NCI Protocol #: 10214
Version Date: January 28, 2021

DATE: January 28, 2021

TO: CTEP Protocol and Information Office

FROM: Evan Lipson, MD

SUBJECT: Amendment in response to the request for rapid amendment from Dr. Streicher, NCI, dated 01/28/2021.

I. SUMMARY OF CHANGES – Protocol

#	Section	Comments
1.	Header, Title Page	Updated version date.

2.	10.1.1	Updated revised CAEPR to Version 2.4, December 2, 2020, with the following changes:
		• The SPEER grades have been updated.
		• Added New Risk:
		  • Less Likely: CD4 lymphocytes decreased
		  • Rare: Enterocolitis; Eye disorders - Other (Vogt-Koyanagi-Harada); Hepatobiliary disorders - Other (immune-mediated hepatitis); Renal and urinary disorders - Other (immune-mediated nephritis)
		• Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
		  • Added: CD4 lymphocytes decreased
		• Provided Further Clarification:
		  • Immune system disorders - Other (sarcoid granuloma) is now reported as Immune system disorders - Other (sarcoidosis).

II. SUMMARY OF CHANGES – Consent Form

#	Section	Comments
1.	Header	Updated version date.
2.	Possible Side Effects of Nivolumab	Added new risks to Rare, and Serious as requested in the RRA: • A syndrome starting with flu-like symptoms and followed by swelling, tenderness which may cause flu-like symptoms, blurred vision, ringing in the ears, changes in hair or hair loss • Swelling of the bowels

		Provided Further Clarification: • Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior; decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting is now reported as Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior; decreased sex drive; weight loss or weight gain; excessive thirst or urination; dizziness or fainting. • A syndrome starting with flu-like symptoms and followed by swelling, tenderness which may cause flu-like symptoms, blurred vision, ringing in the ears, changes in hair or hair loss is now reported as A syndrome starting with flu-like symptoms and followed by swelling, tenderness which may cause blurred vision, ringing in the ears, changes in hair or hair loss • Swelling of the brain (meningitis/encephalitis) which may cause: headache, stiff neck confusion, sleepiness, seizures or injury to the brain which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome) is now reported as Swelling of the brain (meningitis/encephalitis) which may cause: headache, stiff neck confusion, sleepiness, seizures or injury to the brain which may cause headache, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)

NCI Protocol #: 10214

Local Protocol #: ETCTN10214

ClinicalTrials.gov Identifier: NCT03816332

TITLE: Immune Checkpoint Blockade for Kidney Transplant Recipients with Selected Unresectable or Metastatic cancers

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NCI-Supplied Agents: Nivolumab (NSC 748726)
Ipilimumab (NSC 732442)

Other Agents: Tacrolimus (NSC 717865), Commercial
Prednisone (NSC 10023), Commercial

