene and gene-expression signatures into the correlative plan, including emerging data in the field with evaluation and prospective testing of the innate anti-PD-1 resistance (IPRES) gene signature. *(31)* Whole exome sequencing, in addition to exposure of mutation load, will be used to evaluate specific mutations that have been correlated with response and resistance, such as B2M and JAK1/2 mutations (13), BRCA2, mismatch-repair deficiency, and others. *(32,33)* See Appendix 18.1 for methods.

Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	1	0	0	1
Asian	0	1	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	1	2	0	0	3
White	27	59	1	2	89
More Than One Race	0	0	0	0	0
Total	28	63	1	2	94

3.0 DRUG INFORMATION

Investigator Brochures

For information regarding Investigator Brochures, please refer to SWOG Policy 15.

For this study, ipilimumab and nivolumab are investigational and being provided under an IND held by the National Cancer Institute. The current versions of the Investigator Brochures for the agents will be accessible to site investigators and research staff through the PMB Online Agent Ordering Processing (OAOP) application (http://ctep.cancer.gov/branches/pmb/agent_order_processing.htm). 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 e-mail (ibcoordinator@mail.nih.gov).

3.1 Ipilimumab (BMS-734016, MDX-010, YERVOY®) (NSC 732442)

a. PHARMACOLOGY

Mechanism of Action: Cytotoxic T-lymphocyte antigen-4 CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a full human monoclonal immunoglobin (Ig) antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response.

b. PHARMACOKINETICS

1. Absorption: No formal pharmacokinetic drug interaction studies have been conducted with ipilimumab. Ipilimumab is not expected to have pharmacokinetic drug-drug interactions, since it is not metabolized by CYP450 or other drug metabolizing enzymes.

2. Distribution: Ipilimumab is confined mainly to the extracellular fluid. Peak concentration (Cmax), trough concentration (Cmin), and area under the plasma concentration versus time curve (AUC) of ipilimumab increased dose proportionally within the dose range examined ipilimumab is confined mainly to the extracellular fluid. Peak concentration (Cmax), trough concentration (Cmin), and area under the plasma concentration versus time curve (AUC) of ipilimumab increased dose proportionally within the dose range examined. Based on population pharmacokinetic analysis, the mean volume of distribution (% coefficient of variation) at steady state was 7.47 liters (10%).

3. Metabolism: Not applicable. Monoclonal antibodies are usually degraded into amino acids and small peptides, independently from CYP450 or other drug-metabolizing enzymes.

4. Elimination: Clearance increased with body weight, but no dose adjustment is required with dosing on a mg/kg basis. Upon repeated dosing every 3 weeks, the clearance (CL) of ipilimumab was found to be time-invariant, and systemic accumulation was 1.5-fold or less. The mean value (% coefficient of variation) generated through population pharmacokinetic analysis for the terminal half-life (t1/2) was 15.4 days (34%) and for CL was 16.8 mL/h (38%).

c. ADVERSE EFFECTS

1. Adverse Effects: 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 2.10, March 29, 2019[1]

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 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]	
		Pericardial effusion	
EAR AND LABYRINTH DISORDERS			
	Hearing impaired		
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Hyperthyroidism[2]		
	Hypophysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
	Testosterone deficiency[2]		
EYE DISORDERS			
	Eye disorders - Other (episcleritis)[2]		
	Uveitis[2]		
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		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
		General disorders and administration site conditions - Other (systemic inflammatory response syndrome [SIRS])	
		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]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
		Lymphocyte count decreased	
	Neutrophil count decreased		
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		
	Hyperglycemia		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Arthritis		
		Generalized muscle weakness	
	Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]		
NERVOUS SYSTEM DISORDERS			
		Ataxia	
	Facial nerve disorder[2]		
	Guillain-Barre syndrome[2]		
	Headache		
	Myasthenia gravis[2]		
		Nervous system disorders – Other (immune-mediated encephalitis) [2]	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
	Trigeminal nerve disorder		
PSYCHIATRIC DISORDERS			
		Psychiatric disorders - Other (mental status changes)	
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
	Renal and urinary disorders - Other (granulomatous tubulointerstitial nephritis)		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis		
		Respiratory failure	

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 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)	
		Respiratory, thoracic and mediastinal disorders - Other (lung infiltration)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Pruritus		***Pruritus (Gr 3)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
	Skin and subcutaneous tissue 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 receving 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 - Colonic ulcer; Dyspepsia; Dysphagia; Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal hemorrhage[6]; Proctitis
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; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Tumor lysis syndrome
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; 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 (BMS-734016; MDX-010 Transfectoma-derived) 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.

2. Pregnancy and Lactation: There are no adequate and well-controlled studies of Ipilimumab in pregnant women. Use of Ipilimumab during pregnancy only if the potential benefit justifies the potential risk to the fetus. Human IgG1 is known to cross the placental barrier and ipilimumab is an IgG1; therefore, ipilimumab has the potential to be transmitted from the mother to the developing fetus.

   It is not known whether ipilimumab is secreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from ipilimumab, a decision should be made whether to discontinue nursing or to discontinue ipilimumab, taking into account the importance of ipilimumab to the mother.

3. Drug Interactions: No formal pharmacokinetic drug interaction studies have been conducted with ipilimumab. Ipilimumab is not expected to have pharmacokinetic drug-drug interactions, since it is not metabolized by CYP450 or other drug metabolizing enzymes

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan.

Ipilimumab injection is to be administered as 90 minute infusion with an in-line, sterile, nonpyrogenic, low-protein-binding filter (pore size of 0.2 micrometer to 1.2 micrometer). Do not administer as IV push or bolus injection.

e. HOW SUPPLIED

1. Ipilimumab will be supplied free of charge by Bristol-Myers-Squibb (BMS) and distributed by NCI/DCTD.

   If a storage temperature excursion is identified, promptly return Ipilimumab to 2° to 8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

2. Ipilimumab injection is supplied as 200 mg/40 mL (5 mg/mL). It 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.

f. STORAGE, PREPARATION& STABILITY

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

   If a storage temperature excursion is identified, promptly return Ipilimumab to 2° to 8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

2. 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 8^0C) or at room temperature/room light.

3. The product may be infused using a volumetric pump at the protocol-specific dose(s) and rate(s) through a PVC IV solution infusion set with an

in-line, sterile, nonpyrogenic, low-protein-binding filter (pore size of 0.2 micrometer to 1.2 micrometer).

4. Do not administer ipilimumab as an IV push or bolus injection.

5. Stability of prepared IV ipilimumab solution is stable up to 24 hours refrigerated at (2^0 to 8^0C) or at room temperature/ room light.

6. Partially used vials or empty vials of ipilimumab injection should be discarded at the site according to appropriate drug disposal procedures.

g. DRUG ORDERING & ACCOUNTABILITY

1. Drug ordering: 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 (S1616) 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. 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. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB’s website for specific policies and guidelines related to agent management.

2. Drug Handling and Accountability (NCI logs or other)

   a. Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

   b. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF.

3. Drug return and/or disposition instruction

a. Drug Returns: All unused drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when expired vials are recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

4. Contact Information

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
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

PMB IB Coordinator: IBCoordinator@mail.nih.gov

3.2 Nivolumab (BMS-936558, MDX1106, Opdivo®) (NSC 748726)

a. PHARMACOLOGY

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.

b. PHARMACOKINETICS

1. Distribution: Nivolumab has linear pharmacokinetics after single and multiple dosing within the range 0.1 mg/kg to 10 mg/kg. The volume distribution (Vd) is 8L.

2. Elimination: Clearance is independent of dose in the range 0.1 mg/kg to 10 mg/kg. The total body clearance is 9.5 mL/hr, and the elimination half-life of is approximately 26.7 days. Body weight normalized dosing showed approximately constant trough concentrations over a wide range of body weights.

c. ADVERSE EFFECTS

Adverse Effects: 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 Nivolumab.

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 2.4, December 2, 2020[1]

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Myocarditis	
		Pericardial tamponade[2]	
		Pericarditis	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[3]		
	Hyperthyroidism[3]		
	Hypophysitis[3]		
	Hypothyroidism[3]		
EYE DISORDERS			
		Blurred vision	
		Dry eye	
		Eye disorders - Other (diplopia)[3]	

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Eye disorders - Other (Graves ophthalmopathy)[3]	
		Eye disorders - Other (optic neuritis retrobulbar)[3]	
		Eye disorders - Other (Vogt-Koyanagi-Harada)	
	Uveitis		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis[3]		
		Colonic perforation[3]	
	Diarrhea		***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
		Enterocolitis	
		Gastritis	
		Mucositis oral	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[4]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Injection site reaction		***Injection site reaction (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (immune-mediated hepatitis)	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
		Autoimmune disorder[3]	
		Cytokine release syndrome[5]	
		Immune system disorders - Other (GVHD in the setting of allotransplant)[3,6]	

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Immune system disorders - Other (sarcoidosis)[3]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[7]		
INVESTIGATIONS			
	Alanine aminotransferase increased[3]		***Alanine aminotransferase increased[3] (Gr 3)***
	Aspartate aminotransferase increased[3]		***Aspartate aminotransferase increased[3] (Gr 3)***
	Blood bilirubin increased[3]		***Blood bilirubin increased[3] (Gr 2)***
	CD4 lymphocytes decreased		***CD4 lymphocyte decreased (Gr 4)***
	Creatinine increased		
	Lipase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		
	Platelet count decreased		
	Serum amylase increased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Hyperglycemia	***Hyperglycemia (Gr 2)***
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis)[3]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Musculoskeletal and connective tissue disorder - Other (polymyositis)	
		Myositis	
		Rhabdomyolysis	
NERVOUS SYSTEM DISORDERS			
		Encephalopathy[3]	
		Facial nerve disorder[3]	
		Guillain-Barre syndrome[3]	
		Myasthenia gravis[3]	
		Nervous system disorders - Other (demyelination myasthenic syndrome)	
		Nervous system disorders - Other (encephalitis)[3]	
		Nervous system disorders - Other (meningoencephalitis)	
		Nervous system disorders - Other (meningoradiculitis)[3]	
		Nervous system disorders - Other (myasthenic syndrome)	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
		Reversible posterior leukoencephalopathy syndrome[3]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury[3]	
		Renal and urinary disorders - Other (immune-mediated nephritis)	

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleural effusion[3]		
	Pneumonitis[3]		
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)[3]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme[3]	
	Pruritus[3]		***Pruritus[3] (Gr 2)***
	Rash maculo-papular[3]		***Rash maculo-papular[3] (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (bullous pemphigoid)	
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)[3]		
	Skin hypopigmentation[3]		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

[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] Nivolumab 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.

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

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

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

[7] 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.

Adverse events reported on Nivolumab trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Nivolumab caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Heart failure; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - Vestibular disorder
EYE DISORDERS - Eye disorders - Other (iridocyclitis); Optic nerve disorder; Periorbital edema
GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Flatulence; Gastrointestinal disorders - Other (mouth sores); 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 - Blood lactate dehydrogenase increased; GGT increased; Investigations - Other (protein total decreased); 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; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea)
VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Vasculitis

Note: Nivolumab 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.

1. Pregnancy and Lactation:

   Pregnancy: Adverse events were observed in animal reproduction studies. Nivolumab may be expected to cross the placenta; effects to the fetus may be greater in the second and third trimesters. Based on its mechanism of action, nivolumab is expected to cause fetal harm if used during pregnancy. Women of childbearing potential (WOCBP) receiving nivolumab must continue contraception for a period of 5 months after the last dose of nivolumab. Men receiving nivolumab and who are sexually active with WOCBP must continue contraception for a period of 7 months after the last dose of nivolumab.

   Lactation: It is not known if nivolumab is excreted into breast milk. Due to the potential for serious adverse reactions in the nursing infant, the manufacturer recommends women to discontinue breastfeeding during treatment with nivolumab.

2. Potential Drug Interactions: The indirect drug-drug interaction potential of nivolumab was assessed using systemic cytokine modulation data for cytokines known to modulate CYP enzymes. There were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab. This lack of cytokine modulation suggests that nivolumab has no low potential for modulation CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

Route of Administration: Intravenous infusion over 30 minutes. 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.

e. HOW SUPPLIED

1. 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 dihydrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid) and polysorbate 80 (Tween® 80), and water for injection. Dilute solutions of hydrochloric acid and/or sodium hydroxide may be used for pH adjustment (pH 5.5-6.5).

2. 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 fluoropolymer film-laminated rubber stoppers and aluminum seals.

f. STORAGE, PREPARATION & STABILITY

1. Storage: Vials of Nivolumab injection must be stored at 2°-8°C (36°-46°F) and protected from light and freezing. The unopened vials can be stored at room temperature (up to 25°C, 77°F) and room light for up to 48 hours.

   If a storage temperature excursion is identified, promptly return Nivolumab to 2° - 8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

2. Preparation: Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose. When the dose is based on patient weight (i.e. mg/kg), nivolumab injection can be infused undiluted or diluted to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (e.g, 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. For patients weighing less than 40 kilograms (kg), the total volume of infusion must not exceed 4 mL per kg of patient weight. During drug product preparation and handling, vigorous mixing or shaking is to be avoided.

3. Compatibility: Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

4. 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 8 hours of the total 24 hours can be at room temperature (up to 25°C, 77°F) and room light. The maximum 8-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.

g. DRUG ORDERING & ACCOUNTABILITY

1. Drug ordering: 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 (S1616) 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. 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. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB’s website for specific policies and guidelines related to agent management.

2. Drug Handling and Accountability

   a. Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

3. Drug return and/or disposition instruction

   a. Drug Returns: All unused drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when expired vials are recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

   b. Drug Expiration: Shelf life stability studies of the intact vials of ipilimumab are on-going

4. Contact Information

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
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

PMB IB Coordinator: IBCoordinator@mail.nih.gov

4.0 STAGING CRITERIA

STAGE IIIC
Any T N3 M0

Stage IV
Any T Any N M1

Primary Tumor (T)
TX Primary tumor cannot be assessed (e.g., curettaged or severely regressed melanoma)
T0 No evidence of primary tumor
Tis Melanoma in situ
T1a Melanomas ≤1.0 mm in thickness without ulceration; mitosis <1/mm^2
T1b Melanomas ≤1.0 mm in thickness with ulceration or mitoses ≥1/mm^2
T2a Melanomas 1.01–2.0 mm in thickness without ulceration.
T2b Melanomas 1.01–2.0 mm in thickness with ulceration
T3a Melanomas 2.01–4.0 mm in thickness without ulceration
T3b Melanomas 2.01–4.0 mm in thickness with ulceration
T4a Melanomas >4.0 mm in thickness without ulceration
T4b Melanomas >4.0 mm in thickness with ulceration

Regional Lymph Nodes (N)
NX Patients in whom the regional nodes cannot be assessed (e.g., previously removed for another reason)
N0 No regional metastases detected
N1a 1 regional lymph node metastasis with micrometastasis[c]
N1b 1 regional lymph node metastasis with macrometastasis[d]
N2a 2–3 regional lymph node metastases with micrometastasis[c]
N2b 2–3 regional lymph node metastases with macrometastasis[d]
N2c In transit met(s)/satellite(s) without metastatic lymph nodes
N3 ≥4 regional lymph node metastases; or matted nodes; or in transit met(s)/satellite(s) with metastatic lymph node(s)

Distant Metastasis (M)
M0 No detectable evidence of distant metastases
M1a Metastases to skin, subcutaneous or distant lymph nodes and normal serum LDH
M1b Metastases to lung and normal serum LDH
M1c Metastases to all other visceral sites and normal serum LDH or distant metastases to any site combined with an elevated serum LDH

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 or melanomaquestion@crab.org prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. **If Day 14 or 28 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease Related Criteria

a. Patients must have pathologically confirmed melanoma that is either Stage IV or unresectable Stage III. Patients may have primaries of cutaneous, mucosal or unknown origin. Patients with uveal (ocular) primary are not eligible.

b. Patients must have measurable disease per RECIST 1.1 (see Section 10.1). All measurable lesions must be assessed by physical examination, CT scans or MRIs within 28 days prior to registration. If the only measurable disease is cutaneous or subcutaneous, lesions must be at least 10 mm in greatest dimension and able to be serially recorded using calipers and photographs. Tests used to assess non-measurable disease must have been performed within 42 days prior to registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form.

c. Patients with central nervous system (CNS) metastases must have all lesions adequately treated with stereotactic radiation therapy, craniotomy, Gamma Knife® therapy, or whole brain radiotherapy, with no subsequent evidence of CNS progression. Patients must not have required steroids for at least 14 days prior to registration. Patients with a history of central nervous system metastases must have MRI of the brain within 42 days prior to registration.

5.2 Prior/Concurrent Therapy Criteria

a. Patients must have had prior treatment with anti-PD1 or anti-PD-L1 agents and had documented disease progression per the treating physician either while on these agents or after stopping therapy with these agents without intervening therapy. Patients who received adjuvant therapy for previously resected disease with PD-1 or PD-L1 agents may also be eligible if disease recurrence occurred while still receiving the PD-1 or PD-L1 therapy and no intervening therapy was received. Patients must have discontinued anti-PD-1 or anti-PD-L1 therapy at least 21 days prior to registration.

b. Patients must not have achieved a partial or complete response to the anti-PD-1 or anti-PD-L1 agents prior to progression per the treating physician.

c. Patients must not have had any systemic therapy, including anti-PD-1 or anti-PD-L1 agents, within 21 days prior to registration.

d. Patients must not have had prior radiation therapy within 14 days prior to registration (see Section 5.1c).

e. Patients must not have had:

1. Prior treatment with ipilimumab or other CTLA-4 antagonists.

2. Systemic therapy between progression on the anti-PD-1 or anti-PD-L1 agents and registration.

Note: Systemic therapy (including BRAF-targeting agents) prior to anti-PD-1 or anti-PD-L1 therapy is allowed.

f. Patients must not be planning to require any additional form of systemic anti-tumor therapy while on protocol treatment.