IND #:
IND Sponsor: DCTD, NCI

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Revision 1 / October 17, 2018
Revision 2 / January 7, 2019
Amendment 1 / February 27, 2019
Amendment 2 / March 20, 2019
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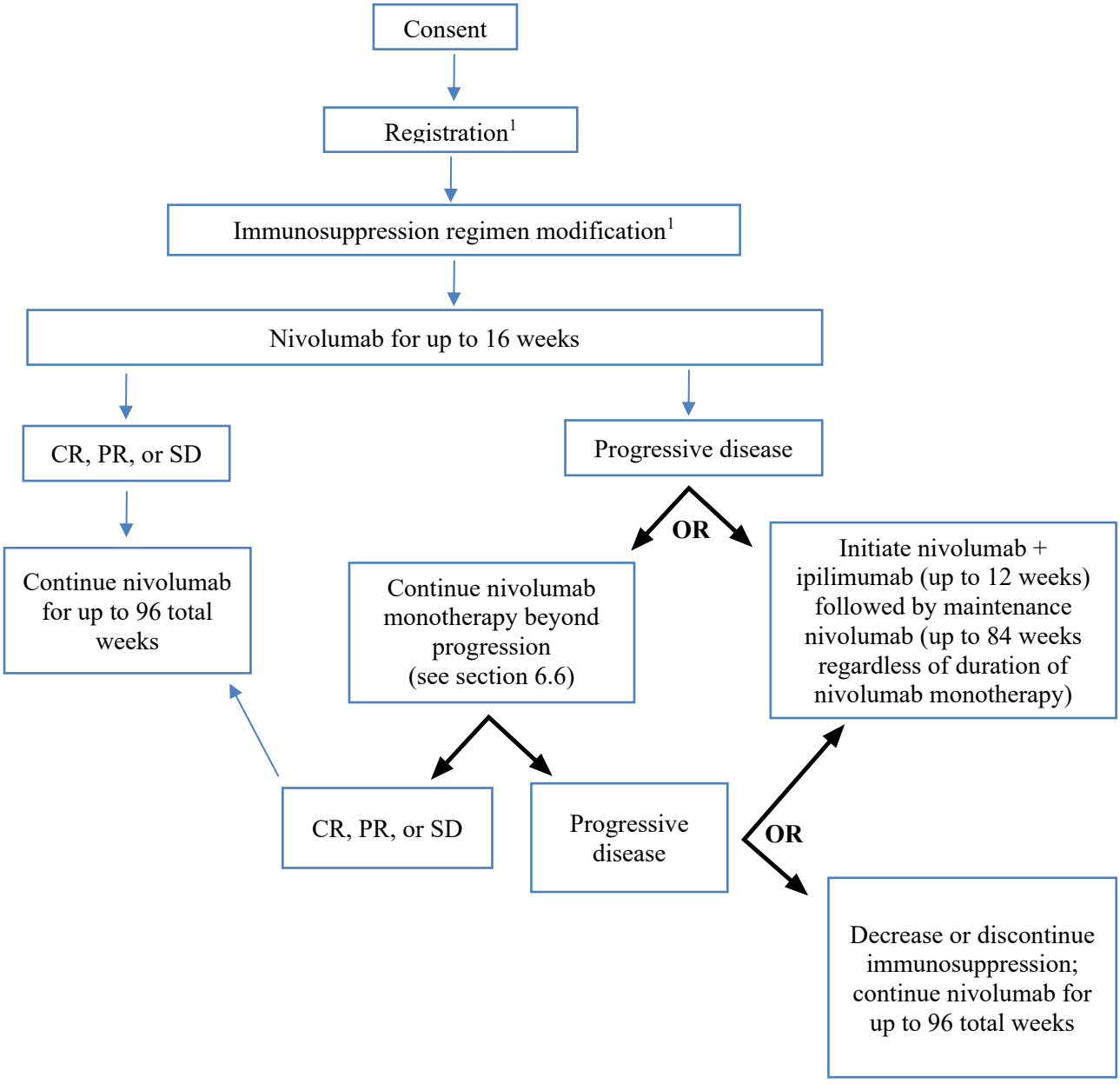
Amendment 4 / May 17, 2019
Amendment 5 / August 5, 2019
Amendment 6 / October 9, 2019
Amendment 7 / December 10, 2019
Amendment 8 / September 23, 2020
Amendment 9 / January 28, 2021

SCHEMA



[1] Protocol-specified immunosuppression regimen may begin prior to registration. Patients whose tacrolimus trough level is not yet within the protocol-specified range of 2-5 ng/ml may start nivolumab after consultation with the Principal Investigator.
- Patients who experience CR/PR/SD followed by disease progression within 1 year of last Nivolumab dose may be eligible to restart nivolumab therapy (see Section 6.5)
- All patients will be followed for survival for 5 years from the date of trial registration or until death, whichever occurs first (see Section 6.8)

CR=complete response, PR=partial response, SD=stable disease

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1. OBJECTIVES

1.1 Primary Objective

1.1.1 To estimate the percent of kidney transplant recipients with selected advanced cancers for whom standard therapies would be insufficient who, 16 weeks after administration of prednisone, tacrolimus, and nivolumab, experience complete response (CR), partial response (PR), or stable disease (SD) without allograft loss.

1.2 Secondary Objectives

1.2.1 To estimate the objective response rate (ORR), rate of allograft loss, and durations of progression-free survival (PFS) and overall survival (OS) in the study population.

1.2.2 To estimate the ORR and rate of allograft loss in patients who experience progressive disease (PD) after administration of nivolumab and 1) receive ipilimumab and nivolumab, or 2) decrease or discontinue immunosuppression.

1.3 Exploratory Objective

1.3.1 To characterize correlates of the host immune response, possibly including, but not limited to:

- Histopathological characteristics of allograft rejection/loss;
- Immunological changes in the tumor microenvironment (*e.g.*, changes in T-cell subset populations or expression of immune checkpoint molecules) in paired biopsies obtained pre-treatment and on-treatment;
- Changes in donor-derived cell-free DNA (dd-cfDNA) as a marker for allograft rejection;
- Characteristics of anti-programmed death-1 (PD-1)-associated immune-mediated adverse reactions (IMARs) in this patient population treated with immunosuppression.

2. BACKGROUND

2.1 Study Disease

2.1.1 Solid Organ Transplant Recipients (SOTRs)

Compared to the general population, SOTRs are at significantly increased risk of developing various cancers (Euvrad *et al.*, 2003; Vajdic *et al.*, 2006; Vajdic and van Leeuwen, 2009). Although multiple pathogenic factors are likely at play, immune dysregulation from the chronic immunosuppressive drug regimens required to maintain allograft tolerance is among the most important. Clinical evidence and murine transplant model data show that the PD-1 pathway is important to maintaining allograft tolerance among SOTRs (Tanaka *et al.*, 2007). Indeed, limited published data (Table 1) suggest that while anti-PD-1 therapy may be an effective cancer treatment strategy for SOTRs, they may also trigger allograft rejection and loss.

2.1.2 Selected Advanced Cancers

Several factors led to the inclusion of only selected tumor types in the proposed study. First, the risk-benefit ratio may be more favorable among patients with tumor types known to have higher response rates in the general population to anti-PD-1, such as melanoma, and Merkel cell carcinoma (MCC), than among patients with tumor types with lower response rates, such as lung or urothelial cancers. See Section 2.2.1.2.2 for nivolumab efficacy data. Second, by including only patients with higher response rates, the study cohort size can be limited to 16 patients (see Section 9, Statistical Considerations), thereby increasing the feasibility of the trial. Of note, cutaneous cancers are the most common malignancies found in organ transplant recipients (Chapman *et al.*, 2013).

Table 1: Summary of outcomes from published reports of anti-PD-1 therapy in SOTRs.

Transplanted organ	Years from transplant	Type of cancer	Checkpoint inhibitor treatment	Tumor regression	Immuno-suppression	Graft rejection/loss	Reference
Kidney (HLA mismatch)	15	Melanoma	Ipilimumab followed by pembrolizumab	NR	Prednisone	Yes / Yes	Alhamad *et al.*, 2016.
Kidney	8	Melanoma	Ipilimumab followed by nivolumab	No	Prednisone 5 mg daily, tacrolimus 2 mg twice daily	No / No	Herz *et al.*, 2016.
Kidney	26	Cutaneous squamous cell carcinoma	Pembrolizumab	Yes	Prednisone 5 mg daily	Yes / Yes	Lipson *et al.*, 2016.
Kidney	14	Melanoma	Ipilimumab followed by nivolumab	Yes	Prednisolone 5 mg daily	Yes / Yes	Spain *et al.*, 2016.
Kidney	3	NSCLC	Nivolumab	NR	Prednisone, cyclosporine (goal trough level <50 ng/mL)	Yes / NR	Boils *et al.*, 2016.
Kidney	12	Melanoma	Nivolumab	Yes	Prednisone 5 mg daily	Yes / Yes	Ong *et al.*, 2016.
Kidney (HLA mismatch)	6	Microsatellite-stable duodenal adenocarcinoma	Nivolumab	Resolution of FDG-avidity associated with hepatic metastases	Prednisone, sirolimus	No / No	Barnett *et al.*, 2017.
Heart	19	Cutaneous squamous cell carcinoma	Nivolumab	NR	Prednisone, tacrolimus	Yes / NR	Owonikoko *et al.*, 2017.
Liver	3	Hepatocellular carcinoma, fibrolamellar type	Nivolumab	NR	Sirolimus	Yes / Yes	Friend *et al.*, 2017.
Liver	1	Hepatocellular carcinoma, fibrolamellar type	Nivolumab	NR	Tacrolimus	Yes / Yes	
Kidney	14	Cutaneous squamous cell carcinoma	Nivolumab	Stable disease	Prednisone 5 mg daily, Sirolimus	No / No	Kittai *et al.*, 2017.
Heart	10	Squamous NSCLC	Nivolumab	Stable disease at 8 months	Mycophenolate mofetil, cyclosporine	No / No	
Liver	20	Melanoma	Pembrolizumab	Yes	Prednisone, tacrolimus,	Yes / No	Schvartsman *et al.*, 2017.
Kidney	14	Melanoma	Pembrolizumab	No	Azathioprine, everolimus	Yes / Yes	Kwatra *et al.*, 2017.
HLA=human leukocyte antigen, NR=not reported, NSCLC=non-small cell lung cancer							

2.2 CTEP IND Agents

2.2.1 Nivolumab

Nivolumab (BMS-936558, MDX-1106, ONO-4538, Opdivo™) is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) that is specific for human PD-1, cluster of differentiation 279 (CD279) cell surface membrane receptor (Nivolumab Investigator's Brochure, 2018). PD-1 is a negative regulatory molecule that is expressed transiently following T-cell activation and on chronically stimulated T-cells characterized by an "exhausted" phenotype. Nivolumab binds to cynomolgus monkey PD-1 but not mouse, rat, or rabbit molecules. Clinical activity of nivolumab has been observed in patients with a variety of cancers. The combination of nivolumab and ipilimumab, an anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) agent, in a phase 1/2 trial showed markedly enhanced clinical activity with an acceptable safety profile in melanoma patients (Wolchok *et al*., 2013). See Section 2.2.2 for more information about ipilimumab.