5.3 Clinical/Laboratory Criteria

a. Patients must be ≥ 18 years of age.

b. Patients must have Zubrod Performance Status of ≤ 2 (see Section 10.4).

c. Patients must have complete history and physical examination within 28 days prior to registration.

d. Patients must have adequate hematologic function as evidenced by all of the following within 28 days prior to registration: absolute neutrophil count (ANC) ≥ 1,500/mcL; hemoglobin ≥ 8 g/dL; and platelets ≥ 100,000/mcL.

e. Patients must have adequate hepatic function as evidenced by all of the following within 28 days prior to registration: total bilirubin ≤ 2.5 x Institutional Upper Limit of Normal (IULN) (except patients with Gilbert's syndrome); and AST and ALT both ≤ 5 x IULN.

f. Patients must have adequate kidney function as evidenced by serum creatinine ≤ 2.0 x IULN within 28 days prior to registration.

g. Patients with a known history of HIV must have CD4 count ≥ institutional lower limit of normal within 28 days prior to registration.

h. Patients must not have known active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection prior to registration.

i. Patients must not have an active infection requiring systemic therapy at time of registration.

j. Patients must not have organ allografts.

k. Patients must not have received systemic treatment with corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days prior to registration. Inhaled or topical steroids, and adrenal replacement doses ≤ 10 mg daily prednisone or equivalent are permitted in the absence of active autoimmune disease.

l. Patients must not have a history of immune-mediated pneumonitis or colitis that required interruption of therapy or treatment of steroids.

m. Patients with a known history of congestive heart failure (CHF), cardiomyopathy, myocarditis, myocardial infarction (MI), exposure to cardiotoxic medications, or with a clinical history suggestive of the above must have an EKG and Echocardiogram (ECHO) performed within 42 days prior to registration and as clinically indicated while on treatment.

n. Patients with new symptoms of congestive heart failure (CHF), cardiomyopathy, myocarditis, myocardial infarction (MI), or exposure to cardiotoxic medications must have a cardiology consultation, creatinine phosphokinase (CPK), and troponin testing at prestudy and as clinically indicated.

o. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, adequately treated Stage 0, I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for two years.

p. Patients must not be pregnant or nursing due to risk of fetal or nursing infant harm. Females of reproductive potential must have negative serum pregnancy test within 2 days prior to registration and agree to use an effective contraceptive method throughout the study and for 5 months after completion of protocol treatment. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. If at any point a previously celibate patient chooses to become heterosexually active during or within 5 months after protocol treatment, she is responsible for beginning effective contraceptive measures.

q. Males who are sexually active with women of reproductive potential must have agreed to use birth control throughout the study and for 7 months after completion of protocol treatment. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (vasectomy). If at any point a previously celibate patient chooses to become heterosexually active during or within 7 months after completion of protocol treatment, he is responsible for beginning effective contraceptive measures.

5.4 Specimen Submission Criteria

a. Patients must submit archival tissue (if available) for translational medicine as described in Section 15.1. Patients must also be willing to undergo biopsies and submit tissue and blood for translational medicine as described in Section 15.1.

b. Patients must be offered the opportunity to participate in specimen banking of leftover tissue for future research as described in Section 15.1b.

5.5 Regulatory Criteria

a. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

b. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

6.0 STRATIFICATION FACTORS

There are no stratification factors for this study.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. VanderWalde (901/683-0055 ext. 63015 or avanderw@uthsc.edu) or Dr. Ribas (310/206-3928 or aribas@mednet.ucla.edu). For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

7.1 Pre-Medication and Concomitant Medications

a. Pre-Medication

Premedication associated with standard drug administration and supportive care (including anti-diarrheals, antibiotics, diuretics or other medications) may be given as indicated by the current American Society of Clinical Oncology (ASCO) guidelines. Premedication for the use of prophylaxis for infusion reactions (e.g., diphenhydramine, acetaminophen, or other medications) may be given per institutional standard.

For patients that experience infusion reactions the following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab or ipilimumab administrations.

As there is potential for hepatic toxicity with nivolumab or nivolumab/ipilimumab combination, drugs with a predisposition to hepatic toxicity should be used with caution in patients treated with nivolumab containing regimen.

b. Concomitant Medications

The following medications are prohibited during the study (unless utilized to treat a drug related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (e.g., prednisone >10 mg daily or equivalent)
- Any concurrent anti-neoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of melanoma)

7.2 Treatment – Arm 1: Ipilimumab Alone

Patients will receive the following treatment until completion of 4 cycles of treatment or meeting one of the criteria in Section 7.5.

Agent	Dose	Route	Day	Schedule*
Ipilimumab	3 mg/kg	IV over 90 mins	1	q 21 days for 4 cycles

* Note: 1 cycle = 21 days

7.3 Treatment – Arm 2: Ipilimumab + Nivolumab

Patients will receive the following treatment until meeting one of the criteria in Section 7.5.

Cycles 1-4

Agent	Dose	Route	Day	Schedule*
Nivolumab	1 mg/kg	IV over 30 mins	1	q 21 days for 4 cycles only.
Ipilimumab**	3 mg/kg	IV over 90 mins	1	q 21 days for 4 cycles only

* Note: 1 cycle = 21 days
**Ipilimumab to start 30 minutes after the end of nivolumab infusion.

Cycles 5+

Agent	Dose	Route	Day
Nivolumab	480 mg	IV over 30 mins	1 of every cycle

Note: 1 cycle = 28 days

7.4 Full CDUS Reporting Requirement

Because this study contains an investigational drug for which CTEP holds the IND, it falls under CTEP requirements for full reporting. This involves required submission of cycle-specific toxicity and dose information (see Section 14.4, the **S1616** Treatment Form, and the **S1616** Adverse Event Form).
A cycle is defined as:

- Arm 1: 21 days
- Arm 2: 21 days for first 4 cycles; 28 days for Cycles 5+

7.5 Criteria for Removal from Protocol Treatment

a. Progression of disease as defined in Section 10.2d. However, the patient may continue to stay on protocol treatment as long as, in the opinion of the treating investigator, the patient is continuing to clinically benefit from treatment. This may occur if there are lesions that continue to respond to the therapy despite others progressing, or if there is symptomatic relief of symptoms on therapy.

b. Completion of 4 cycles on Arm 1.

c. Symptomatic deterioration (as defined in Section 10.2e).

d. Unacceptable toxicity (see also Section 8.0).

e. Treatment delay for any reason > 12 weeks.

f. The patient may withdraw from the study at any time for any reason.

7.6 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.7 Follow-Up Period

All patients will be followed until death or 3 years after registration, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

Two different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used on this study.

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 will be utilized **for SAE reporting only**. The CTCAE Version 5.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 4.0 for routine toxicity reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General considerations

a. No dose reductions are allowed.

b. The maximum dose delay for any reason is 84 calendar days (12 weeks).

c. 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.

8.3 Dose Delay Criteria Ipilimumab (Arm 1)

Dose modifications for ipilimumab by adverse event type are detailed in Table 8.1. General considerations for dose modifications are as follows.

a. It is necessary to avoid study drug dosing and initiate appropriate evaluation and/or treatment for the following adverse events:
- Any ≥ Grade 3 skin related adverse event regardless of causality.
- Any ≥ Grade 2 non-skin related adverse event (including immune-mediated adverse reactions), except for easily corrected laboratory abnormalities that do not reflect underlying organ pathology.
- Any ≥ Grade 3 laboratory abnormality.
- Any adverse event, laboratory abnormality or intercurrent illness that, in the opinion of the treating investigator, presents a substantial clinical risk to the patient with continued dosing.
- It may be necessary to hold study drug to evaluate Grade 1 events that suggest ongoing or incipient autoimmune disease including GI toxicity, diarrhea, pancreatitis, hepatitis, pituitary insufficiency, early evidence of neurologic events, skin toxicity until diagnosis and progression are determined.

b. Ipilimumab may be restarted if/when the adverse event(s) resolve(s) in severity or returns to baseline within 2 weeks of initial dose administration:

- If the adverse event has been determined not be related to ipilimumab or is not an autoimmune/inflammatory event. If more than 1 dose is to be skipped or > 2 week delay is expected due to current events not related to study the dosing schedule modifications must be discussed with the study chairs prior to implementation.
- If the *adverse event has resolved to* **≤ Grade 1** , ipilimumab dosing may be restarted at the next scheduled timepoint per protocol. Please follow guidelines for specific events. Please note that re-initiating treatment may be associated with recurrence or exacerbation of autoimmune or inflammatory events. In some instances clinical resolution of events such as colitis may be associated with residual pathologic changes and should require evaluation of complete resolution prior to restarting therapy.
- If the adverse event has not resolved in the protocol-specified dosing window (3 weeks [±3 calendar days]), the next scheduled dose will be skipped and dosing will be resumed at the subsequently scheduled dose.
- Events which require intervention with immunosuppressant therapy, steroids, surgery, or hormone replacement generally require permanently stopping study treatment.

c. Permanently discontinue ipilimumab for any of the following:
- Persistent adverse reactions that require holding more than 2 treatment doses.
- Any related Grade 3 or 4 event (see exceptions below)
- Any event that requires immunosuppressive treatment or systemic steroids which cannot be discontinued during the time in which it takes to hold more than 2 treatment doses
- Severe or life-threatening adverse reactions, including any of the following:
  - Colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more over baseline), stool incontinence, need for IV hydration for more than 24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times the upper limit of normal or total bilirubin >3 times the upper limit of normal
- Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations
- Severe motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis
- Severe immune-mediated reactions involving any organ system (*e.g.*, nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)
- Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy
- Any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, presents organ specific injury and/or a substantial clinical risk to the patient with continued dosing.

NOTE: **The following neurological adverse events require permanent discontinuation of ipilimumab and define unacceptable neurotoxicity:**
- Any motor neurologic toxicity ≥ Grade 3 regardless of causality
- Any ≥ Grade 3 treatment related sensory neurologic toxicity

Please refer to Appendix 18.3 and Appendix 18.4 for specific treatment algorithms.

d. Exceptions to Permanent Discontinuation of Ipilimumab

- Potentially reversible inflammation (< Grade 4), attributable to a local anti-tumor reaction and a potential therapeutic response. This includes inflammatory reactions at sites of tumor resections or in draining lymph nodes, or at sites suspicious for, but not diagnostic of metastasis.
- Hospitalization for ≤ Grade 2 adverse events where the primary reason for hospitalization is to expedite the clinical work-up.
- Patients with the following conditions where in the treating investigator's opinion continuing study drug administration is justified based on the potential for continued clinical benefit:
  - Patients treated with systemic steroids for less than 2 weeks without evidence of autoimmune disease requiring steroids treatment
  - Grade 2 skin rash treated with topical steroids for less than 4 weeks
  - Grade 2 ocular toxicity that has completely responded to topical therapy within 4 weeks
  - Endocrinopathies where clinical symptoms are controlled with appropriate hormone replacement therapy. **Note:** Ipilimumab may not be restarted while the patient is being treated with systemic corticosteroids except for patients on stable doses of hormone replacement therapy such as hydrocortisone.

e. Allowance for ipilimumab dose delay

- In general, patients who meet criteria to resume ipilimumab will also have met criteria to resume nivolumab with ipilimumab, so it should be feasible to synchronize dosing of both drugs when resuming ipilimumab. In order to facilitate this, the dosing calendar days of nivolumab and ipilimumab may be adjusted within a +/- 5 day window, as long as consecutive nivolumab doses are given at least 12 calendar days apart.
- If an ipilimumab dose is delayed beyond 6 weeks from the prior ipilimumab dose, then subsequent nivolumab doses should be rescheduled to maintain at least a 3-week interval between consecutive ipilimumab doses.

- Dosing delays to manage drug-related adverse events, such as prolonged steroid tapers, are allowed. Disease assessments should continue as per protocol even if dosing is delayed.

- Dosing delays resulting in no ipilimumab dosing for > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Study Chairs. Disease assessments should continue as per protocol even if dosing is delayed.
- In event of any Grade 2 adverse event experienced while on combination nivolumab plus ipilimumab therapy, patient may resume treatment/may be continued on nivolumab monotherapy alone, at the discretion of the treating investigator
- Ipilimumab will not be given as monotherapy for Arm 2.

NOTE: If adverse events result in permanent discontinuation of ipilimumab, then subsequently manage dose delays under Management/Next Dose for nivolumab alone

8.4 Dose Delay Criteria for Nivolumab in Combination with Ipilimumab (Arm 2)

Dose modifications for nivolumab in combination with ipilimumab by adverse event type are detailed in Table 8.1. General considerations for dose modifications are as follows.

For the initial induction period, patients with Grade 2 or 3 events requiring discontinuation of treatment with the combination may consider continuing treatment with single agent nivolumab when the event resolves to baseline. However, patients with renal, CNS, or pulmonary toxicity must be removed from study.

a. In addition to the AEs identified in the table below, ipilimumab and nivolumab dose should be delayed for any AE, laboratory abnormality or inter-current illness which, in the judgment of the treating investigator, warrants delaying the dose of study medication.

b. Patients requiring a delay of > 6 weeks or who experience immune-related toxicity with inability to decrease prednisone ≤10 mg PO daily must go off protocol therapy entirely.

c. Patients who received systemic corticosteroids for management of any drug-related immunologic toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone 10 mg/day.

d. Nivolumab monotherapy may be continued at treating investigator discretion if there is evidence of clinical benefit. In this event, patient will continue nivolumab until AE is resolved and ipilimumab may be re-started or if ipilimumab is permanently discontinued (in congruence with guidelines in table below), then patient will continue nivolumab alone until cycles are completed. At completion of 4 cycles, patient may continue on nivolumab alone, as per protocol. If ipilimumab is permanently discontinued prior to receipt of 4 doses, nivolumab dosing should remain at the Cycle 1-4 dosing (1 mg/kg every 2 weeks) until completion of Cycle 4 and should then switch to Cycle 5+ dosing (480 mg every 4 weeks).

Table 8.1 Dose Modification for Related Adverse Events

Treatment-related Adverse Event	Grade of Event	*Nivolumab and/or Ipilimumab*
Nausea	≤ Grade 1	No dose modification
	Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below) [1]
	Grade 3	Off protocol therapy (exceptions as noted below) [1]
	Grade 4	Off protocol therapy
[*]Patients requiring a delay of >2 weeks must go off protocol therapy.		
Recommended management: antiemetics.		
Diarrhea (immune-related enterocolitis)	≤ Grade 1	No dose modification
	Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below) [1]
	Grade 3	Off protocol therapy (exceptions as noted below) [1]
	Grade 4	Off protocol therapy
[*]Patients requiring a delay of >2 weeks must go off protocol therapy		
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used. See GI AE Algorithm for management of symptomatic colitis. Patients with Grade 2 symptoms but normal colonoscopy and biopsies may be retreated after resolution. Patients who require steroids must be taken off study treatment. 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.		
Vomiting	≤ Grade 1	No dose modification
	Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below) [1]
	Grade 3	Off protocol therapy (exceptions as noted below) [1]
	Grade 4	Off protocol therapy
[*]Patients requiring a delay of >2 weeks must go off protocol therapy.		
Recommended management: antiemetics.		
Other GI	≤ Grade 1	No dose modification
	Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below) [1]
	Grade 3	Off protocol therapy (exceptions as noted below[1])
	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.		
Neurologic events (new,	≤ Grade 1	No dose modification
	Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below) [1]

Treatment-related Adverse Event	Grade of Event	*Nivolumab and/or Ipilimumab*
motor, sensory, encephalitis)	Grade 3	Off protocol therapy (exceptions as noted below) [1]
	Grade 4	Off protocol therapy
Fatigue	≤ Grade 1	No dose modification
	Grade 2	No dose modification
	≥Grade 3	Off protocol therapy (exceptions as noted below) [1] – if fatigue is found related to endocrinopathy and clinical symptoms are managed with hormone replacement, patient resume therapy
	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		
Fever	≤ Grade 1	Evaluate and continue
	Grade 2	Hold until ≤ Grade 1.
Treatment-related Adverse Event	**Grade of Event**	***Nivolumab and/or Ipilimumab***
Fever (continued)	Grade 3	Hold until ≤ Grade 1.
	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 calendar days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever		
Skin drug-related AE	≤ Grade 1	No dose modification
	Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below) [1]
	Grade 3	Off protocol therapy (exceptions as noted below) [1]
	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: See AE management guidelines		
Pneumonitis, broncho-spasm, pulmonary toxicity or interstitial lung disease	≤ Grade 1	No dose modification. See Section 18.3 for Management recommendations.
	Grade 2	Hold dose pending evaluation. Resume after pulmonary and/or ID consultation excludes autoimmune related causes. Patient must be removed from protocol therapy if steroids are required
	Grade 3	Off protocol therapy
	Grade 4	Off protocol therapy

Treatment-related Adverse Event	Grade of Event	*Nivolumab and/or Ipilimumab*
	Above does not include infusion reactions.	
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		
Thrombocyto-penia	≤ Grade 1	No dose modification
	Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below) [1]
	Grade 3	Off protocol therapy
	Grade 4	Off protocol therapy
Neutropenia	≤ Grade 1	No dose modification
	Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below) [1]
	Grade 3	Off protocol therapy
	Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks must go off protocol therapy.		
Renal	≤ Grade 1	*No dose modification*
	Grade 2	Hold until ≤ Grade 1.
	Grade 3	Off protocol therapy
	Grade 4	Off protocol therapy
See Section 18.3 for Management recommendations.[5]		
Endocrine Hypophysitis Adrenal Insufficiency	≤ Grade 1	No dose modification
	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.
Treatment-related Adverse Event	**Grade of Event**	***Nivolumab and/or Ipilimumab***
Endocrine Hypophysitis Adrenal Insufficiency (continued)	Grade 3	Hold until patients are on a stable replacement hormone regimen. If treated with steroids patients must be stable off steroids for two weeks.
	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.		