The clinical use of monoclonal antibodies to T-cell inhibitory receptors has provided transformative information on the nature of the immune system and cancer (Nivolumab Investigator's Brochure, 2018). An emerging picture suggests that endogenous immune responses can mediate effective tumor regression and/or improved survival even in patients with large volume tumors resistant to other forms of therapy. Some of the unique features of this type of therapy, based largely on experience in advanced melanoma, include: improved OS with or without radiographic responses or improved PFS; responses that may be delayed or occur after radiographic disease progression; combinations of immune modulators with enhanced or novel activities (in the example of ipilimumab and nivolumab); and toxicity that is almost exclusively immune or inflammatory in nature. It is not yet clear what factors determine responses and which components of the immune system are needed for this to occur. It seems likely that both memory helper and effector cells would be needed to sustain long-term responses. Increasing emphasis has been placed on understanding the relationships of the tumor, cellular infiltrate, and immunologic milieu surrounding each tumor.

PD-1, a 55-kDa type 1 transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that include Ig super family member CD28, CTLA-4, inducible co-stimulator (ICOS), and B and T lymphocyte attenuator (BTLA) (Nivolumab Investigator's Brochure, 2018). PD-1 is transiently, but highly expressed on activated T-cells and functions to limit immune effectors at the site of activation. Chronic stimulation may prevent the re-methylation of the PD-1 gene leading to continuous expression and characterizes a state of "exhausted" T-cells that lose function and proliferative capacity while enhancing a suppressive tumor microenvironment. PD-1 may act together with other T-cell modulating molecules, including CTLA-4, TIM-3 (T-cell immunoglobulin mucin 3), lymphocyte-activation gene 3 (LAG-3) as well as indoleamine-pyrrole 2,3-dioxygenase 1 (IDO-1), cytokines, and transforming growth factor beta (TGF-beta).

Two ligands specific for PD-1 have been identified: PD-ligand 1 (PD-L1, also known as B7-H1 or CD274, expressed on tumor, antigen-presenting cells [APCs], and dendritic cells [DCs]) and

PD-L2 (also known as B7-DC or CD273, expressed on endothelial cells). The interaction of PD-1 with PD-L1 and PD-L2 results in negative regulatory stimuli that down-modulate the activated T-cell immune response through SHP-1 phosphastase.

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

PD-L1 expression is found on a number of tumors, and is associated with poor prognoses based on OS in many tumors, including melanoma (Taube *et al*., 2012), renal (Thompson *et al*., 2004; Thompson *et al*., 2005; Thompson *et al*., 2006), esophageal (Ohigashi *et al*., 2005), gastric (Wu *et al*., 2006), ovarian (Dong *et al*., 2003), pancreatic (Nomi *et al*., 2007), lung (Zitvogel *et al*., 2006), and other cancers (Nivolumab Investigator's Brochure, 2018).

The PD-1/PD-L1 axis plays a role in human infections, particularly in hepatitis C virus (HCV) and human immunodeficiency virus (HIV). In these cases, high expression levels of PD-1 were found in viral-specific CD8+ T-cells that also display a non-responsive or exhausted phenotype. Non-responsive PD-1-high T-cells were observed in simian immunodeficiency virus (SIV) infection in rhesus macaques. Treatment of SIV-infected macaques with an anti-PD-1 mAb (3 mg/kg × 4) resulted in decreased viral loads and increased survival along with expanded T-cells with increased T-cell functionality.

2.2.1.1 Nonclinical Development of Nivolumab

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab alone was well tolerated (Nivolumab Investigator's Brochure, 2018). Combination studies have highlighted the potential for toxicity when combined with ipilimumab, MDX-1408, and BMS-986016. Nivolumab bound specifically to PD-1 (and not to related members of the CD28 family such as CD28, ICOS, CTLA-4, and BTLA) with a dissociation constant (K_d) of 3.06 nM. A surrogate rat anti-mouse PD-1 antibody (4H2) was derived and expressed as chimeric IgG1 murine antibody. Antitumor activity was seen for several tumor models, including colon carcinoma and fibrosarcoma.

2.2.1.2 Clinical Development of Nivolumab

Nivolumab has demonstrated clinical activity, and has been approved for use in non-small cell lunch cancer (NSCLC), melanoma, renal cell carcinoma (RCC), classical Hodgkin's Lymphoma (cHL), squamous cell carcinoma (SCC) of the head and neck, and urothelial carcinoma as monotherapy and in combination with ipilimumab and other therapeutics (Nivolumab Investigator's Brochure, 2018). It has also demonstrated activity in other tumor types. The majority of responses were durable and exceeded 6 months. In randomized, controlled studies, nivolumab monotherapy demonstrated statistically significant improvement in OS over standard

of care in subjects with advanced or metastatic melanoma, subjects with advanced or metastatic NSCLC, subjects with advanced RCC, and subjects with recurrent or metastatic SCCHN. In randomized, controlled studies, nivolumab in combination with ipilimumab demonstrated statistically significant improvement in PFS and ORR over ipilimumab monotherapy in subjects with advanced or metastatic melanoma.

Nivolumab monotherapy (Opdivo™) was first approved on July 4, 2014 in Japan for unresectable melanoma and followed by approval in multiple countries, including the U.S., and in the E.U. Since then it has been approved for several other indications, including metastatic NSCLC, advanced RCC, cHL, and urothelial carcinoma. Nivolumab is also approved in combination with ipilimumab (Yervoy™) for unresectable or metastatic melanoma.

Nivolumab is also being evaluated in several other cancers, including small cell lung cancer (SCLC), gastric and esophageal cancer, hepatocellular carcinoma, colorectal cancer, glioblastoma, and MCC.

2.2.1.2.1 Pharmacokinetics

Pharmacokinetics (PK) of nivolumab was linear in the range of 0.3 to 10 mg/kg, with dose-proportional increases in maximum serum concentration (C_{max}) and area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), with low to moderate inter-subject variability observed at each dose level (Investigator Brochure, 2018). Clearance of nivolumab is independent of dose in the dose range (0.1 to 10 mg/kg) and tumor types studied. Body weight normalized dosing showed approximately constant trough concentrations over a wide range of body weights. The mean terminal elimination half-life of nivolumab is 17 to 25 days consistent with the half-life of endogenous IgG4.

2.2.1.2.2 Efficacy

In a randomized, open-label, phase 3 trial, patients with unresectable or metastatic melanoma who had progressed after treatment with ipilimumab were given either IV nivolumab (3 mg/kg every 2 weeks) or investigator's choice chemotherapy (ICC; dacarbazine 1000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 combined with carboplatin area under the curve [AUC] = 6 every 3 weeks) (Weber *et al.*, 2015). Of the first 120 patients treated with nivolumab, objective responses (CR or PR) were seen in 38 (31.7%) versus 5 (10.6%) out of 47 patients in the ICC arm. Grade 3-4 adverse events (AEs) related to nivolumab included increased lipase, increased alanine aminotransferase, anemia, and fatigue. Grade 3-4 drug-related serious adverse events (SAEs) were noted in 12 (5%) nivolumab-treated patients. No treatment-related deaths occurred.

In a phase 1/2 trial, patients with virus-positive and -negative solid tumors, including MCC, were given 240 mg nivolumab IV every 2 weeks (Nivolumab Investigator's Brochure, 2018). As of the February 16, 2017 data cutoff, of 25 patients with MCC who had received nivolumab, objective responses (PR or CR) were seen in 16 patients (64%, 95% confidence interval [CI] 42.5%-82%). Median duration of response (DOR), PFS, and OS have not been reached.

In a randomized, open-label, phase 3 trial, patients with recurrent SCC of the head and neck were given either IV nivolumab (3 mg/kg every 2 weeks) or standard systemic therapy (methotrexate, docetaxel, or cetuximab) (Ferris *et al.*, 2016). The median OS was 7.5 months (95% CI, 5.5 to 9.1 months) in the nivolumab group versus 5.1 months (95% CI, 4 to 6 months) in the group that received standard therapy. OS was significantly longer with nivolumab than with standard therapy (hazard ratio for death, 0.70; 97.73% CI, 0.51 to 0.96; *P*=0.01), and the estimates of the 1-year survival rate were approximately 19% higher with nivolumab than with standard therapy (36.0% vs. 16.6%). The median PFS was 2 months (95% CI, 1.9 to 2.1 months) with nivolumab versus 2.3 months (95% CI, 1.9 to 3.1 months) with standard therapy (hazard ratio for disease progression or death, 0.89; 95% CI, 0.70 to 1.13; *P*=0.32). The PFS rate at 6 months was 19.7% with nivolumab versus 9.9% with standard therapy. The response rate was 13.3% in the nivolumab group versus 5.8% in the standard-therapy group. Treatment-related AEs of grade 3 or 4 occurred in 13.1% of the patients in the nivolumab group versus 35.1% of those in the standard-therapy group. Physical, role, and social functioning was stable in the nivolumab group, whereas it was meaningfully worse in the standard-therapy group.