Treatment-related Adverse Event	Grade of Event	*Nivolumab and/or Ipilimumab*
Recommended management: See Endocrine Management Algorithm		
Abnormal liver function (AST/ALT, Total bilirubin, immune-related hepatitis)	≤ Grade 1	No dose modification
	Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below) [1]
	Grade 3	Off protocol therapy
	Grade 4	Off protocol therapy
Continued treatment of active immune mediated hepatitis may exacerbate ongoing inflammation. Holding drug to evaluate LFT changes and early treatment are recommended. LFT changes may occur during steroid tapers from other events and may occur together with other GI events including cholecystitis/pancreatitis.		
Recommended management: see Hepatic AE management algorithm		
Amylase or lipase, associated with GI symptoms	≤ Grade 1	No dose modification
	Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below) [1]
	Grade 3	Hold until baseline and asymptomatic. Patients who develop symptomatic pancreatitis or DM must be taken off treatment[5]
	Grade 4	Off protocol therapy
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		
Any other laboratory abnormality (except AST/ALT, Total bilirubin, thrombocytopenia, neutropenia, lymphopenia)	≤ Grade 1	No change.
	Grade 2	No change.
	Grade 3	Off protocol therapy unless is unrelated to underlying organ pathology and can be managed with electrolyte replacement, hormone replacement, insulin, or no therapy
	Grade 4	Off protocol therapy unless is unrelated to underlying organ pathology and can be managed with electrolyte replacement, hormone replacement, insulin, or no therapy
	[2] Grade 4 lymphopenia or leukopenia or does not require drug discontinuation. 3 Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset do not require drug discontinuation. [4] Resolved, well-controlled, or asymptomatic hypothyroidism does not require approval by Study	

Treatment-related Adverse Event	Grade of Event	*Nivolumab and/or Ipilimumab*
	Chairs prior to restarting therapy.	
Treatment-related Adverse Event	**Grade of Event**	***Nivolumab and/or Ipilimumab***
Cardiac*	≤ 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 calendar 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. 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.		
Infusion Reaction	≤ Grade 1	*No dose modification*
	Grade 2	Interrupt study drug. Upon recovery from symptoms, resume study drug at one half the initial infusion rate, then increase incrementally to the initial infusion rate
	Grade 3	Off protocol therapy
	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 calendar days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever		
All other events	≤ Grade 1	No dose modification

Treatment-related Adverse Event	Grade of Event	*Nivolumab and/or Ipilimumab*
	Grade 2	Hold until ≤ Grade 1 OR baseline(exceptions as noted below) [1]
	Grade 3	Off protocol therapy
	Grade 4	Off protocol therapy

Table 8.1 Footnotes

[1]Recommended management: As clinically indicated

Exceptions:

- 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 must go off protocol treatment
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the treating investigator, presents a substantial clinical risk to the patient with continued study drug dosing must go off protocol treatment.
- 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.

[5] Recommended management: As clinically indicated

- See Section 18.3 for recommended management
- See Section 8.4 for treatment management

8.5 Treatment of Infusion Reactions Associated with Ipilimumab and/or Nivolumab

Since ipilimumab contains only human protein sequences, and since nivolumab is a fully human monoclonal antibody, it is less likely that any allergic reaction will be seen in patients receiving these agents. However, it is possible that infusion of ipilimumab or nivolumab will induce a cytokine release syndrome that could be evidenced by fever, chills, rigors, rash, pruritus, hypotension, hypertension, bronchospasm, or other symptoms. No prophylactic pre-medication should be given unless indicated by previous experience in an individual patient. Reactions should be treated based upon the following recommendations.

- For mild symptoms (*e.g.*, localized cutaneous reactions such as mild pruritus, flushing, rash):
  - Decrease the rate of infusion until recovery from symptoms, remain at bedside and monitor patient.
  - Complete the infusion at the initial planned rate.
  - Diphenhydramine 50 mg IV may be administered at the discretion of the treating physician and patients may receive additional doses with close monitoring.
  - Premedication with diphenhydramine may be given at the discretion of the investigator for subsequent doses.

- For moderate symptoms (any symptom not listed above [mild symptoms] or below [severe symptoms] such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP >80 mmHg):
  - Interrupt infusion of offending agent.
  - Administer diphenhydramine 50 mg IV.
  - Monitor patient closely until resolution of symptoms.
  - Corticosteroids may abrogate any beneficial immunologic effect, but may be administered at the discretion of the treating physician.
  - Resume infusion after recovery of symptoms.
  - At the discretion of the treating physician, infusion may be resumed at *one half the initial infusion rate, then increased incrementally to the initial infusion rate*.
  - If symptoms develop after resumption of the infusion, the infusion should be discontinued and no additional ipilimumab or nivolumab should be administered that day.
  - The next dose will be administered at its next scheduled time and may be given with pre-medication (diphenhydramine and acetaminophen) and careful monitoring, following the same treatment guidelines outlined above.
  - At the discretion of the treating physician additional oral or IV antihistamine may be administered prior to dosing.

- For severe symptoms (e.g., any reaction such as bronchospasm, generalized urticaria, systolic blood pressure < 80 mm Hg, or angioedema):
  - Immediately discontinue infusion, and disconnect infusion tubing from the patient.
  - Consider bronchodilators, epinephrine 1 mg IV or subcutaneously, and/or diphenhydramine 50 mg IV, with solumedrol 100 mg IV, as needed.
  - Patients should be monitored until the investigator is comfortable that the symptoms will not recur.
  - No further ipilimumab (if related to ipilimumab) or nivolumab (if related to nivolumab) will be administered.

8.6 Treatment of Ipilimumab-Related Isolated Drug Fever

In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the ipilimumab or to an infectious etiology. If a patient experiences isolated drug fever, for the next dose, pre-treatment with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion) should be instituted and a repeated antipyretic dose at 6 and 12 hours after ipilimumab infusion, should be administered. The infusion rate will remain unchanged for future doses. If a patient experiences recurrent isolated drug fever following premedication and post dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be decreased to 50% of the previous rate. If fever recurs following infusion rate change, the investigator should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further ipilimumab.

8.7 Monitoring and Management of Immune-mediated Adverse Reactions

Immune-mediated Enterocolitis

The clinical presentation of GI immune-related AEs included diarrhea, increase in the frequency of bowel movements, abdominal pain, or hematochezia, with or without fever. However, inflammation may occur in any part of the GI tract including esophagitis and gastritis. Fatalities due to GI perforation have been reported in clinical trials of ipilimumab.

Patients should be carefully monitored for GI symptoms that may be indicative of immune-related colitis, diarrhea, or GI perforation. Diarrhea or colitis occurring after initiation of ipilimumab therapy should be evaluated to exclude infectious or alternate etiologies. In clinical trials, immune-related colitis was associated with evidence of mucosal inflammation, with or without ulcerations, and lymphocytic infiltration.

Monitor patients for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, rule out infectious etiologies and consider endoscopic evaluation to establish etiology and for persistent or severe symptoms. C.difficile toxin has been detected in several patients with colitis and may be an independent entity or may co-exist with ipilimumab induced inflammatory colitis.

Withhold ipilimumab and/or nivolumab dosing for any patients with enterocolitis pending evaluation; administer anti-diarrheal treatment and, if persistent evaluate with colonoscopy and initiate systemic corticosteroids at a dose of 0.5 mg/kg/day prednisone or equivalent.

Permanently discontinue ipilimumab and nivolumab in patients with severe enterocolitis and initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least one month. In clinical trials, rapid corticosteroid tapering has resulted in recurrence or worsening symptoms of enterocolitis in some patients.

Patients have been treated with anti-TNF agents for persistent colitis not responding to steroids.

Please note autoimmune pancreatitis may cause abdominal pain and should be included in all evaluations. Enteritis may occur occasionally with other autoimmune events including hepatitis, pancreatitis, and endocrine insufficiency, which should be evaluated as clinically indicated.

<u>Immune-mediated Hepatitis and Pancreatitis</u>
Hepatic immune-related AEs were mostly clinically silent and manifested as transaminase or bilirubin laboratory abnormalities. Fatal hepatic failure has been reported in clinical trials of ipilimumab. Serum transaminase and bilirubin must be evaluated before each dose of ipilimumab and nivolumab as early laboratory changes may be indicative of emerging immune-related hepatitis/ pancreatitis and elevations in liver function tests (L**FTs) may develop in the absence of clinical symptoms.** Increase in LFT or total bilirubin should be evaluated to exclude other causes of hepatic injury, including infections, disease progression, or other medications, and monitored until resolution. Liver biopsies from patients who had immune-related hepatotoxicity showed evidence of acute inflammation (neutrophils, lymphocytes, and macrophages).

Monitor liver function tests (hepatic transaminase and bilirubin levels) and assess patients for signs and symptoms of hepatotoxicity/ pancreatitis before each dose of ipilimumab and nivolumab. In patients with hepatotoxicity, rule out infectious or malignant causes and increase frequency of liver function test monitoring until resolution. Withhold ipilimumab and nivolumab in patients with Grade 2 hepatotoxicity.

Permanently discontinue ipilimumab and nivolumab in patients with Grade 3–5 hepatotoxicity/pancreatitis and administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When liver function tests show sustained improvement or return to baseline, initiate corticosteroid tapering and continue to taper over 1 month. Across the clinical development program for ipilimumab, mycophenolate

treatment has been administered in patients who have persistent severe hepatitis despite high-dose corticosteroids.

Immune-mediated Dermatitis
Skin immune-related AEs presented mostly frequently as a rash and/or pruritus. Some patients reported vitiligo associated with ipilimumab administration. Fatal toxic epidermal necrolysis has been reported in clinical trials of ipilimumab.

Monitor patients for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated.

Permanently discontinue ipilimumab and nivolumab in patients with Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations. Administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month. Withhold ipilimumab and nivolumab dosing in patients with moderate to severe signs and symptoms.

For mild to moderate dermatitis, such as Grade 2 localized rash and pruritus, treat symptomatically. For persistent Grade 2, Grade 3, or greater, topical steroids may be administered. Administer topical or systemic corticosteroids as indicated if there is no improvement of symptoms within 1 week.

Immune-related Neurological Events
Fatal Guillain-Barré syndrome has been reported in clinical trials of ipilimumab. Patients may present with muscle weakness and myasthenia gravis, cranial nerve palsy (n VII Bell's palsy), and aseptic meninigits, encephalopathy. Unexplained motor neuropathy, muscle weakness, or sensory neuropathy lasting more than 4 calendar days should be evaluated and non-inflammatory causes such as disease progression, infections, metabolic syndromes, nerve entrapment, and medications should be excluded as causes.

Withhold ipilimumab and nivolumab dosing in patients with any evidence of neuropathy pending evaluation.

Monitor for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Permanently discontinue ipilimumab and nivolumab in patients with severe neuropathy (interfering with daily activities) such as Guillain-Barré-like syndromes. Institute medical intervention as appropriate for management of neuropathy and other neurologic events. Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe neuropathies.

Immune-mediated Endocrinopathies
Ipilimumab and/or nivolumab can cause inflammation of endocrine organs including thyroid (Hashimoto's thryroiditis with positive antibodies) and adrenal glands, hypophysitis, hypopituitarism, and resulting thyroid and adrenal insufficiency, low ADH, prolactin, FSH, LH. Hyperthyroid with Graves' disease and positive antibody has been reported. Patients may present with subtle and nonspecific symptoms. The most common clinical presentation includes headache and fatigue. Symptoms may also include visual field defects, behavioral changes, and electrolyte disturbances including hyponatremia and hypotension. Adrenal crisis as a cause of the patient's symptoms should be excluded. Based on the available data with known outcome, most of the patients symptomatically

improved with hormone replacement therapy. Long-term hormone replacement therapy with HC and Synthroid will typically be required for patients developing hypophysitis/hypopituitarism after treatment with ipilimumab alone or with nivolumab. Some patients have regained partial function following steroid treatment.

Monitor patients for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism. Headache is often the first symptoms of hypophysitis. Patients may present with fatigue, headache, mental status changes, loss of libido, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-mediated and drugs withheld pending evaluation. Patients may demonstrate both central (hypophysitis) and peripheral adrenal and thyroid insufficiency. Evaluation of hypophysitis should include pituitary MRI.

Endocrine evaluation, including TSH, should be performed at baseline prior to initial treatment. Monitor thyroid function tests and clinical chemistries at the start of treatment and hold blood for possible evaluation should clinical events require determining baseline function and anti-thyroid antibodies. In a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland.

Withhold ipilimumab and nivolumab dosing in patients symptomatic for hypophysitis. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent, and initiate appropriate hormone replacement therapy.

<u>Other Immune-mediated Adverse Reactions, Including Ocular Manifestations</u>
Ocular inflammation, manifested as Grade 2 or Grade 3 episcleritis or uveitis, was associated with concomitant diarrhea in a few patients (< 1%) and occasionally occurred in the absence of clinically apparent GI symptoms. Other presumed immune-related AEs reported include, but were not limited to, arthritis/arthralgias, pneumonitis, pancreatitis, autoimmune (aseptic) meningitis, autoimmune nephritis, pure red cell aplasia, noninfective myocarditis, polymyositis, and myasthenia gravis, of which were individually reported for < 1% of patients.

The following clinically significant immune-mediated adverse reactions were seen in less than 1% of ipilimumab-treated patients in Study 1: nephritis, pneumonitis, pulmonary granuloma resembling sarcoidosis, meningitis, pericarditis, uveitis, iritis, ITP, neutropenia and hemolytic anemia.

Across the clinical development program for ipilimumab, the following likely immune-mediated adverse reactions were also reported with less than 1% incidence: myocarditis, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, pancreatitis, arthritis, and autoimmune thyroiditis.

Permanently discontinue ipilimumab and nivolumab for clinically significant or severe immune-mediated adverse reactions. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe immune-mediated adverse reactions.

Administer corticosteroid eye drops to patients who develop uveitis, iritis, or episcleritis. Permanently discontinue ipilimumab for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

a. Overall, immune-related AEs commonly started within 3 to 10 weeks from first dose, were successfully managed in most instances by omitting doses, discontinuing dosing, and/or through administering symptomatic or immunosuppressive therapy, including corticosteroids, as mentioned above and detailed in Section 7.0. Immune-related AEs generally resolved within days to weeks in the majority of patients

8.8 White Blood Cell Growth Factors

If used, white blood cell growth factors, including biosimilars, must be used per ASCO guidelines (http://jco.ascopubs.org/content/24/19/3187.full) and NCCN Guidelines® Myeloid Growth Factors (http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf).

8.9 Dose Modifications Contacts

For treatment or dose modification questions, please contact Dr. VanderWalde (901/683-0055 ext 63015 or avanderw@uthsc.edu) or Dr. Ribas (310/206-3928 or aribas@mednet.ucla.edu).

8.10 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.1 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

9.1 Arm 1

	Pre-registration [G]	Cycle (1 cycle = 21 days)												Follow-up prior to progression	Follow-up after progression
		1			2			3			4				
		Week [K]													
		1	2	3	4	5	6	7	8	9	10	11	12		
PHYSICAL															
History and physical exam	X	X [L]			X			X			X			X [N]	X [Q]
Weight and performance status [R]	X	X [L]			X			X			X			X [N]	X [Q]
Toxicity notation		X			X			X			X			X [P]	X [P]
Baseline abnormalities		X													
Disease assessments	X												X [M]	X [N]	
Biopsy [A]		X				X									
LABORATORY															
ANC, platelets, and hemoglobin	X	X [L]			X			X			X			X [P]	X [P]
AST, ALT, and total bilirubin	X	X [L]			X			X			X			X [P]	X [P]
Serum creatinine	X	X [L]			X			X			X			X [P]	X [P]
Pregnancy test	X [H]														
Creatinine phosphokinase (CPK), Troponin, and Cardiology consultation [B]	X														
CD4	X [J]														
TSH, Free T4, Free T3 [C]		X			X			X			X				

Calendar continued on next page. Click here for Footnotes

	Pre-registration [G]	Cycle (1 cycle = 21 days)												Follow-up prior to progression	Follow-up after progression
		1			2			3			4				
		Week [K]													
		1	2	3	4	5	6	7	8	9	10	11	12		
X-RAYS AND SCANS															
MRI or CT for disease assessment [S]	X												X [M]	X [N]	
Electrocardiogram (ECG) and Echocardiogram (Echo) [D]	X														
SPECIMEN SUBMISSION															
Archival tissue [E]		X													
Tissue block or slides from biopsy		X				X									
Blood [F]		X				X									
Fresh Frozen Tissue from biopsy [T]		X				X									
TREATMENT															
Ipilimumab		X			X			X			X				

Calendar continued on next page. Click here for Footnotes

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Note: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://swog.org/Visitors/Download/QA/Best%20Practices%20upddate.pdf.

Footnotes

A To be performed on or prior to Day 1 and on Day 21-35 (Day 28 +/- 7 days). The first biopsy should be performed within 28 days prior to Day 1. If it is not feasible to obtain this biopsy, tissue that was collected at any time since demonstrated progression on PD-1 or PD-L1 therapy may be substituted provided that 30 unstained slides are available.

B Only for patients with symptoms of congestive heart failure (CHF), cardiomyopathy, myocarditis, myocardial infarction, or exposure to cardiotoxic medications. Required pre-registration (see Section 5.3n). After that, perform as clinically indicated.

C Free T3 and Free T4 are only required if TSH results are abnormal.

D Only for patients with a known history of congestive heart failure (CHF), cardiomyopathy, myocarditis, myocardial infarction, exposure to cardiotoxic medications, or with a clinical history suggestive of any of these conditions. Required pre-registration (see Section 5.3m). After that, perform as clinically indicated.

E Collected prior to previous anti-PD-1 or anti-PD-L1 treatment

F To be drawn on or prior to Day 1 (after registration and within 28 days) and on Day 21-35 (Day 28 +/- 7 days). If feasible, Day 1 blood should be drawn on the same day as the baseline tissue biopsy. Day 28 Blood must be drawn on same day as the Day 28 tissue biopsy.

G Required time frame is detailed in Section 5.0.

H Only for females of reproductive potential (see Section 5.3p)

J Only required for patients with a known history of HIV (see Section 5.3g)

K Weeks measured from start of treatment, provided that the patient does not have any treatment delays

L If pre-registration exam/lab was performed within 14 days prior to Cycle 1 Day 1, this exam/lab does not need to be repeated on Cycle 1 Day 1.

M Performed at completion of Week 12

N Every 12 weeks until progression

P Every 3 weeks until resolution of adverse events

Q At least every 6 months (+/- 2 weeks) until 2 years after registration, then annually (+/- 4 weeks) until 3 years after registration.

R Though weight should be checked at each visit, weight-based dosing should be calculated using baseline weight unless weight has changed from last dose by more than 10%.

S CT or MRI of the chest, abdomen, and pelvis should be performed at baseline and all subsequent assessments. Additionally, for patients with known assessable scalp or neck disease, a CT or of the head/face/neck should be performed at baseline and all subsequent assessments. Patients with known assessable extremity disease should have the affected extremity also measured by CT or MRI at baseline and all subsequent visits. Patients with a history of central nervous system metastases must have MRI of the brain at baseline and at all subsequent assessments.