In an open-label, phase 2 trial, patients with recurrent or metastatic colorectal cancer assessed as MSI-high were given 3 mg/kg IV nivolumab every 2 weeks as monotherapy, or in combination with 1 mg/kg IV ipilimumab every 3 weeks for 4 doses followed by 3 mg/kg IV nivolumab every 2 weeks (Nivolumab Investigator's Brochure, 2018; Overman *et al.*, 2017). As of the September 19, 2016 data cut-off, 74 patients had received nivolumab monotherapy and 30 had received combination nivolumab/ipilimumab therapy. At a median follow-up of 12 months, 23 of 74 nivolumab-treated patients (31.1%, 95% CI, 20.8%-42.9%) achieved an objective response and 51 patients (69%, 95% CI, 57%-79%) had disease control for 12 weeks or longer. As of the data cut-off, median DOR had not yet been reached; all responders were alive, and eight had responses lasting 12 months or longer (Kaplan-Meier 12-month estimate 86%, 95% CI, 62%-95%). Median PFS was 7.6 months (95% CI, 3 months-NR). The 6- and 12-month PFS rates were 51.5% (95% CI, 38.9%-62.8%) and 45.6% (95% CI, 32.2%-58.1%), respectively. The 6- and 12-month OS rates were 83.4% (95% CI, 72.5%-90.2%) and 73.8% (95% CI, 59.8%-83.5%), respectively. The most common grade 3 or 4 drug-related AEs were increased concentrations of lipase (six patients, 8%) and amylase (two patients, 3%). Twenty-three patients (31%) died during the study; none of these deaths were deemed to be treatment related by the investigator. Out of 30 patients who had received nivolumab and ipilimumab combination therapy, 27 were evaluable for response (Nivolumab Investigator's Brochure, 2018). Of these, objective responses were seen in 9 patients (33.3%, 95% CI, 18.6%-50.9%). The 6-month PFS rate was 66.6% (95% CI, 45.5%-81.1%) and the 6-month OS rate was 85.1% (95% CI, 65.0%-94.2%).

2.2.1.2.3 Toxicology

A maximum tolerated dose (MTD) of nivolumab was not reached at any dose up to 10 mg/kg (Topalian *et al*., 2012; Nivolumab Investigator's Brochure, 2018). There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. Most AEs were low-grade (Grade 1-2) with relatively few drug-related high-grade (Grade 3-4) AEs. The safety profile of nivolumab combination therapy varies with the agent combined with nivolumab but is generally consistent with the safety profiles observed with either agent alone and, in some cases, both

frequency and severity of AEs were greater than that observed with either agent alone. The safety profile of nivolumab + ipilimumab combination therapy was consistent with the mechanisms of action of nivolumab and ipilimumab (Nivolumab Investigator's Brochure, 2018). A dose of 3 mg/kg nivolumab/3 mg/kg ipilimumab exceeded the MTD, and both 1 mg/kg nivolumab/3 mg/kg ipilimumab and 3 mg/kg nivolumab/1 mg/kg ipilimumab were identified as the MTD. For nivolumab monotherapy and combination therapy, most high-grade events were manageable with use of corticosteroids or hormone replacement therapy (endocrinopathies).

The overall safety experience with nivolumab is based on experience in approximately 16,900 subjects as either monotherapy or in combination with other therapeutics (Nivolumab Investigator's Brochure, 2018). In general, for monotherapy, the safety profile is similar across tumor types. The only exception is pulmonary inflammation AEs, which may be numerically greater in subjects with NSCLC, possibly because in some cases, it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes. The most frequently reported treatment-related AE is fatigue, which is almost always of low grade.

2.2.1.2.4 Pharmacodynamics/Biomarkers

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

2.2.2 Ipilimumab

Ipilimumab (BMS-734016, MDX010, MDX-CTLA4, Yervoy™) is an Ig-G1κ HuMAb specific for human cytotoxic T lymphocyte antigen 4 (CTLA-4, CD152), which is expressed on a subset of activated T-cells (Ipilimumab Investigator's Brochure, 2019). CTLA-4 is a negative regulator of T-cell activation. Ipilimumab binds to CTLA-4 and inhibits its interaction with ligands on APCs. The proposed mechanism of action for ipilimumab's effects in subjects with melanoma is indirect, possibly through T-cell potentiation and mediation of antitumor immune responses.

Ipilimumab has been approved for the treatment of unresectable metastatic melanoma in over 40 countries including the United States (US, March 2011), the European Union (July 2011), and Australia (July 2011).

BMS and Medarex (acquired by BMS in September 2009) have co-sponsored an extensive clinical development program for ipilimumab, encompassing >22,500 subjects in several cancer types in completed and ongoing studies, including a compassionate use program (Ipilimumab Investigator Brochure, 2019). The focus of the clinical program is in melanoma, prostate cancer, and lung cancer, with advanced melanoma being the most comprehensively studied indication. Ipilimumab is being investigated both as monotherapy and in combination with other modalities such as chemotherapy, radiation therapy, and other immunotherapies.