T Select sites will, at each prospective biopsy timepoint, obtain additional cores. See Section 15.1c.4 for details.

9.2 Arm 2: Cycles 1 through 4 (see Section 9.3 for Arm 1 Cycles 5+)

	Pre-registration [G]	Cycle (1 cycle = 21 days)											
		1			2			3			4		
		Week [K]											
		1	2	3	4	5	6	7	8	9	10	11	12
PHYSICAL													
History and physical exam	X	X [L]			X			X			X		
Weight and performance status [N]	X	X [L]			X			X			X		
Toxicity notation		X			X			X			X		
Baseline abnormalities		X											
Disease assessments	X												X [M]
Biopsy [A]		X				X							
LABORATORY													
ANC, platelets, and hemoglobin	X	X [L]			X			X			X		
AST, ALT, and total bilirubin	X	X [L]			X			X			X		
Serum creatinine	X	X [L]			X			X			X		
Pregnancy test	X [H]												
Creatinine phosphokinase (CPK), Troponin, and Cardiology consultation [B]	X												
CD4	X [J]												
TSH, Free T4, Free T3 [C]		X			X			X			X		

Calendar continued on next page. Click here for footnotes.

	Pre-registration [G]	Cycle (1 cycle = 21 days)											
		1			2			3			4		
		Week [K]											
		1	2	3	4	5	6	7	8	9	10	11	12
X-RAYS AND SCANS													
MRI or CT for disease assessment [O]	X												X [M]
Electrocardiogram (ECG) and Echocardiogram (Echo) [D]	X												
SPECIMEN SUBMISSION													
Archival tissue [E]		X											
Tissue block or slides from biopsy		X				X							
Blood [F]		X				X							
Fresh Frozen Tissue from biopsy [P]						X							
TREATMENT													
Nivolumab 1 mg/kg		X			X			X			X		
Ipilimumab		X			X			X			X		

Click here for footnotes.

Note: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). The schedule for submission of these forms is listed in Section 14.0

Note: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://swog.org/Visitors/Download/QA/Best%20Practices%20upddate.pdf.

Footnotes

A To be performed on or prior to Day 1 and on Day 21-35 (Day 28 +/- 7 days). The first biopsy should be performed within 28 days prior To Day 1. If it is not feasible to obtain this biopsy, tissue that was collected at any time since demonstrated progression on PD-1 or PD-L1 therapy may be substituted provided that 30 unstained slides are available.

B Only for patients with symptoms of congestive heart failure (CHF), cardiomyopathy, myocarditis, myocardial infarction, or exposure to cardiotoxic medications. Required pre-registration (see Section 5.3n). After that, perform as clinically indicated.

C Free T3 and Free T4 are only required if TSH results are abnormal.

D Only for patients with a known history of congestive heart failure (CHF), cardiomyopathy, myocarditis, myocardial infarction, exposure to cardiotoxic medications, or with a clinical history suggestive of any of these conditions. Required pre-registration (see Section 5.3m). After that, perform as clinically indicated.

E Collected prior to previous anti-PD-1 or anti-PD-L1 treatment. See Section 15.1.

F To be drawn on or prior to Day 1 (after registration and within 28 days prior) and on Day 21-35 (Day 28 +/- 7 days). f feasible, Day 1 blood should be drawn on the same day as the baseline tissue biopsy. Day 28 blood must be drawn on same day as the Day 28 tissue biopsy.

G Required time frame is detailed in Section 5.0.

H Only for females of reproductive potential (see Section 5.3p)

J Only required for patients with a known history of HIV (see Section 5.3g)

K Weeks measured from start of treatment, provided that the patient does not have any treatment delays

L If pre-registration exam/lab was performed within 14 days prior to Cycle 1 Day 1, this exam/lab does not need to be repeated on Cycle 1 Day 1.

M Performed at completion of Week 12

N Though weight should be checked at each visit, weight-based dosing should be calculated using baseline weight unless weight has changed from baseline by more than 10%.

O CT or MRI of the chest, abdomen, and pelvis should be performed at baseline and all subsequent assessments. Additionally, for patients with known assessable scalp or neck disease, a CT or of the head/face/neck should be performed at baseline and all subsequent assessments. Patients with known assessable extremity disease should have the affected extremity also measured by CT or MRI at baseline and all subsequent visits. Patients with a history of central nervous system metastases must have MRI of the brain at baseline and at all subsequent assessments.

O CT or MRI of the chest, abdomen, and pelvis should be performed at baseline and all subsequent assessments. Additionally, for patients with known assessable scalp or neck disease, a CT or of the head/face/neck should be performed at baseline and all subsequent assessments. Patients with known assessable extremity disease should have the affected extremity also measured by CT or MRI at baseline and all subsequent visits. Patients with a history of central nervous system metastases must have MRI of the brain at baseline and at all subsequent assessments.

P Select sites will, at each prospective biopsy timepoint, obtain additional core. See Section 15.1c.4 for details.

9.3 Arm 2 Cycles 5+

	Cycle (1 cycle = 28 days) [R]												Follow-up prior to progression	Follow-up after progression
	5				6				7+					
	Week [K]													
	13	14	15	16	17	18	19	20	21	22	23	24		
PHYSICAL														
History and physical exam	X				X				X				X [N]	X [Q]
Weight and performance status	X				X				X				X [N]	X [Q]
Toxicity notation	X				X				X				X [P]	X [P]
Disease assessments												X [M]	X [M]	
LABORATORY														
ANC, platelets, and hemoglobin	X				X				X				X [P]	X [P]
AST, ALT, and total bilirubin	X				X				X				X [P]	X [P]
Serum creatinine	X				X				X				X [P]	X [P]
Creatinine phosphokinase (CPK), Troponin, and Cardiology consultation [B]														
TSH, Free T4, Free T3 [C]	X				X				X					
X-RAYS AND SCANS														
MRI or CT for disease assessment [S]												X [M]	X [M]	
Electrocardiogram (ECG) and Echocardiogram (Echo) [D]														
TREATMENT														
Nivolumab 480 mg	X				X				X					

Click here for footnotes.

Note: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). The schedule for submission of these forms is listed in Section 14.0.

Note: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in http://swog.org/Visitors/QA/Documents/Best%20Practices%20upddate.pdf.

Footnotes

B Only for patients with symptoms of congestive heart failure (CHF), cardiomyopathy, myocarditis, myocardial infarction, or exposure to cardiotoxic medications. Required pre-registration (see Section 5.3n). After that, perform as clinically indicated.

C Free T3 and Free T4 are only required if TSH results are abnormal.

D Only for patients with a known history of congestive heart failure (CHF), cardiomyopathy, myocarditis, myocardial infarction, exposure to cardiotoxic medications, or with a clinical history suggestive of any of these conditions. Required pre-registration (see Section 5.3m). After that, perform as clinically indicated.

K Weeks measured from start of treatment, provided that the patient does not have any treatment delays

M Performed every 12 weeks (i.e., at *completion* of Week 24, 36, etc.) for 3 years from time of registration or until progression.

N Every 12 weeks until progression

P Every 4 weeks until resolution of adverse events

Q At least every 6 months (+/- 2 weeks) until 2 years after registration, then annually (+/- 4 weeks) until 3 years after registration.

R Protocol treatment and parameters will continue on this same schedule until one of the criteria in Section 7.5 is met.

S CT or MRI of the chest, abdomen, and pelvis should be performed at baseline and all subsequent assessments. Additionally, for patients with known assessable scalp or neck disease, a CT or of the head/face/neck should be performed at baseline and all subsequent assessments. Patients with known assessable extremity disease should have the affected extremity also measured by CT or MRI at baseline and all subsequent visits. Patients with a history of central nervous system metastases must have MRI of the brain at baseline and at all subsequent assessments.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Measurability of Lesions

a. **Measurable disease**: Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans (see below for additional considerations for size based on the imaging approach), or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm 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 non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**

1. For CT and MRIs, 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 by performed with breath-hold scanning techniques, if possible.

2. PET-CT: At present, the low dose or attenuation correction CT portion of a 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, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

4. 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.

5. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default

measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

10.2 Objective Status at Each Disease Evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as ***target*** lesions at baseline. 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. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR):** Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable:** Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.2e).

Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.

2. No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g., CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**. Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. **Objective status notes:**

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.

3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.

6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.

7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.3 Best Response

This is calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	**DESCRIPTION**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.5 Progression-Free Survival (PFS)

From date of registration to date of first documentation of progression or symptomatic deterioration (as defined above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last contact.

10.6 Time to death

Measured from the date of registration until death from any cause, with patients last known to be alive censored at the date of last contact

11.0 STATISTICAL CONSIDERATIONS

11.1 Accrual Goal

Although the primary objective aims to assess whether combination therapy ipilimumab and nivolumab is superior to single therapy ipilimumab in patients who have previously progressed on anti-PD-1 or anti-PD-L1 therapy, major additional objectives of this study include assessment of key biomarkers and genomic correlatives, particularly for patients who receive combination therapy. This study will use a design in which 63 patients will be randomized to receive combination therapy ipilimumab and nivolumab and 21 patients will be randomized to receive single therapy ipilimumab. Assuming an ineligibility rate of 10% the total accrual goal is 94 patients.

The unbalanced randomization is motivated by the necessity of evaluating the first secondary objective. In particular, the underlying rationale for the combination therapy is that initial progression on PD-1 blockade alone results from poor T cell recruitment. If the combination therapy is superior to single agent ipilumimab, evaluation of this hypothesis by comparing T cell infiltration between patients who have an objective response (confirmed and unconfirmed partial or complete response per RECIST 1.1) and patients who do not have an objective response to combination therapy will elucidate mechanisms that are imperative for design and development of further studies of combination therapy in this population. Thus, unbalanced randomization is necessary to ensure adequate sample size for evaluating this hypothesis. Assuming a response rate of 25% and 90% compliance in tissue and biopsy submission, then we anticipate accruing 14 eligible objective responders and 43 eligible objective non-responders in the combination therapy arm.

11.2 Primary Analysis and Interim Analysis

For our primary objective, we will compare the PFS between arms using a log-rank test. Kaplan-Meier plots will be constructed and median PFS for each arm with corresponding 95% Brookmeyer-Crowley confidence intervals will be estimated.

Combination therapy will be considered superior to single therapy ipilimumab if median progression-free survival (PFS) is doubled. Based on Hodi et al., we assume the median PFS for patients randomized to single therapy ipilimumab to be 3 months such that the target alternative PFS for patients randomized to combination therapy is 6 months (corresponding to a hazard ratio of 0.5). We assume exponential survival, 24 months of accrual, 12 additional months of follow-up after the last patient is randomized, and that the final analysis will be conducted at the one-sided alpha = 10% level. One interim analysis for futility will be performed after approximately 50% information under the null (corresponding to approximately 41 events across both arms which is expected to occur 16-17 months after accrual starts). If the hazard ratio favors the control arm (is greater than 1), the study will be stopped due to futility. Given the modest sample size, no plans for formal interim analysis of efficacy are included. Using simulations (10,000 replicates), this design has overall type I error of 9.0% and power of 89%. Under the null, the probability of stopping early for futility at the interim analysis is 50% and under the alternative, the probability of stopping early is 4.1%.

11.3 Secondary Objectives

An important hypothesis underlying the rationale for the combination therapy is that initial progression on PD-1 blockade alone results from poor T cell recruitment. Consequently, our first secondary endpoint will evaluate this by comparing the quantitative CD8+ expression levels between patients who eventually respond and patients who do not respond using a two-sample t-test and control the type I error at the two-sided 0.05 level. Assuming that the trial accrues to completion, 90% compliance in tissue and biopsy

submission, there will be 56 patients to evaluate this hypothesis. If it is further assumed that 25% of these patients respond, then we anticipate 80% power to detect a mean difference in CD8+ expression of 0.875 standard deviations. Evaluation of this hypothesis motivates the unbalanced randomization.

For the additional secondary objectives, the study will estimate the response rate (confirmed and unconfirmed, complete and partial responses) in each arm and construct 95% binomial confidence intervals. All randomized patients will be included in the analysis of response. Patients who cannot have their exact response determined due to inadequate disease assessments will be counted in the denominator as non-responders.

We will also construct Kaplan-Meier plots and estimate the median Overall Survival (OS) and construct 95% Brookmeyer-Crowley Confidence intervals. We will be able to estimate the ORR or the OS rates at a particular time point (e.g. 13 weeks) to within 12.3% (95% confidence interval (CI)) and 21.4% in the combination therapy and ipilimumab alone arms, respectively. Waterfall plots will be constructed to represent each patient's best change in tumor burden.

Toxicity will be assessed in each arm separately. Any toxicity with at least 5% chance of occurring has 93.7% and 60.3% chance of being observed at least once in the combination therapy and ipilimumab alone arms, respectively. We will be able to estimate the rate of occurrence of any particular toxicity to within 12.3% (95% CI) and 21.4% in the combination therapy and ipilimumab alone arms, respectively.

11.4 Data and Safety Monitoring

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of the SWOG, 3 SWOG members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistical Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

12.0 DISCIPLINE REVIEW

Discipline review is not applicable.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than seven calendar days prior to planned start of treatment).

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

a. CTEP Investigator 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>.

b. CTEP Associate Registration Procedures

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 will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

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>.

c. CTSU Registration Procedures

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Note: 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 initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

1. Downloading Site Registration Documents:

   Site registration forms may be downloaded from the **S1616** protocol page located on the CTSU members' website. Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
   - Click on the Protocols tab in the upper left of your screen
   - Click on the SWOG link to expand, then select **S1616**. Click on the Site Registration Documents link.

2. Requirements for **S1616** *S*ite Registration:

   - CTSU IRB Certification (for sites not participating via the NCI CIRB)
   - CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

3. Submitting Regulatory Documents:

   Submit completed forms along with a copy of your IRB Approval to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

   ONLINE: www.ctsu.org (members section) →Regulatory Submission Portal

   CTSU Regulatory Office
   1818 Market Street, Suite 1100
   Philadelphia, PA 19103
   Phone: 1-866-651-2878
   Fax: 215-569-0206
   E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

4. Checking Your Site's Registration Status:

   Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)
   - 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 tab
   - Enter your 5-character CTEP Institution Code and click on Go

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is strongly encouraged, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)

- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org, from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

d. Further instructional information is provided on the OPEN tab on the CTSU members' side of the 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.

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3a for details.

14.3 Data Submission Procedures

a. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, you must have an active CTEP-IAM account (check at https://eapps-ctep.nci.nih.gov/iam/index.jsp) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO 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 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 at www.ctsu.org/RAVE/ or by contacting the CTSU help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

b. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG web site (http://swog.org) and logon to the Members Area using your SWOG Roster ID Number and password. After you have logged on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,

2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU) please refer to the CTSU Participation Table.

14.4 Data Submission Overview and Timepoints

a. WITHIN 24 HOURS AFTER BASELINE blood COLLECTION:

Submit Blood within 24 hours of collection at baseline, as outlined in Section15.0.

b. WITHIN 7 CALENDAR DAYS AFTER REGISTRATION:

Submit the following:

S1616 Onstudy Form

S1616 Baseline Abnormalities Form

Baseline Tumor Assessment Form (RECIST 1.1)

Pathology Report documenting histologic confirmation of melanoma*

Submit radiology reports from all scans performed to assess disease at baseline.*

*NOTE: Upload reports via the Source Documentation: Baseline form in Rave®.

c. WITHIN 21 to 35 CALENDAR DAYS AFTER REGISTRATION:

Submit tissue specimens as outlined in Section 15.0.

Note: Blood for PBMCs must be submitted **within 24 hours of collection** at Day 28 (+/-) 7 calendar days.

d. WITHIN 14 CALENDAR DAYS AFTER EACH CYCLE OF TREATMENT

Submit the following:

S1616 Treatment Form

S1616 Adverse Event Form

e. WITHIN 14 CALENDAR DAYS AFTER EACH DISEASE ASSESSMENT UNTIL PROGRESSION/RELAPSE (SEE STUDY CALENDAR FOR SCHEDULE):

Submit the following:

Follow Up Tumor Assessment Form (RECIST 1.1)

Submit radiology reports from all scans performed to assess disease.*

*NOTE: Upload reports via the Source Documentation: Follow-Up form in Rave®.

f. WITHIN 14 CALENDAR DAYS AFTER DISCONTINUATION OF TREATMENT:

Submit the following:

S1616 Off Treatment Notice

S1616 Treatment Form

S1616 Adverse Event Form

g. WITHIN 14 CALENDAR DAYS AFTER PROGRESSION:

Follow Up Tumor Assessment Form (RECIST 1.1)

Submit radiology reports from all scans performed to assess disease.*

*NOTE: Upload reports via the Source Documentation: Follow-Up form in Rave®.

h. AFTER PROGRESSION, SUBMIT EVERY 6 MONTHS FOR THE FIRST 2 YEARS AND THEN ANNUALLY UNTIL 3 YEARS FROM REGISTRATION:

Submit the following:

Advanced Melanoma Follow Up Form

Late Effects Form (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] long term toxicity that has not been previously reported)

i. WITHIN 4 WEEKS AFTER KNOWLEDGE OF DEATH:

Submit the Notice of Death documenting death information.

Also submit:

If the patient was still on protocol treatment, the materials specified in Section 14.4e.

or

Advanced Melanoma Follow-Up Form (if the patient was off protocol treatment)

15.0 SPECIAL INSTRUCTIONS

15.1 Translational Medicine (required for patient):

Timepoint	Specimen	Preferred	Acceptable alternate
Prior to previous anti-PD-1, anti-PD-l1 therapy	Archival tissue (if available) ***	30 slides, 4 mcm each	
On or prior to Day 1 of protocol treatment	Cores from biopsied lesion	One block from each biopsied lesion	30 slides, 4 mcm each, from each block
Day 28 of protocol treatment	Cores from biopsied lesion	One block from each biopsied lesion	30 slides, 4 mcm each, from each block
On or prior to Day 1 of protocol treatment	Blood for PBMCs	50 mL in purple top EDTA tubes	
Day 28 of protocol treatment	Blood for PBMCs	50 mL in purple top EDTA tubes	

a. Specimens must be submitted at the timepoints listed below. Collection instructions are outlined in Section 15.1c and submission instructions are outlined in Section 15.1e.

b. Specimens must be submitted at the following times (see Section 9.0)

1. If available, 30 slides 4 um each, unstained of archival tissue (biopsy from prior to anti-PD-1 or anti-PD-L1 therapy).

2. FFPE tissue. At least 2 passes/cores from 14-gauge coring needle, or 3 passes/passes from 18-gauge coring needle from each biopsied lesion. While cores may be formalin fixed in the same container, each core should be embedded in a separate paraffin block. Tissue from each block should be submitted. If no block can be shipped, submit 30 slides (4 mcm) each from each block. Tissue must be collected within 28 calendar days prior to Day 1 of protocol treatment* and again 28 calendar days (+/- 7 calendar days) after starting protocol treatment**.

3. 50 mL of peripheral blood collected in purple-top EDTA tubes at baseline (within 28 calendar days prior to starting protocol treatment on Day 1) and on the same day as the Day 28 (+/- 7 calendar days) tissue collection**.

* Biopsy on or prior to Day 1 should be performed within 28 days prior to Day 1. If it is not feasible to prospectively obtain this biopsy, tissue collected at any time since demonstrated progression on PD-1 or PD-L1 therapy may be substituted provided that 30 unstained slides are available.

** The tissue samples may be batch shipped after collection of tissue from Day 28(+/- 7 calendar days) biopsy. Tissue blocks should be stored at 4ºC before shipping.

*** **Blood must be sent via overnight courier (e.g. FedEx) within 24 hours of collection**. **Specimens may be shipped Monday through Thursday using only overnight delivery to arrive Monday through Friday. No blood should be collected or shipped on Friday or right before a holiday. Additionally, since blood must be logged and shipped the day of**

collection, blood should not be collected prior to subject registration. Please see additional collection/shipping instructions in Sections 15.1c and 15.1e (below).

**** If archival tissue is not available for submission, proceed as usual per directed time points for biopsy collection. Archival tissue is required if available.

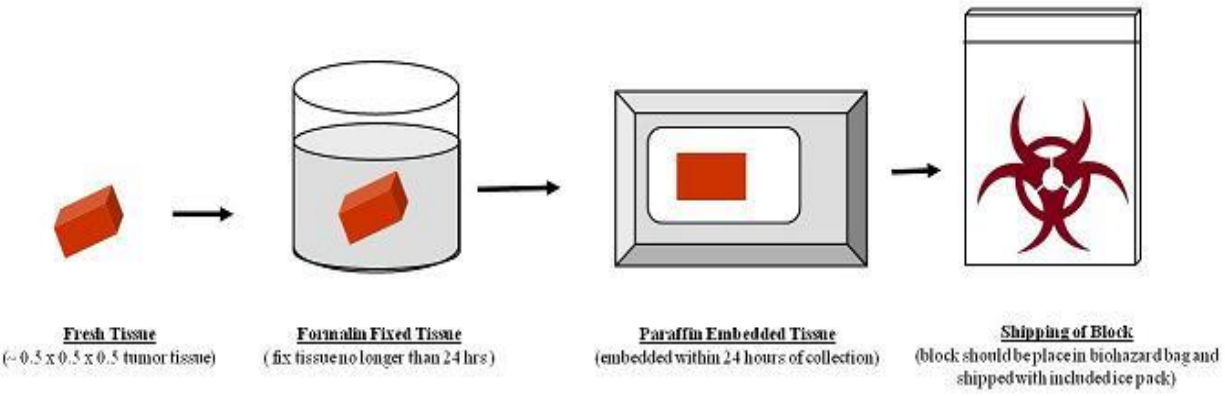
With patient consent, remaining specimens will be banked for future use.

c. Specimen Collection Instructions

1. Standard collection of Paraffin Embedded Tissue Block.
   - Place the fresh tissue in formalin. Do Not Exceed 24 hours fixation time.
   - Fixed tissue must be paraffin embedded within 24 hours.
   - Send H & E (Hematoxylin and Eosin) stained section if it is routine practice for the site. Otherwise, sending the block without the H&E slide is adequate.

2. Standard Instructions for Shipping Paraffin Embedded Tissues:
   - Include in shipment:
     - Tissue as outlined above
     - Archived tissue only: A pathology report (indicating the morphological diagnosis).
     - A copy of the packing/shipping list produced by the SWOG Online Specimen Tracking System.
   - Ship paraffin embedded tissue according to the shipping guidelines for ambient specimens in the General Specimen Submission Instructions below.

NOTE: Paraffin tissue blocks will NOT be returned to the submitting institution unless it is required for patient care. If the block is needed for patient care, a written request must be submitted to the bank with a rationale for the return.



3. Standard Instructions for Collecting and Shipping Fresh Whole Blood Specimens.
   - Use 10 ml vacutainer tubes with EDTA to collect whole blood.
     - If your site does not have the recommended size of vacutainer tubes required by the treatment protocol, other sized tubes may be used to collect the required/requested amount of blood.
     - Avoid using < 3mL collection tubes.

- Pre-label vacutainer tube(s) according to specimen labeling requirements indicated in the General Specimen Submission Instructions.

- Use aseptic techniques and draw blood from the patient into the vacutainer tube(s). The amount of blood required will vary per protocol.
- Immediately after the blood is drawn, thoroughly mix the blood with the anticoagulant by gently inverting the vacutainer tube(s) multiple times.
- Store whole blood prior to shipping at room temperature. Do not freeze the whole blood. Storage time longer than 24 hours should be noted on the specimen shipping form.
- Whole blood should be shipped the same day (day of collection) preferably using Federal Express, Priority Overnight service. Use of other courier services may delay package receipt.
    - **Specimens may be shipped Monday through Thursday using only overnight delivery to arrive Monday through Friday. No blood should be collected or shipped on Friday or right before a holiday. For specimens collected before a holiday, please process and ship the specimens according the instructions outlined below (#2).**
    - During the months of April-September, ship fresh specimens on a cold pack. During the months of October-March, insulate fresh specimens to keep from freezing due to weather (ex. wrap specimen in bubble wrap).

4. Standard Instructions for Collecting and Shipping Flash Frozen Tissue Samples:

    - Selected sites will, at each prospective biopsy time point, obtain additional cores (at least one core, more if deemed possible) to be immediately placed in RNAlater (Sigma, Cat # R0901), stored at 4ºC overnight for full penetration, and moved to -80ºC the next day until shipment. Samples should be shipped on dry ice.

      NOTE: Select sites have already been selected and are aware of their duties.

For packaging instructions, refer to the shipping guidelines for ambient specimens in the General Specimen Submission Instructions outlined above.

d. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

e. SHIPPING SAMPLES

1. SWOG Specimen Tracking System (STS)

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) Non- SWOG users may log into SpecTrack using their CTSU UserID and password on the SpecTrack login page located at

https://spectrack.crab.org (select the option “SWOG – SWOG – CTSU”). SpecTrack start-up instructions (both written and demo) are available after signing in to SpecTrack.

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag. The Specimen Submission Form is NOT required when the online system is used.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (https://spectrack.crab.org/Instructions); or contact the Data Operations Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

In the online specimen tracking system, the appropriate SWOG laboratory for submission of tissue and blood samples is identified as follows:

Lab #224: The Ribas Laboratory
Attention: Agustin Vega-Crespo
Medical Receiving – Study **S1616**
CHS 54-200
650 Charles E. Young Dr. South.
UCLA Medical Center
Los Angeles, CA 90095
Phone: 310-825-2676
Fax: 310-825-2493

Contact: Agustin Vega-Crespo
E-mail: avegacrespo@mednet.ucla.edu

2. Federal guidelines for the shipment of blood products:

a. The tube must be wrapped in an absorbent material.

b. The tube must then be placed in an AIRTIGHT container (like a resealable bag).

c. Pack the resealable bag and tube in a Styrofoam shipping container.

d. Pack the Styrofoam shipping container in a cardboard box.

e. Mark the box "Biohazard".

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Publication and Industry Contact

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 Pharmaceutical Compan(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 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 investigational 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 which 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 exclusively 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 the Collaborator(s) for Phase III 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 calendar 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 calendar days in order to ensure that Collaborator's confidential and proprietary data, in addition to the 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) calendar 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: E-mail: ncicteppubbs@mail.nih.gov.

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

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically by the SWOG Data Operation Center to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

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. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

Expedited AE reporting for this study must only use CTEP-AERS (CTEP-Adverse Event Reporting System), accessed via the CTEP Web site, https://eapps-ctep.nci.nih.gov/ctepaers. 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.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event specified in Table 16.1.

Any supporting documentation should be submitted to CTEP per NCI guidelines for AE reporting located at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. Expedited reporting for investigational agents

Expedited reporting is required if the patient has received at least one dose of the investigational agents as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agents used in both arms of this study are ipilimumab and nivolumab. [Please note – the post dosage expedited reporting

requirement window has been extended to **90** calendar days rather than the normal 30 day requirement.] If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND within 90 Calendar Days of the Last Administration of the Investigational Agent/Intervention[1] Ipilimumab and Nivolumab (Arm 1 and Arm 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 CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

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 or [Section 16.1f.]

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS 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 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

May 5, 2011

f. Additional Instructions or Exceptions to CTEP-AERS Expedited **Reporting Requirements for Phase 1 and Early Phase 2 Studies Utilizing an Agent under a CTEP IND:**

1. **Group-specific instructions.**

Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements In addition, you may be asked to submit supporting clinical data to the SWOG Operations Offices in order to complete the evaluation of the event. If requested, the supporting data should be sent within **5 calendar days** by fax to 210-614-0006. Supporting clinical data submitted should include:

- Printed copy of the first page of the CTEP-AERS Report.
- Copies of clinical source documentation of the event.
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center copies of Off Treatment Notice and/or Notice of Death.

2. The adverse events listed below also require expedited monitoring for this trial:
Any > Grade 3 pneumonitis, colitis, dermatitis, hepatitis, infusion-related reaction, neuro or ocular toxicity, or endocrinopathy.

g. Reporting Secondary Malignancy, including AML/ALL/MDS

1. 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 to be reported 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.

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

For more information see:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

2. Any supporting documentation should be submitted to CTEP per NCI guidelines for AE reporting located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

   A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 calendar days by fax to 210-614-0006 or mail to the address below:

   - a copy of the pathology report confirming the AML/ALL /MDS diagnosis
   - (if available) a copy of the cytogenetics report

   SWOG
   ATTN: SAE Program
   4201 Medical Drive, Suite 250
   San Antonio, Texas 78229

   NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

h. Reporting Pregnancy, Fetal Death, and Death Neonatal

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Fetal Death** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions** SOC.

3. **Death Neonatal** Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 calendar days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

   A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

NOTE: When submitting CTEP-AERS reports for “Pregnancy, “Pregnancy loss”, or “Neonatal loss”, the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the “Description of Event” section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

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18.0 APPENDIX

18.1 Translational Medicine Details

18.2 Translational Medicine Procedures

18.3 Management of Immune-Related Adverse Events, Diarrhea, Hepatotoxicity, Endocrinopathy, and Neuropathy for Ipilimumab

18.4 Management of Algorithms for Endocrinopathy, Gastrointestinal, Hepatic Neurological, Pulmonary, Renal, and Skin Adverse Events for Nivolumab

18.5 Specimen Banking Instructions for the Ribas Laboratory

18.1 Translational Medicine Details

a. Background

Combined therapeutic checkpoint blockade of cytotoxic T-lymphocyte antigen 4 (CTLA-4, ipilimumab) and programmed death 1 protein (PD-1, nivolumab) has demonstrated higher objective response rates when compared to either ipilimumab or nivolumab as single agents in advanced melanoma patients but is associated with increased toxicities (Grade 3/4 treatment-related adverse events of55%). *(1)*

A key challenge in oncology today is how to select for patients that are likely to respond to single agent anti-PD1.Furthermore, in patients unlikely to respond to single agent anti-PD1, it remains unclear which patients are likely to benefit from combined ipilimumab/nivolumab. Immunodiagnostics that predict and monitor response will be key to addressing this challenge and are urgently needed considering the number of combinations entering oncology in the next 5 years. *(2)*

To date, no immune assay has been adopted in the clinic to assist with clinical decision-making. We propose to systematically investigate the predictive utility of four immunodiagnostic approaches that measure distinct parameters within tumors: i) quantitative multiplexed immunohistochemistry (qmIHC) which provides spatially resolved, multiparametric information and measures the density, location and phenotype of immune cell types (Tumeh et al. nature 2014); ii) immunosequencing of the T-cell receptor (TCR) repertoire which is based on bulk reads and measures the clonality and repertoire of TCRs (Tumeh et al. nature 2014); and iii) whole exome sequencing which generates signal based on bulk measurements and identifies all non-synonymous mutations(Shin et al. Cancer Discovery 2017); and iv) RNASeq which, through analysis of mRNA expression levels, can identify changes in the functional characteristics of different cells in the tumor microenvironment (Hugo et al. Cell 2016). These approaches have shown preliminary predictive potential by independent groups across different cancer types. *(3,4,5)* No study to date, however, has investigated the relationship between these factors or their predictive value when interrogating the same tumor. By defining the relationships between these four factors in terms of response, we anticipate that our approach will lead to clinically actionable information as well as key insights into why certain tumors are immunogenic and others are not.

Figure 1a and b show CD8 T-cell density and TCR clonality in terms of response to single agent anti-PD1 in patients with advanced melanoma. Figure 1c and d show images of multiplexed immunophenotyping that enable the identification of distinct immune cell types in a spatially resolved manner. *(6)* Table 1 provides preliminary data comparing CD8+ T-cell density, clonality and mutational load derived from the same melanoma tumors. Note that Patient 1 and 2 had relatively high mutation load but low CD8+ T-cells at the invasive margin and progressed on single agent anti- PD1 while Patient 5 had low mutational burden but high CD8+ T-cells and clonality and responded to therapy.

We hypothesize that the integration of all four approaches into a predictive model will show incremental predictive value over any single parameter. Additionally, we will be able to determine the relationships between immune cell types density and location, TCR clonality, mutation load and/or type and mRNA expression levels

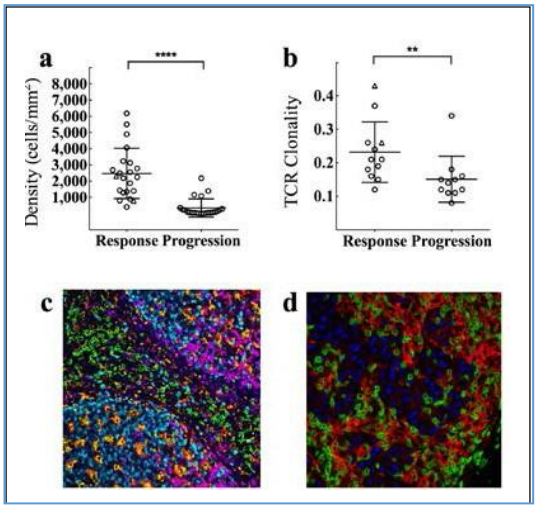

Figure 1. **Baseline CD8 density and clonality in melanoma** .
a, CD8 density (cells/mm2) in terms of response to single agent anti-PD1**.**
b, Clonality in terms of response to single agent anti-PD1.
c, d, Quantitative multiparametric IHC using spectral imaging. Immunofluorescence (6-plex) images using spectral deconvolution enables identification of distinct phenotypes and spatial relationships in melanoma (c, CD8xPD1xPDL1xFoxp3xTopoII and d, CD8xPDL1xSOX10)

Table 1 provides preliminary data comparing CD8+ T-cell density, clonality and mutational load derived from the same melanoma tumors.

	CD8+ density	Clonality	Mutation Load	Clinical Response
Patient 1	145 (low)	0.11 (low)	2136 (high)	Progression
Patient 2	74 (low)	0.15 (mod)	969 (high)	Progression
Patient 3	1343 (high)	0.15 (mod)	487 (mod)	Response
Patient 4	2188 (high)	0.18 (high)	651 (mod)	Response
Patient 5	2549 (high)	0.37 (high)	308 (low)	Response

Table 1. **Comparison of CD8 density, clonality and mutational load in melanoma tumors in terms of response to single agent anti-PD1**. Each parameter is assigned a "high" and "low" descriptive where "low" would predict progression and "high" would predict response. The clinical response is provided.

b. Experimental Approach and Analysis

Data storage and computational infrastructure: To optimally perform computational analysis on the large amount of genomic and imaging data to be generated from this study, it is expected that appropriate cloud computing infrastructure with the necessary analysis pipeline is required for the storage and computation of these data. One such computational infrastructure and resource available for this study is through the collaboration with the Parker Institute for Cancer Immunotherapy.

Objective 1: To compare the predictive value of four baseline tumor factors: T-cell density, T-cell receptor (TCR) clonality mutational load, mRNA and other phenotypical expression levels, and circulating tumor DNA. The following provides information about the methods for each approach. Samples will be obtained within 28 calendar days of starting combined ipilimumab/nivolumab for analysis (or, if not feasible, obtained at any point since documented progression on PD-1 or PD-L1

therapy alone). Critical to understanding how these antibodies promote tumor rejection is the identification of immune cell types that are altered during therapy. Samples obtained during treatment will also be analyzed in order to understand how distinct immune cell types evolve in terms of density, effector activity, proliferative status and cell:cell proximity during intervention according to response. Additionally, we will investigate how the T-cell repertoire and mutational landscape evolve in responsive vs. non-responsive tumors. Finally, we will obtain a subset of samples that are amenable to analysis of mRNA by RNASeq.

Quantitative multiplexed IHC: Measuring the density, phenotype and location of different cell types: Samples will be obtained from patients at baseline and during ipi/nivo on Day 28 (+/- 7 days) of therapy and fixed in 10% neutral buffered formalin and paraffin embedded according to standard institution protocols. Twenty slides with tissue section cuts of 3-4 um thick will be provided for analysis from each FFPE block. At selected study sites, the biopsy will be processed as fresh frozen tissue for RNASeq and other analyses. Slides will be stained with a set of multiple biomarkers to comprehensively define the innate and adaptive immune system in tumors and the functional characteristics of different cells in the tumor microenvironment. Note that each antibody used is an in vitro diagnostic antibody for IHC, meets the highest level of sensitivity and specificity requirements, and have been optimized for single staining and multiplexed staining in our lab. Slides will be analyzed using quantitative imaging analysis optimized by the translational as well as previously described. *(7, 8)*

Lymphocyte receptor sequencing: Defining the T-cell receptor (TCR) repertoire in tumors: Genomic DNA will be isolated from FFPE blocks (or from fresh frozen samples if available) derived from tumor biopsies performed at baseline and at Day 28 (+/- 7 days) of therapy. The V beta and alpha chains of TCRs will be captured using the ImmunoSeq assay as previously described. (9) The analysis will define the repertoire, diversity and clonality of tumor samples.