CTEP's clinical development of ipilimumab focuses on cervical, GI, ovarian, prostate cancer, chronic lymphocytic leukemia, head and neck squamous cell carcinoma, solid tumors, Hodgkin and non-Hodgkin lymphomas, melanoma, and myelodysplastic syndrome. While the toxicity and clinical responses overlap, mechanisms of immune activation and range of responses appear to be different for each of the single agents.

Available preclinical data support the combinations of nivolumab and ipilimumab (Curran *et al.*, 2010). The combination of ipilimumab with nivolumab has been reported to result in improved responses in advanced melanoma, including decreased time to response, increased number of responses, improved depth and duration of responses, and increased PFS and OS compared to single agent ipilimumab (Wolchok *et al.*, 2013).

The combination is being evaluated in other disease settings typically with 3 mg/kg nivolumab and 1 mg/kg ipilimumab every 3 weeks for 4 induction doses.

2.3 Other Agents

2.3.1 Prednisone

Prednisone is a synthetic adrenocortical steroid drug with predominantly corticosteroid properties (Rayos™ package insert, 2012). Naturally occurring corticosteroids such as hydrocortisone and cortisone, which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs, such as prednisone, are primarily used for their potent anti-inflammatory effects in disorders of many organ systems. Corticosteroids, such as prednisone, cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli. Some of these properties reproduce the physiological actions of endogenous glucocorticosteroids, but others do not necessarily reflect any of the adrenal hormones' normal functions and are seen only after administration of large therapeutic doses of the drug. The pharmacological effects of prednisone which are due to its corticosteroid properties include: promotion of gluconeogenesis; increased deposition of glycogen in the liver; inhibition of the utilization of glucose; anti-insulin activity; increased catabolism of protein; increased lipolysis; stimulation of fat synthesis and storage; increased glomerular filtration rate and resulting increase in urinary excretion of urate (creatinine excretion remains unchanged); and increased calcium excretion. Depressed production of

eosinophils and lymphocytes occurs, but erythropoiesis and production of polymorphonuclear leukocytes are stimulated. Inflammatory processes (edema, fibrin deposition, capillary dilatation, migration of leukocytes and phagocytosis) and the later stages of wound healing (capillary proliferation, deposition of collagen, cicatrization) are inhibited. For more information, see the package inserts for Rayos™ (2012) or PrediSONE™ (2012)

2.3.2 Tacrolimus

Tacrolimus, previously known as FK506, is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis* (Prograf® package insert, 2018). Tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin (a ubiquitous mammalian intracellular enzyme) is then formed, after which the phosphatase activity of calcineurin is inhibited. Such inhibition prevents the dephosphorylation and translocation of various factors such as the nuclear factor of activated T-cells (NF-AT), and nuclear factor kappa-light-chain enhancer of activated B-cells (NF-κB). Tacrolimus inhibits the expression and/or production of several cytokines that include interleukin (IL)-1 beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, gamma interferon, tumor necrosis factor-alpha, and granulocyte macrophage colony stimulating factor (GMCF). Tacrolimus also inhibits IL-2 receptor expression and nitric oxide release, induces apoptosis and production of transforming growth factor beta that can lead to immunosuppressive activity. The net result is the inhibition of T-lymphocyte activation and proliferation as well as T-helper-cell-dependent B-cell response (*i.e.*, immunosuppression). For more information, see the Prograf® package insert.

2.4 Rationale

Activating anti-tumor immunity through blockade of the pathway mediated by the interaction between PD-1 and its primary ligands, PD-L1 and PD-L2, has demonstrated efficacy in multiple tumor types (Lipson *et al.*, 2015). However, there is a paucity of data about the safety and efficacy of anti-PD-1 in SOTRs. The same is true of agents blocking another immune checkpoint molecule, CTLA-4, such as ipilimumab. Further, little is known about the impact of combining immune checkpoint inhibitors with medications used to prevent allograft rejection on rates of tumor regression and allograft loss. These unmet needs have arisen over the last few years as clinical trials testing the above-referenced drugs have excluded SOTRs. This protocol aims to test the safety, tolerability, and efficacy of an anti-allograft-rejection regimen combined with nivolumab (anti-PD-1) +/- ipilimumab (anti-CTLA-4) in kidney transplant recipients with selected advanced cancers for whom standard anti-neoplastic treatment options would be insufficient.

The cases described in Table 1 illustrate two important concepts that underpin the current study. First, anti-PD-1 can be effective against malignancies arising in the setting of long-term immunosuppression. This efficacy signal provides a clear rationale for administration of anti-PD-1 to treat SOTRs with advanced cancer for whom standard treatment options would be insufficient. Second, the PD-1 pathway is critical in maintaining allograft tolerance in humans. It is for this reason that only patients with a transplanted kidney, generally considered a “life-enhancing” rather than “life-sustaining” organ, will be included in the proposed study.