Whole exome sequencing: Defining the mutational landscape: Genomic DNA will be isolated from FFPE tissue blocks and matched peripheral blood mononuclear cells (PBMCs). This will allow us to differentiate germline variants (non-cancer variants) from non-synonymous mutations (cancer specific). Following whole exome sequencing, the Genome Analysis Toolkit (GTAK) and workflow to process the raw dataset for downstream analysis. To ensure accurate identification of non-synonymous mutations, each variant will require discovery identification with at least two variant discovery software tools (MuTect and Vascan2). The analysis will determine the mutation load and provide for further investigation into the spatial diversity of mutations and HLA binding predictions of specific mutations in terms of response.

mRNA expression analysis: Identifying predictive genes and signatures: A subset of clinical sites will provide samples from patients at baseline and during ipi/nivo during Week 5 of which a portion of tissue will stabilized and preserved using RNAlater reagent and then frozen, while a portion will be flash frozen on site using liquid nitrogen. Tissue obtained from both mechanisms will be transferred to the laboratory at UCLA where further analysis will be performed. Using single cell RNASeq and drop-Seq approaches we will be able to analyze protein expression levels by tracking changes in different cells that make up the tumor microenvironment. Following standard preprocessing mRNA based signatures will be obtained.

Circulating tumor DNA analysis: Detecting tumor-specific mutations in the circulating tumor DNA (ctDNA) as a way to monitor treatment responses: Whole blood will be processed to separate peripheral blood mononuclear cells (PBMCs) and plasma, which can be used for ctDNA profiling. This study proposes to perform ctDNA from patient-matched baseline and on-treatment plasma samples to determine the amount or fraction of ctDNA corresponding to the genetic profile of the patient tumor biopsies.

Objective 2: To determine the incremental prognostic value of T-cell density, TCR clonality,mutational load, and mRNA expression levels in response

To capture the complexity of the immune system's response to tumors, our group proposes to integrate four parameters (T-cell density, clonality, mutational load, mRNA expression signature) into a single predictive model. By doing so, our aim is to define the relationship between the immune system and tumor according to treatment outcome that would not be possible with any single approach. We hypothesize that the integration of all four parameters into a predictive model will show incremental predictive value over any single parameter.

Consistent with previous publications, preliminary data in melanoma shows that there are patients who show high CD8+ T-cells in tumors despite having a low mutational load. (10,11,12) Conversely, there are patients that lack a CD8+ T-cell response to their tumor but have high mutational load. We anticipate that our approach will lead to defined signatures (TIL, Clonality, Mutation Score) that are driven by clinical relevance. Investigating the density and repertoire of T-cells in terms of mutational burden will allow us to gain insight into the type of mutations that are associated with clinical response.

Objective 3: To identify T-cell poor subtypes associated with response

The T-cell status of tumors represents a key determinant of response to anti-PD1. Tumors infiltrated with T-cells show sensitivity to single agent anti-PD1 but represent a minority of patients. The majority of tumors lack T-cells and are inherently non-responsive to therapy. T-cell poor tumors represent a heterogeneous group and remain poorly defined. A challenge in the field is to develop immunodiagnostics that have the ability to subtype T-cell poor tumors into immune 'activity' signatures that are clinically actionable.

The response rates observed with combination checkpoint inhibition indicate that there is a responsive subgroup within the T-cell poor group that would otherwise be non-responsive to single agent PD1 inhibitor. We propose to define this subgroup by using multi-parameter flow cytometry and multiplexed multi-parameter immunohistochemistry to analyze the peripheral blood and tumor, respectively, within the same patient. In this way we can compare circulating immune cells and tumor infiltrating immune cells within a given patient and according to treatment outcome groups. Immune cell types within the innate the adaptive system will be defined and monitored within the blood and in tumors. Our rationale for this approach is based on the necessary mobilization of TILs from the peripheral blood in order to infiltrate a tumor responding to combination to combination therapy. Our goal is to define the innate and adaptive immune landscape in baseline tumors that are CD8+ T-cell poor but undergo unique alterations during response that are absent in non- responsive tumors.

c. Statistical Plan:

1. Objective 1: Assess the independent prognostic value of baseline T-cell density, T-cell receptor (TCR) clonality, ctDNA fraction, and mutational load in terms of response in each arm.

   We will consider each treatment arm separately. Then for each arm, we will assess whether each of the IHC markers, T-Cell clonality, ctDNA fraction, mutational load and mRNA signatures can be used to identify patients who respond. Under our first objective, we will assess each variable individually. In particular, we will use logistic regression to regress dichotomous response status on each variable, one-at-a-time. Since our primary objective is to develop a classification model for identifying responders, we will estimate standard model classification characteristics including misclassification error, sensitivity, specificity, and AUC for each variable where the threshold for the logistic probabilities for defining predicted responder vs. non-responder will be tuned via leave-one-out cross validation (LOOCV). We will estimate both the in-sample classification characteristics as well as the cross-validated (where the full procedure is cross-validated, with potential nested LOOCV for tuning parameter selection) characteristics with corresponding 95% confidence intervals. The in-sample estimates represent optimistic values while the LOOCV estimates represent pessimistic values such that the smallest lower 95% CI and highest upper 95% CI bound for each characteristic on each variable will provide conservative coverage of the true characteristic value. For Arm 1 (ipilumimab alone), with a sample size of 21 patients, assuming we have 90% compliance on tissue submission, then we will be able to estimate the in-sample or cross validated misclassification error to within 22.5% (95% CI). For Arm 2 (combination therapy), with a sample size of 63 patients and again assuming 90% compliance on tissue submission, then we will be able to estimate the in-sample or cross validated misclassification error to within 13.0% (95% CI).

   Although our primary analysis will focus on developing classification models, we will also assess the association between response and each individual marker, clonality, mutational load, mRNA expression signature, and ctDNA fraction. The analysis will be again conducted separately by treatment arm. For each of the IHC markers, clonality, and ctDNA fraction, we will test for difference in mean levels between responders and non-responders using two-sample t-tests. We assume we obtain data on 90% of patients and that the response rates are 15% and 30% in arms 1 and 2, respectively. Then at the nominal alpha=0.05 level, we anticipate 80% power to detect a difference in marker level, clonality, or ctDNA fraction between responders and non-responders of 1.9 and 0.83 standard deviations in Arms 1 and 2, respectively. Further, we will also assess whether individual mRNA transcripts and genes are associated with response. Specifically, we will compare the expression between patients who respond and who do not respond using two-sample t-tests again. We will accommodate multiple testing by controlling the false discovery rate. With the same response rate and sample size assumptions as before, and further assuming that 80% of genes are not associated with response, then at the FDR = 5% level, we anticipate 80% power to detect a difference in expression level of 2.43 and 1.33 standard deviations in Arms 1 and 2, respectively. Note that t-tests are used since they can be more powerful than logistic regression, but for all association analyses in this objective and subsequent translational medicine objectives, we will consider the use of alternative approaches, e.g. data transformation, Wilcoxon tests or logistic regression, if there are outliers or influential points.

Since mutational load is far from normally distributed, we will use a Wilcoxon test to test for difference in mutational burden. To assess power, we conducted simulations under the assumption that we will collect exome sequencing data on 90% of patients and that we will control the type I error rate at the two-sided alpha=0.05 level. To simulate mutational load, we used an internal, private data exome sequencing data set comprised of 13 non-responder patients to first line anti-PD1 therapy and sampled from the interpolated empirical cumulative distribution function (ECDF) via the inverse probability integral transform. For power analyses, data from this distribution were taken to be null. To simulate under the alternative, we shifted all of the mutational load values by a scalar δ and re-sampled from the interpolated ECDF of the shifted data. For Arm 1, assuming response rate of 15%, with 18 total patients, we anticipate 80% power to detect a shift in mutational load distribution of δ=13.9. For Arm 2, assuming response rate of 30%, with 54 total patients, we anticipate 80% power to detect a shift in mutational load distribution of δ=2.7. We again emphasize that alternative approaches will be considered if Wilcoxon tests do not perform well, e.g. due to heteroscedasticity etc.

2. **Objective 2**: Prognostic Value of T-cell Density, TCR Clonality, and Mutational Load

We will assess the joint capacity of the IHC markers, T-Cell clonality, ctDNA fraction, and mutational load, and gene expression signatures to identify patients who respond to each therapy. In particular, analyzing each arm separately, we will use the logistic elastic net to model the joint effect on response of the multiple markers and variables simultaneously. We will select the tuning parameters for elastic net via a two-dimensional grid search and LOOCV. We will again estimate the in-sample and cross-validated (of the entire procedure with nested LOOCV for tuning) model classification characteristics and corresponding 95% confidence intervals, again noting that these represent optimistic and pessimistic bounds for each characteristic. Since the elastic net essentially enforces linearity in the effects of the variables, we will also consider the use of alternative strategies, including large margin (e.g. support vector machines) and tree based classifiers in order to accommodate potential nonlinear and potentially interactive effects. Independent of the specific classification method used, for Arm 1, with a sample size of 21 patients and again assuming we have 90% compliance on tissue submission, then we will be able to estimate the in-sample or cross validated misclassification error to within 22.,5% (95% CI). For Arm 2, with a sample size of 63 patients, 90% compliance on tissue submission, then we will be able to estimate the in-sample or cross validated misclassification error to within 13% (95% CI)

3. **Objective 3**: Identification of T-cell Poor Subtype(s) Associated with Response

We will first define the range of CD-8+ T-cell density in the tumor sample characterizing a patient as T-cell poor using a supervised approach: this range is currently undefined for patients who have already failed on an anti-PD1 or anti-PD-L1 agent. Specifically, we will consider a range of thresholds for CD8 expression above which the patients are classified as T-cell rich and below which patients are classified as T-cell poor. For each candidate threshold, we will estimate the proportion of responders above and below the threshold. The final threshold defining T-cell poor status will be selected as the threshold which leads to the highest difference in

proportion of responders above vs. below the threshold. We will also consider un-supervised approaches based on identifying gaps in the distribution of CD8 expression and will tune this according to our supervised results.

After defining the range characterizing patients as T-cell poor, we will restrict further analyses to the patients determined to be T-cell poor. We will then repeat the approach used in Objective 2 to develop a signature identifying T-cell poor patients who respond to therapy. We will again estimate the in-sample and cross validated classifier operating characteristics and construct 95% confidence intervals. Assuming that 90% of patient samples are available for analysis, for Arm 1, we will be able to estimate the in-sample or cross-validated misclassification error to within 25.2%, 23.7%, or 23.1% (95% CI) if 80%, 90%, or 95%, respectively, of patients are determined to be T-cell poor. For Arm 2 we will be able to estimate the in-sample or cross-validated misclassification error to within 14.6%, 13.7%, or 13.4% (95% CI) if 80%, 90%, or 95%, respectively, of patients are determined to be T-cell poor.

We will repeat this analysis using the data collected from blood samples.

References for 18.1

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18.2 Translational Medicine Procedures

Whole exome sequencing to analyze mutational load: To test whether there is a correlation of tumor mutational load and response to PD-1 antibody therapy, DNA will be isolated from thick slides of FFPE tissues and *PBMC via commercial kit (i.e. Qiagen AllPrep DNA/RNA FFPE kit, cat 80234). Whole exome sequencing (WES), including probe-based exon capture, library preparation, and high throughput 100bp paired-end sequencing on the Illumina HiSeq2500 platform will be performed at the UCLA Immunogenetics core laboratory (CLIA approved lab). DNA from the same patient's PBMC (preferably) or other non-cancerous tissue will be isolated and sequenced for baseline comparison and differentiation of germline SNPs from true somatic mutations. Read mapping and data preprocessing will be performed according to the Broad Institute Best Practices Guidelines for the Genome Analysis Toolkit (version 3), and mutation detection will require a consensus call among several published programs (Varscan2, MuTect, GATK HaplotypeCaller). Mutational load will be quantified as the number of nonsynonymous somatic mutations per MB.

Quantitative analysis of T cell infiltration: To analyze whether baseline CD8+ cell infiltration is correlated with response to anti-PD1 therapy, and whether PD-1 blockade can increase CD8+ cell infiltration in DM patients, slides taken from standard formalin-fixed paraffin-embedded (FFPE) tissue blocks obtained from baseline, 4 week (on treatment), and 9 week biopsies will be stained by immunohistochemistry (IHC) for S100 and CD8 to determine the presence of CD8+ T cells inside tumors and in the invasive margin. Slides will be analyzed using quantitative digital pathology following the methods described (10). This analysis will provide a predictive score for response or lack of response to pembrolizumab based on the baseline CD8+ T cell infiltration.

Method: Slides will be stained with S100 and CD8 (one slide per stain) at the UCLA Anatomic Pathology IHC Laboratory (CLIA approved lab). Immunostaining will be performed on Leica Bond III autostainers using Leica Bond ancillary reagents and REFINE polymer DAB detection system (Leica DS9800). Antibodies used will include rabbit polyclonal S100 (DAKO, 1/1,000 dilution, low pH retrieval), mouse anti-CD8 clone C8/144B (DAKO, 1/100, low PH retrieval), and all staining will be performed on Dako autostainers, and visualized with DAB. Slides will be baked for 60 minutes at 60°C. Procedure involves dewaxing, heat-retrieved in Bond ER1 (pH6) buffer for 20 minutes, and sequential incubations with primary antibody, post-primary reagent, and polymer for 15 minutes, 8 minutes, and 8 minutes, respectively, and subsequent DAB chromogen application and Hematoxylin counterstaining. All stained slides will be evaluated in a blinded fashion by one dermatopathologist and one investigator trained to identify the features of melanoma, and the presence of CD8 within the tumor parenchyma (tumor) and the connective tissue surrounding the tumor (invasive margin) will be examined.

All slides will be scanned at an absolute magnification of X200 (resolution of 0.5 mm/pixel). An algorithm was designed based on pattern recognition that quantified immune cells within S100-positive areas (tumor) and S100-negative areas (invasive margin). Image analysis based on RGB (red, green, blue) spectra will be used to detect all cells by counterstaining with haemotoxylin (blue), and DAB or fast red. The algorithm calculated the density (cells mm^{-2}) and percentage cellularity (% positive cells/all nucleated cells) using Indica Labs Halo platform.

Analysis of TCR clonality in tumors: To answer the question whether the T cell response is targeting specific tumor antigen (mono-clonal) or a non-specific process (poly-clonal) in the tumors, we will analyze TCR clonality by deep sequencing the TCR Vβ CDR region using the ImmunoSeq assay from Adaptive Biotech as described (10). From thick slides of

FFPE tissues taken at baseline, 4 weeks, and 9 weeks, we will isolate DNA and submit it for TCR Vβ sequencing. This analysis will provide information about the clonality or diversity of T cells infiltrating tumors in DM samples. DNA analysis will be performed by the UCLA Immunogenetics core laboratory (CLIA approved lab).

DNA will be isolated from FFPE thick cuts followed by extraction using a DNeasy kit (Qiagen). Melanin will be removed from visibly pigmented melanoma samples using a PCR Inhibitor Removal kit (ZymoResearch). TCR Vβ CDR3 regions will be amplified and sequenced using the survey ImmunoSeq assay in a multiplexed PCR method using 45 forward primers specific to TCR Vβ gene segments and 13 reverse primers specific to TCR Vβ gene segments (Adaptive Biotechnologies). Reads of length 87bp will be obtained using the Illumina HiSeq System. For each sample, Shannon entropy will be calculated on the clonal abundance of all productive TCR sequences in the data set. Shannon entropy will be normalized to the range by dividing Shannon entropy by the logarithm of the number of unique productive TCR sequences in the data set. This normalized entropy value will be then inverted (12 normalized entropy) to produce our clonality metric.

Analysis of adaptive immune resistance mechanism in tumors: Slides taken from standard FFPE tissue blocks obtained from baseline, and the on treatment biopsy will be stained by immunohistochemistry (IHC) for PD-L1 (SP142, Spring Bioscience) to evaluate whether PD-L1 can be induced by PD-1 blockade, and which it is correlated with response. Slides will be analyzed using quantitative digital pathology following the methods described for Quantitative analysis of T cell infiltration. Analysis will be performed at the UCLA Anatomic Pathology IHC Laboratory (CLIA approved lab).

Method:

1. Bake slides for 1 hour at 65°C.

2. Deparaffinize slides in xylene (3 changes) and rehydrate through graded ethanol to deonized-H2O.

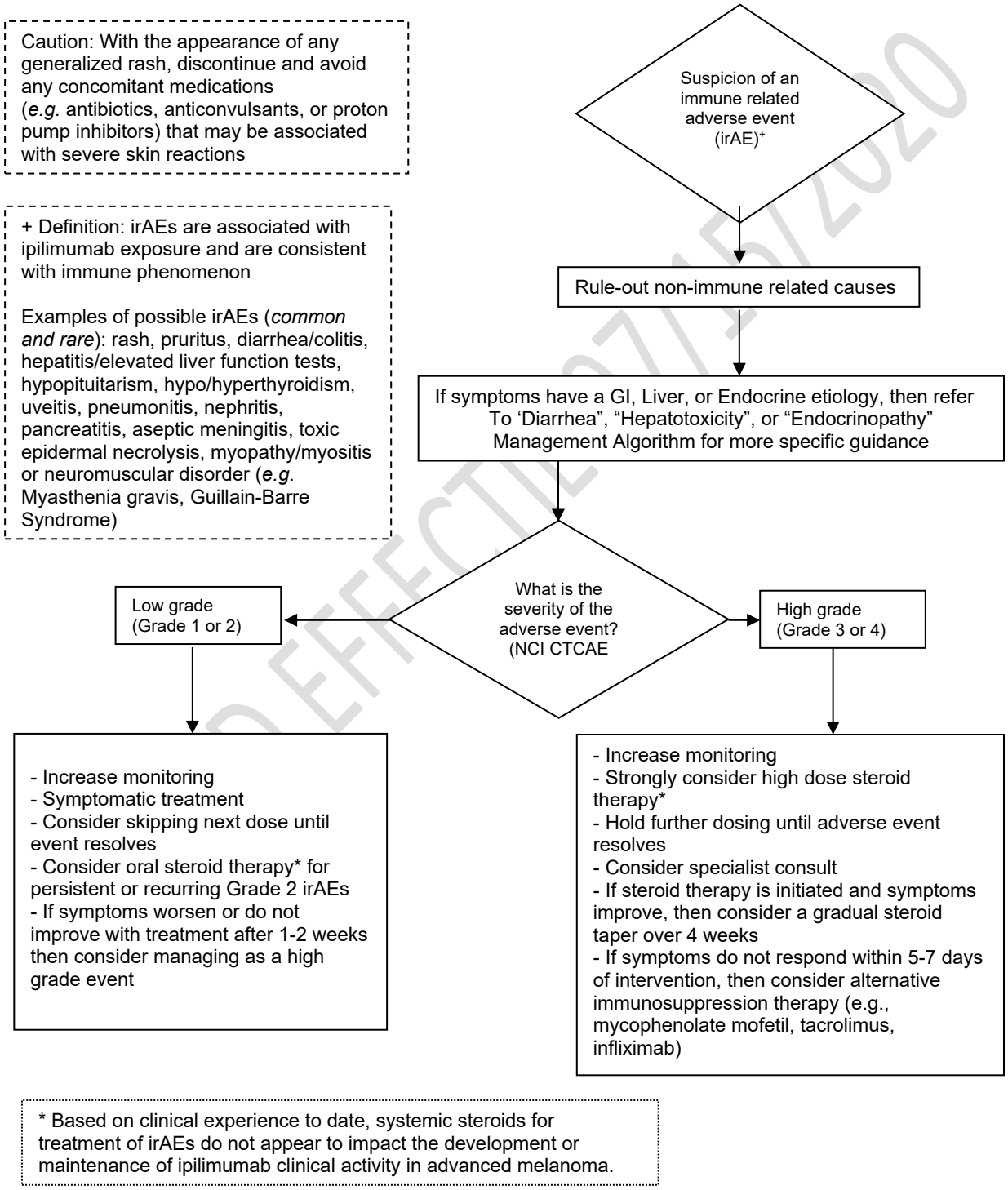
3. Perform antigen retrieval in pressure cooker for 5 minutes with Tris-EDTA pH9 buffer (Leica ER2). Cool for 15 minutes at room temperature and rinse in DI-water.

   Perform IHC on Leica Bond III autostainer with Refine Polymer Detection (Leica DS9800); autostainer was programmed for primary antibody at 1/200 dilution in daVinci Green Diluent (Biocare Medical) for 60 minutes, Polymer for 15 minutes, Peroxidase block for 5 minutes, DAB for 10 minutes, and offline manual steps 0.5% cupric sulfate for 10 minutes and Hematoxylin for 5 minutes. Usual Bond washes between steps. Use Bond Refine Polymer Detection kit (DS9800), which includes reagents for all steps after primary antibody, except for cupric sulfate and hematoxylin counterstain.

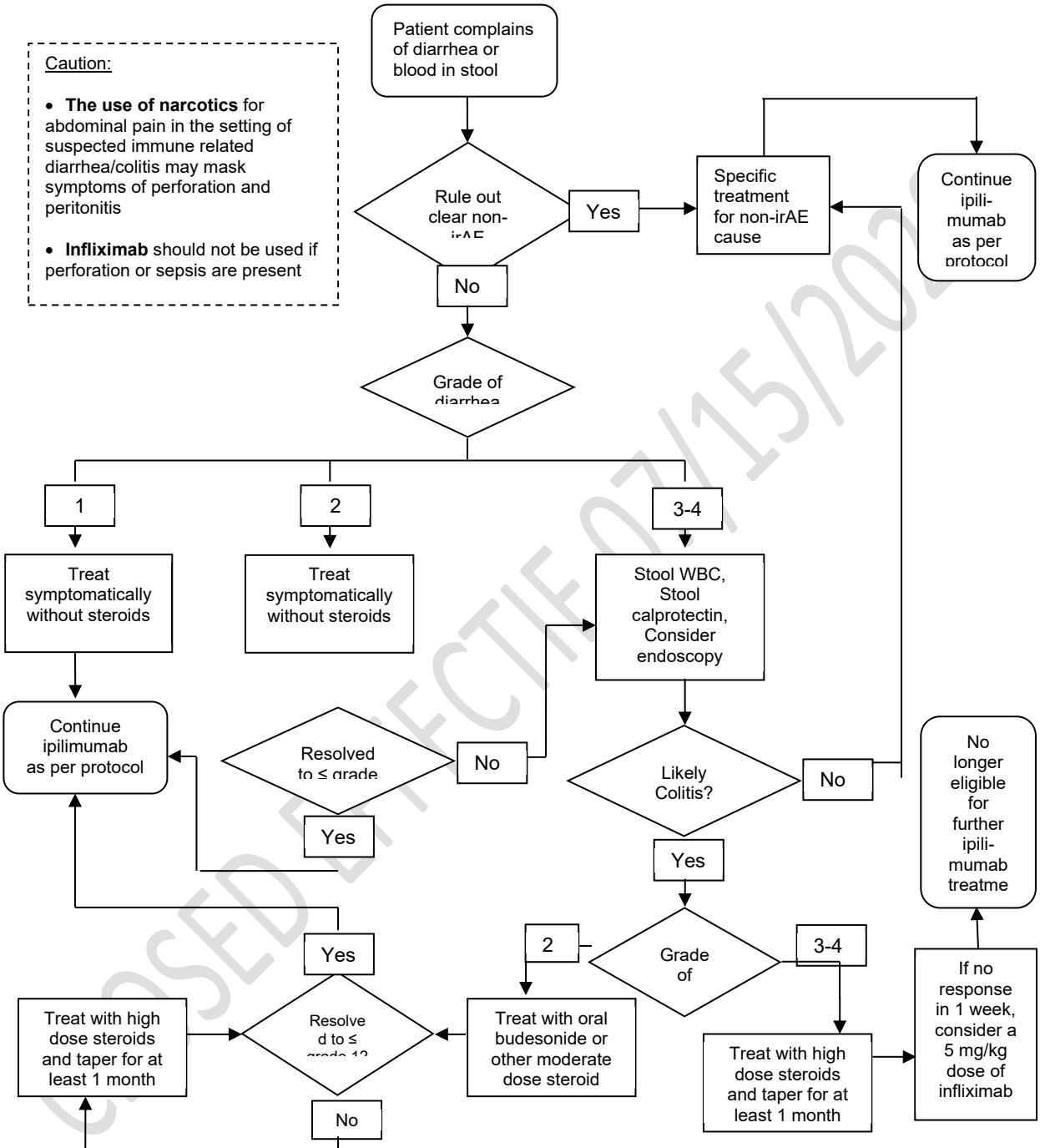
18.3 Management of Immune-Related Adverse Events, Diarrhea, Hepatotoxicity, Endocrinopathy, and Neuropathy for Ipilimumab *

*Investigator's Brochure (2011)

General Recommendations for Management of Suspected Inflammatory Events



Diarrhea Management Algorithm



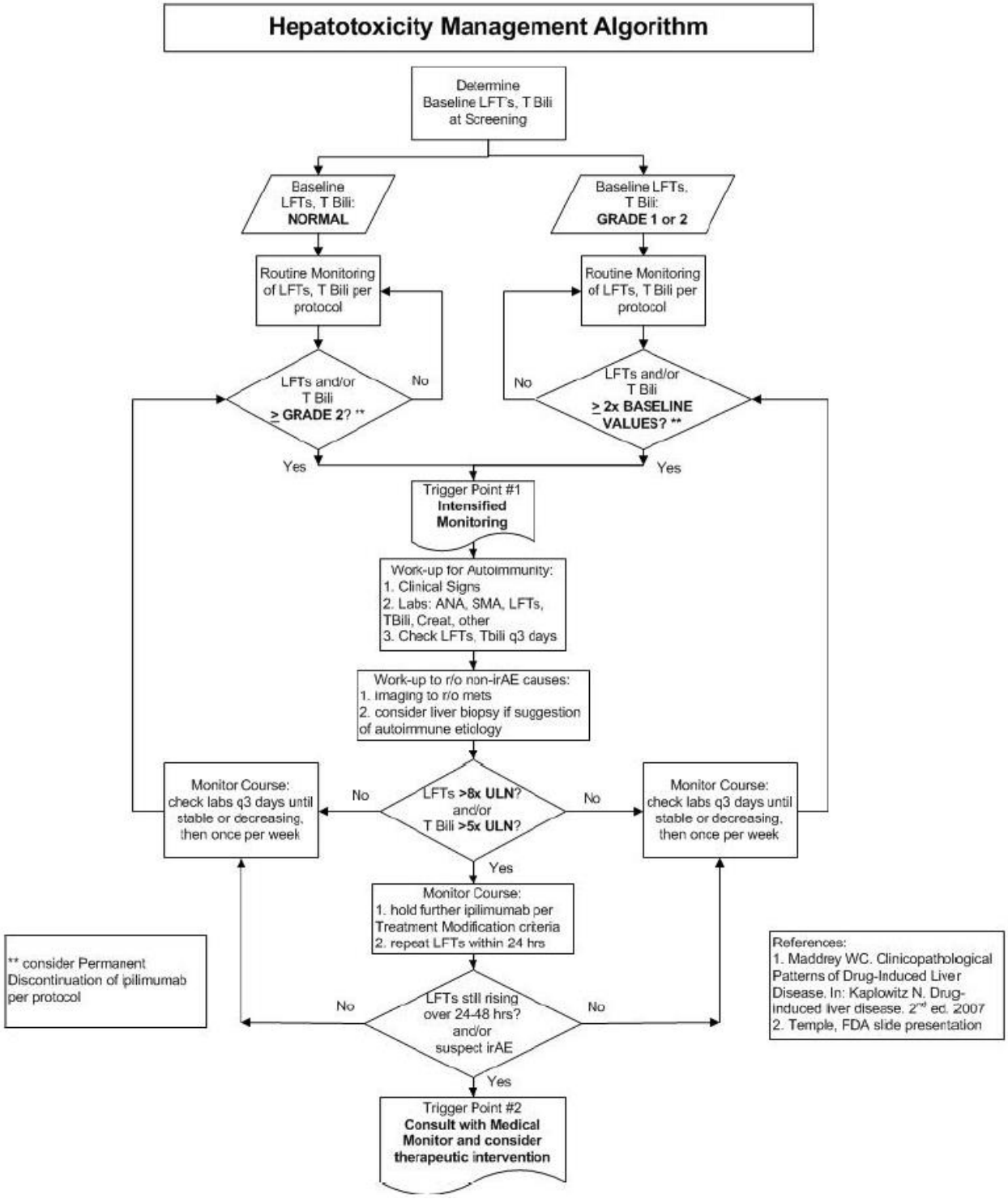
Diarrhea				
GRADE 1 Increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline	**GRADE 2** Increase of 4-6 stools per day over baseline; IV fluids indicated < 24 hrs; moderate increase in ostomy output compared to baseline; not interfering with activities of daily living (ADL)	**GRADE 3** Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥ 24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with ADL	**GRADE 4** Life-threatening consequences (*e.g.*, hemodynamic collapse)	**GRADE 5** Death

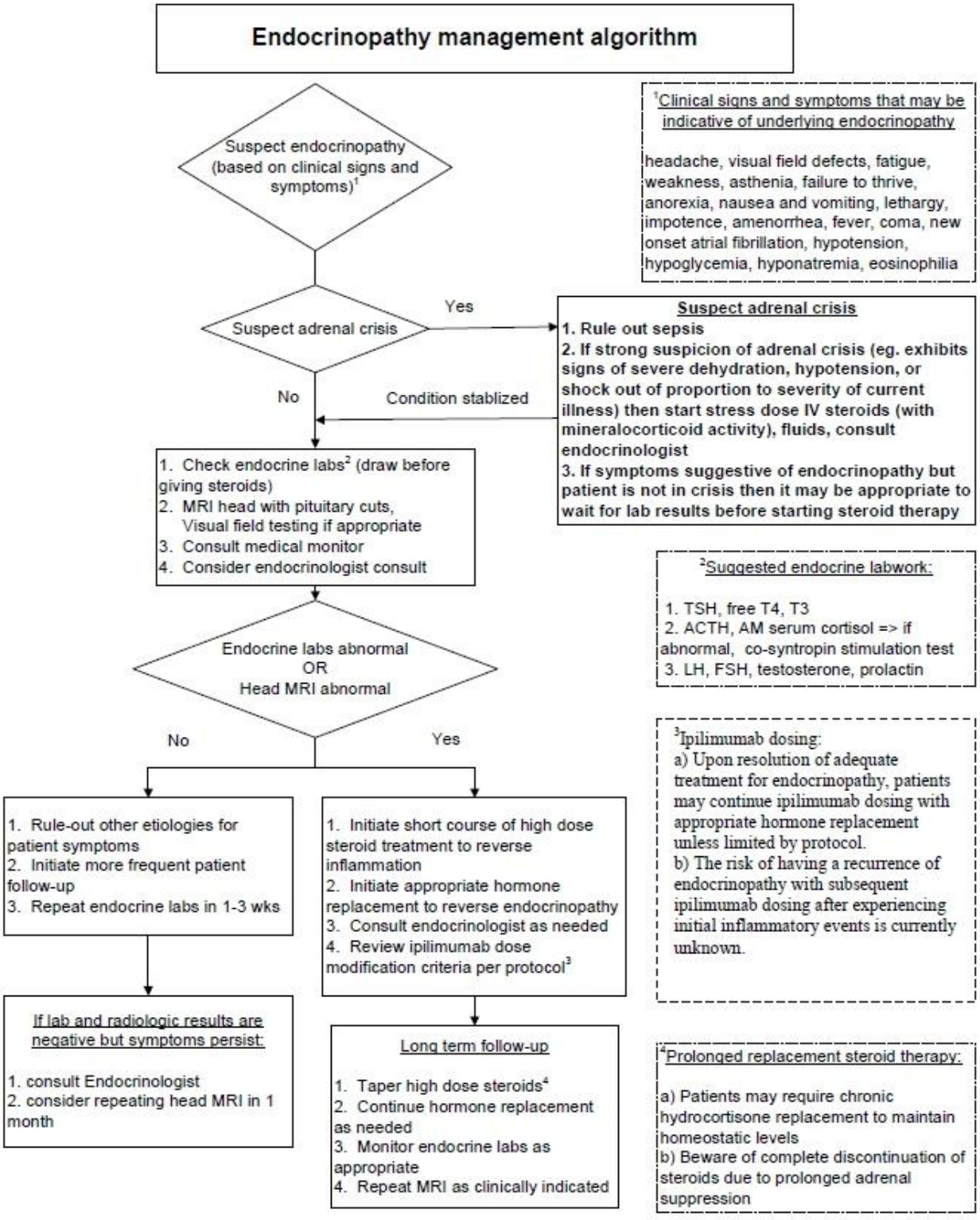
Hepatoxicity Management Algorithm

Situation: rising liver function tests (LFTs) >8X ULN or suspected immune-mediated Hepatitis

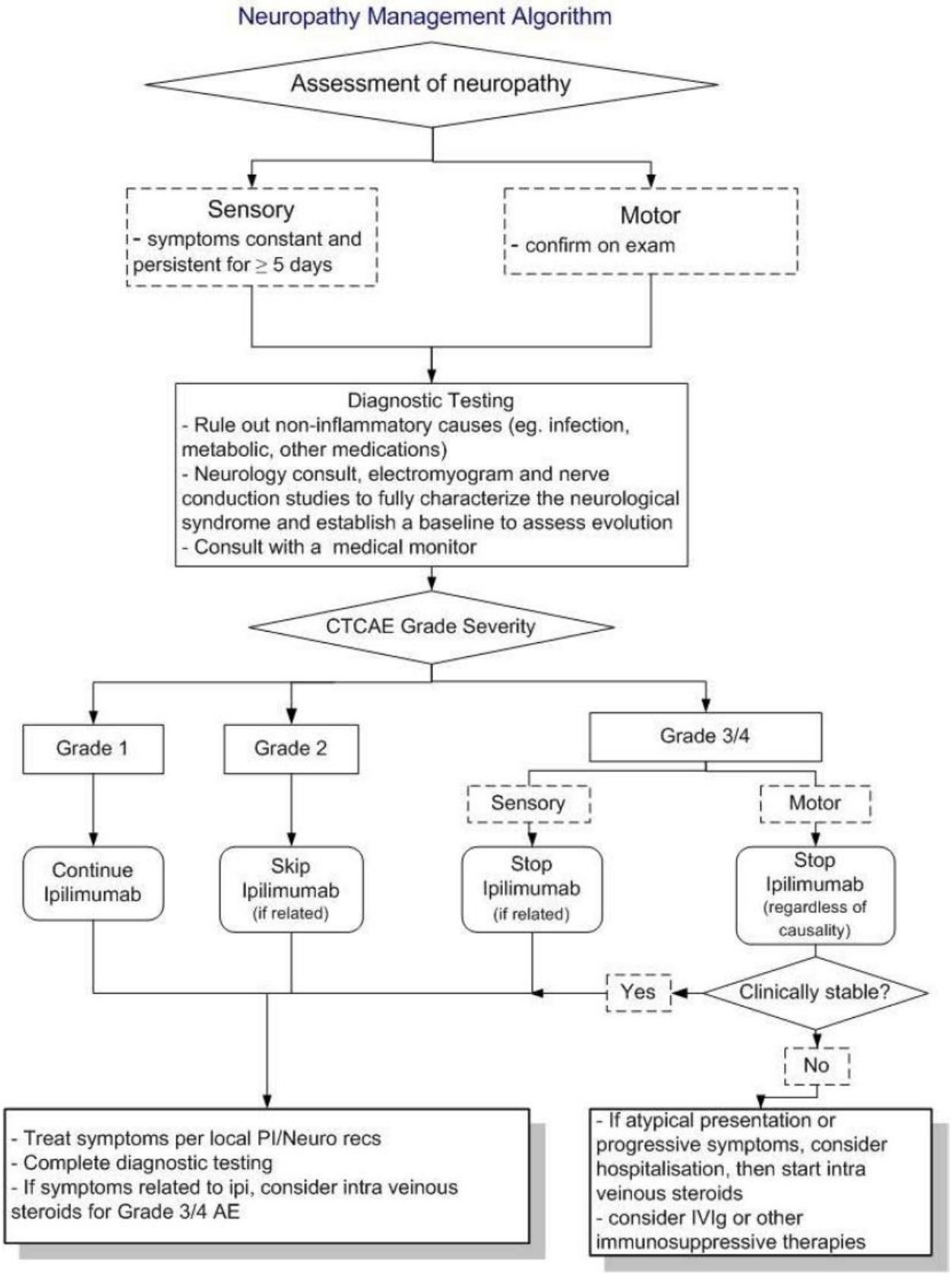
1) Admit subject to hospital for evaluation and close monitoring
2) Stop further ipilimumab dosing until hepatotoxicity is resolved. Consider permanent discontinuation of ipilimumab per protocol
3) Start at least 120 mg methylprednisolone sodium succinate per day, given IV as a single or divided dose
4) Check liver laboratory test values (LFTs, T-bilirubin) daily until stable or showing signs of improvement for at least 3 consecutive calendar days
5) If no decrease in LFTs after 3 calendar days or rebound hepatitis occurs despite treatment with corticosteroids, then add mycophenolate mofetil 1g BID per institutional guidelines for immunosuppression of liver transplants (supportive treatment as required, including prophylaxis for opportunistic infections per institutional guidelines)
6) If no improvement after 5 to 7 calendar days, consider adding 0.10 to 0.15 mg/kg/day of tacrolimus (trough level 5-20 ng/mL)
7) If target trough level is achieved with tacrolimus but no improvement is observed after 5 to 7 calendar days, consider infliximab, 5 mg/kg, once
8) Continue to check LFTs daily for at least 2 weeks to monitor sustained response to treatment

A flow chart of the algorithm is depicted on the following page.





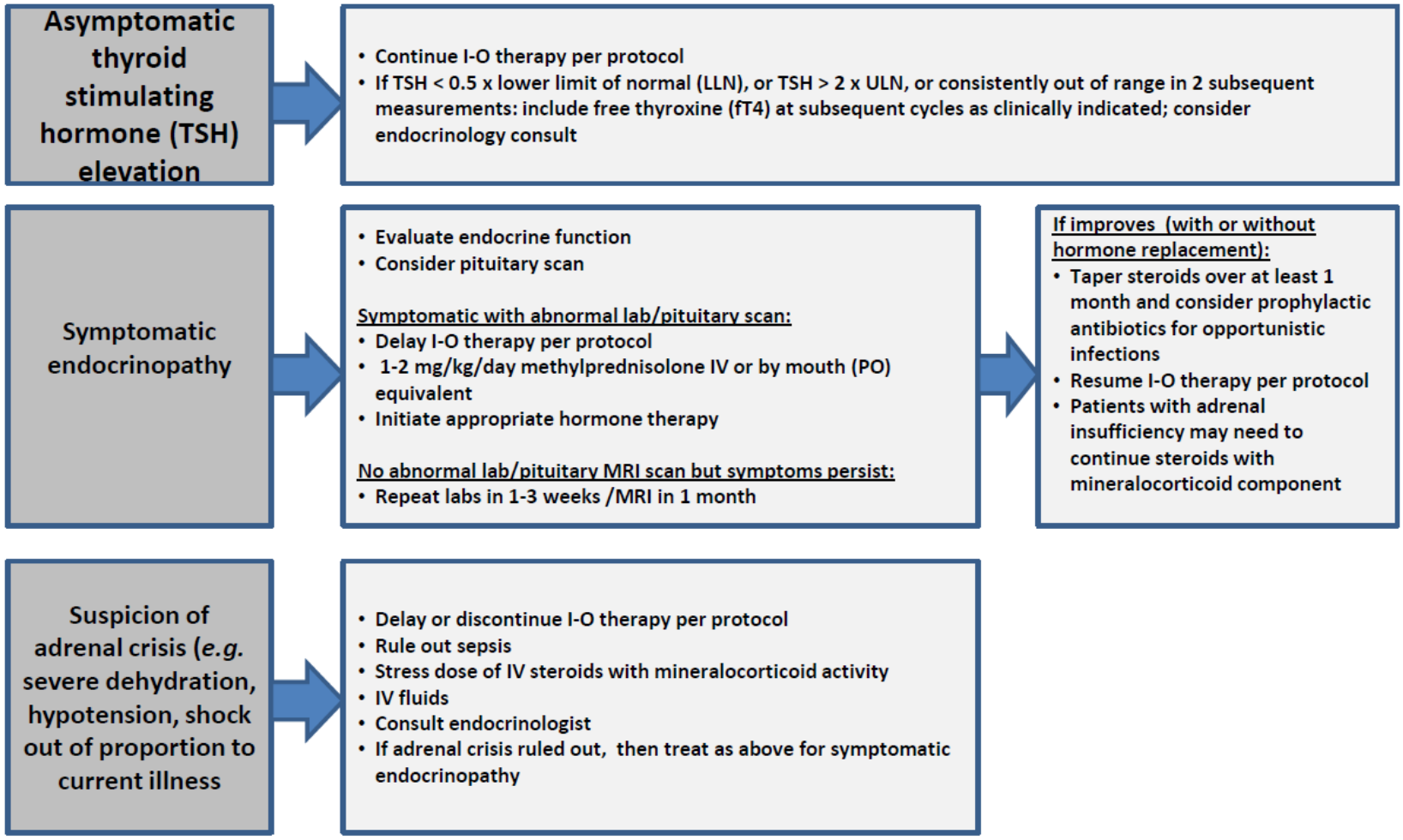
Footnote
For numbered footnotes ([1,2,3,4]), please refer to further explanation and text found in the corresponding dotted line boxes to the right side of the algorithm



18.4 Management of Algorithms for Endocrinopathy, Gastrointestinal, Hepatic Neurological, Pulmonary, Renal, and Skin Adverse Events for Nivolumab

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

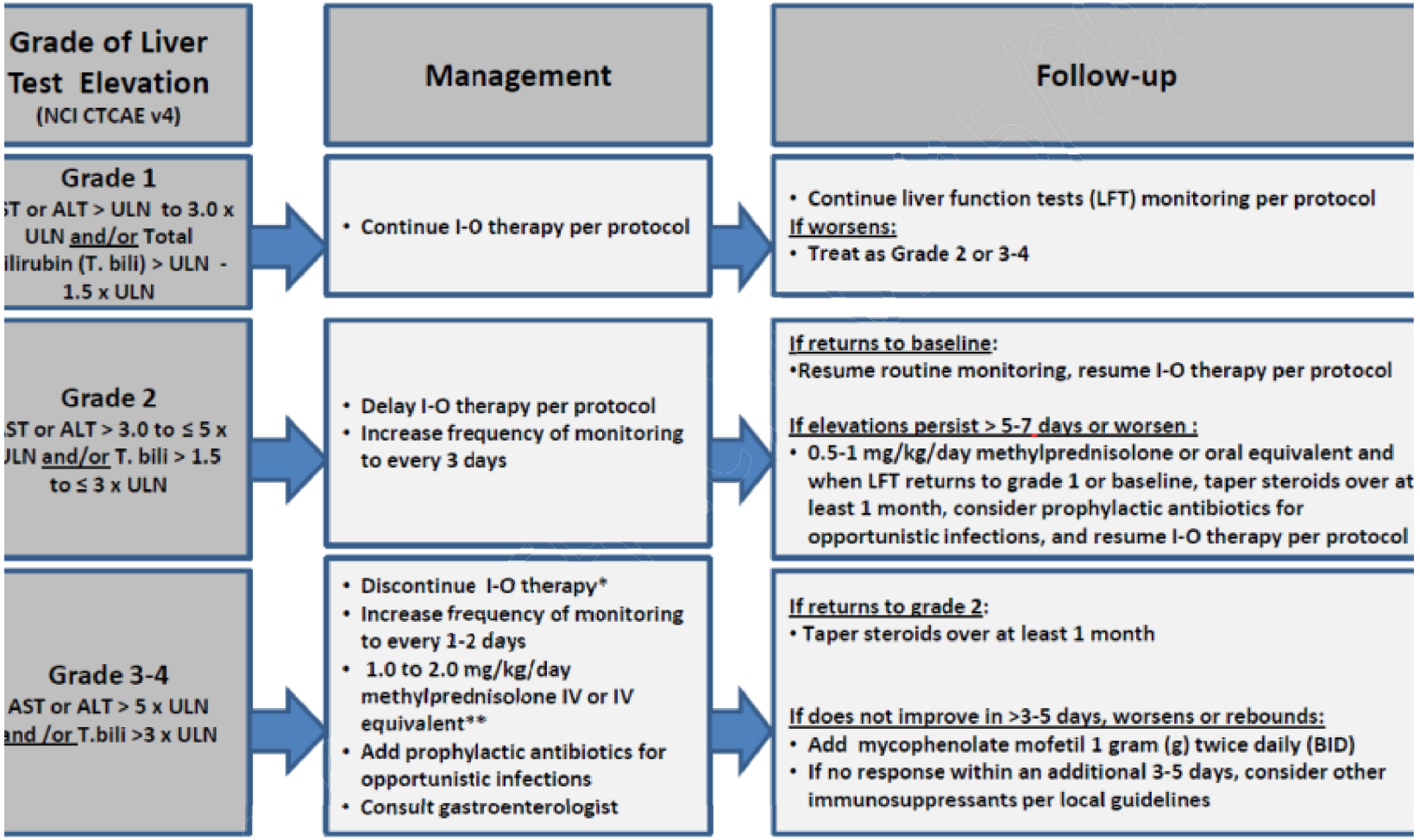
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade (G) 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hours (hrs); not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with activities of daily living (ADL) Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: 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.



ents 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 rovement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

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

he 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

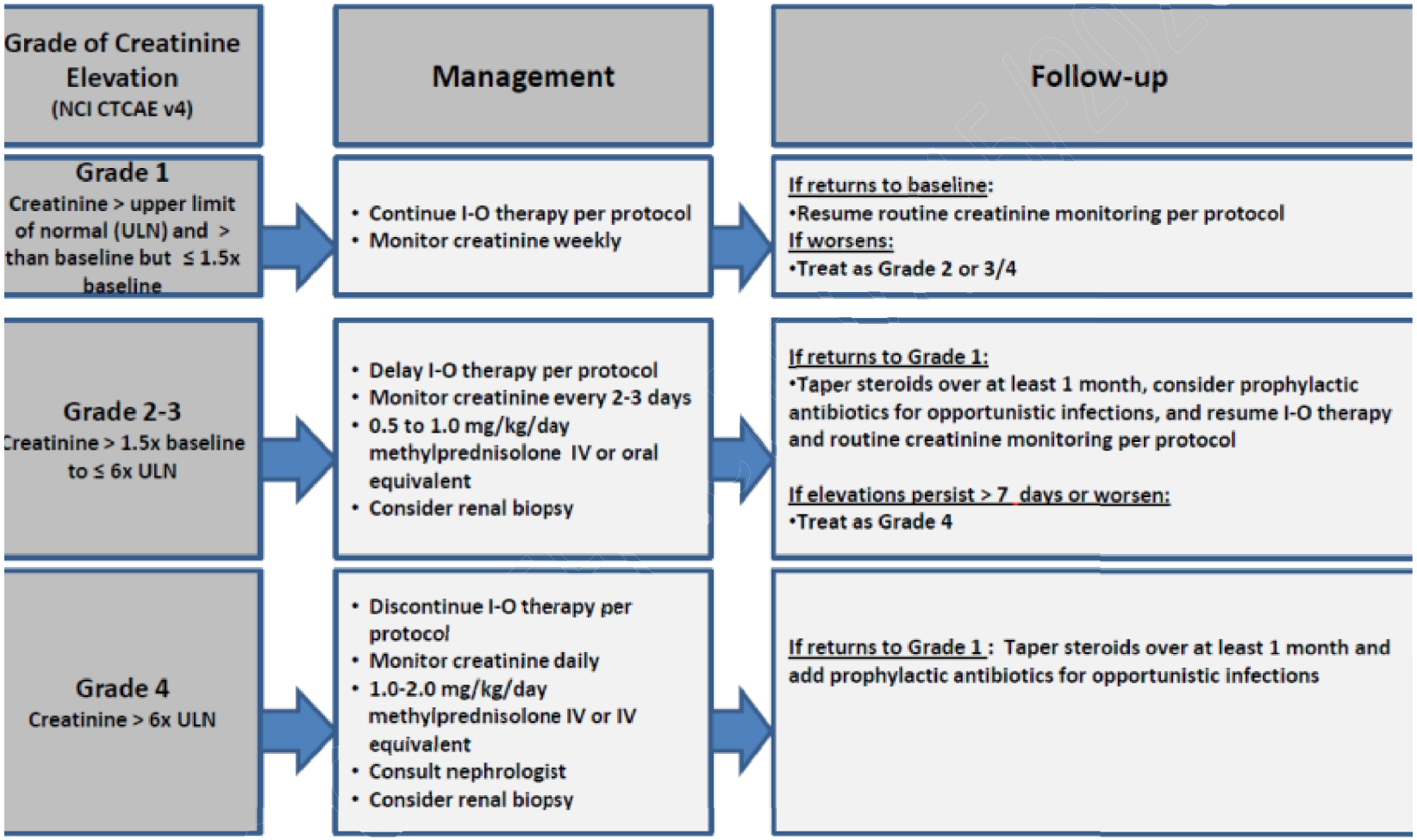
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and Infectious Disease (ID) consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression (e.g. infliximab, cyclophosphamide, intravenous immunoglobulin (IVIG), or mycophenolate mofetil)

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

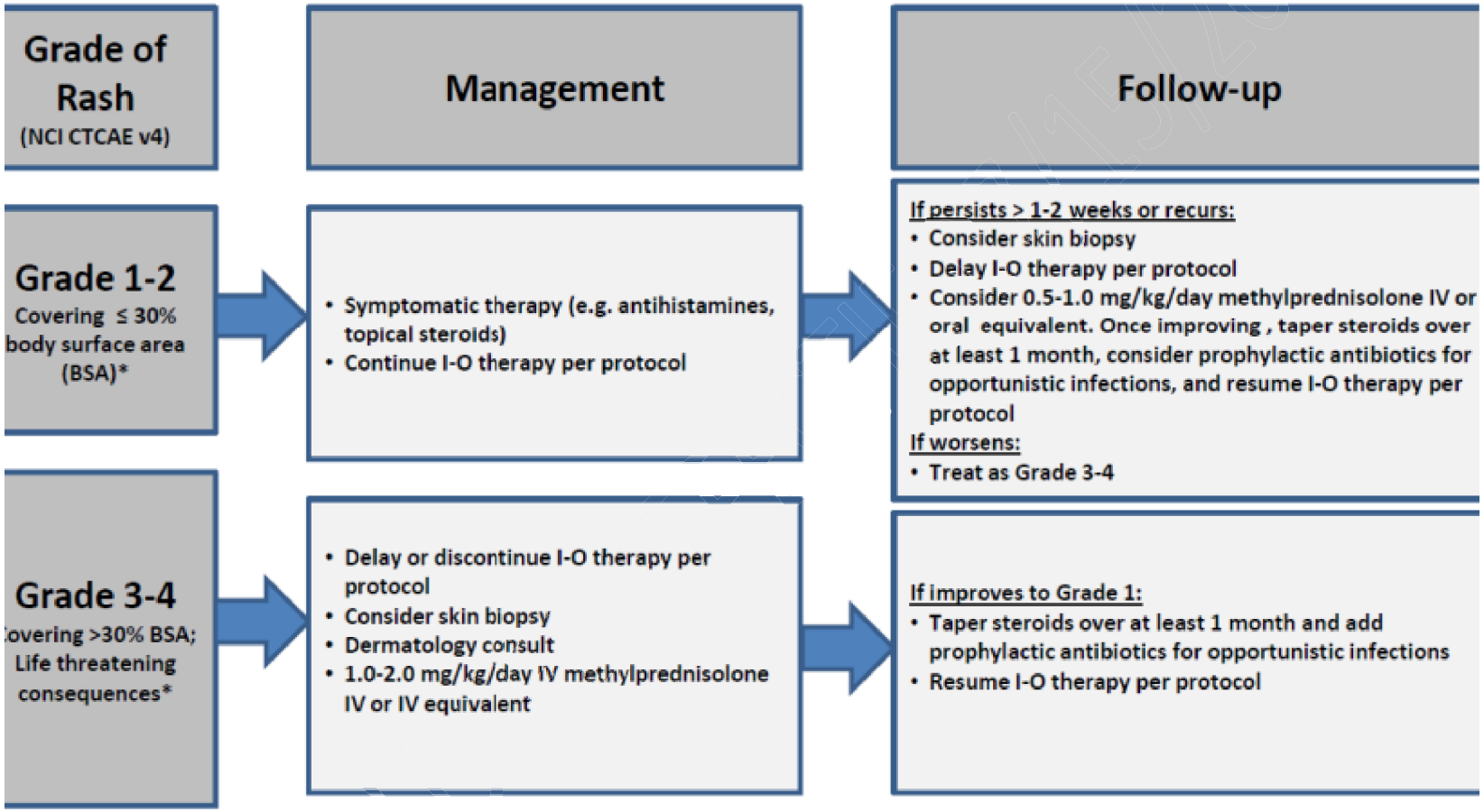
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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.



ients 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 provement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
efer to NCI CTCAE v4 for term-specific grading criteria.

18.5 Specimen Banking Instructions for the Ribas Laboratory

Any leftover tissue from Section 15.1 will be stored at the Ribas Laboratory for future if the patient consents. Upon receipt, the Bank will accession, barcode, and store FFPE material at room temperature. Fresh Frozen tissue from select sites will be stored at -80ºC for future use. The SWOG Statistical and Data Management Center will provide a distribution case list for specimens for subsequent analysis.