The first published report of a PD-1 inhibitor administered to a kidney transplant recipient involved a 57-year-old woman who received a kidney allograft from a deceased donor in 1989 (Lipson *et al.*, 2016). The patient was maintained on standard long-term immunosuppression, including cyclosporine and prednisone. In 2014, she presented with metastatic cutaneous squamous cell carcinoma and, after progressing through two lines of therapy, received pembrolizumab (anti-PD-1). Two months after initiation of anti-PD-1, the patient developed acute allograft rejection. Despite administration of high-dose glucocorticoids, the patient's transplanted kidney did not recover. Histologic and immunohistochemical evaluation of the explanted kidney demonstrated changes consistent with advanced cell-mediated rather than antibody-mediated rejection (Figure 1).

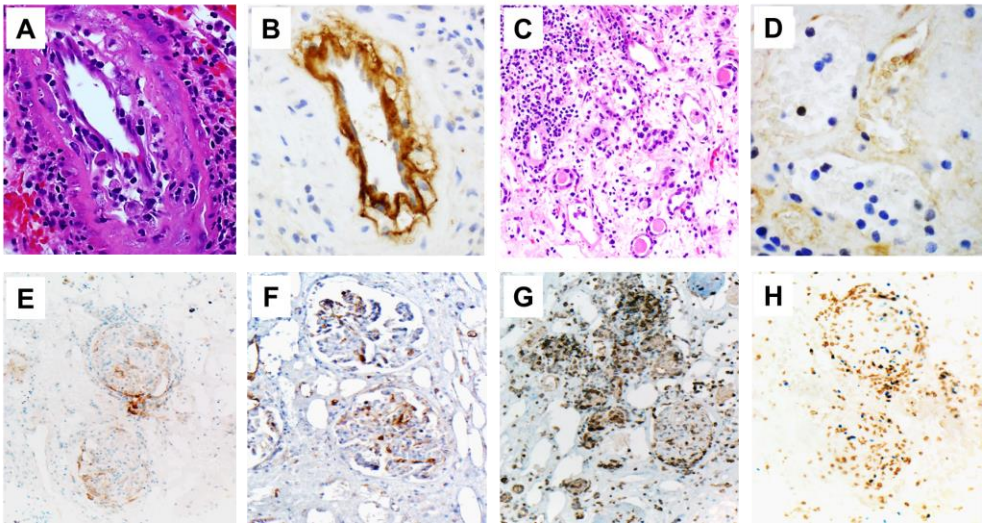


Figure 1. Explanted renal allograft showing evidence of rejection and expression of PD-1 pathway molecules after administration of PD-1 antibody.
A: Hematoxylin and eosin (H&E) staining of arteries showing intimal arteritis and focal intimal foam cells, consistent with chronic vasculopathy in the allograft. **B:** Artery endothelium showing strong immunostaining for C4d (a product of the classical complement pathway). **C:** H&E staining showing glomerulitis, severe tubular loss, tubulitis, interstitial edema, and interstitial inflammation. **D:** Peritubular capillaries showing capillaritis but negative C4d immunostaining, which, along with a lack of serum HLA antibody, suggests an absence of anti-donor humoral activity and argues against a component of antibody-mediated rejection. **E and F:** Immunostaining for PD-L1 and PD-L2, respectively, show that these molecules are present on endothelial cells and infiltrating immune cells associated with glomeruli. **G:** Infiltrating T-cells expressing PD-1 are associated with cells expressing PD-L1 and PD-L2. **H:** Infiltrating immune cells are predominantly CD8-positive (brown) and are co-expressed with Ki-67 (blue), consistent with an activated cytotoxic T-cell phenotype.

Computed tomography (CT) scans performed 8 months after initiation of pembrolizumab revealed an 85% reduction in tumor burden according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Her response is ongoing (off-therapy) >3 years after having initiated pembrolizumab. The patient tolerates hemodialysis without unacceptable AEs. Her Eastern Cooperative Oncology Group (ECOG) performance status returned to 0.

Similarly, limited data are available regarding the impact of anti-CTLA-4 in SOTRs with advanced cancer. The first published report of a CTLA-4 pathway blocker (ipilimumab)

administered to kidney transplant recipients involved two patients with melanoma (Lipson *et al.*, 2014). Both patients experienced a partial response to therapy, one of which is ongoing at >6 years. Neither patient experienced allograft rejection as a consequence of anti-CTLA-4 administration. These cases and others suggest that blocking the CTLA-4 pathway in SOTRs with advanced melanoma may be an effective cancer treatment strategy, and perhaps less likely to trigger allograft rejection and loss than PD-1-pathway blockers (Morales *et al.*, 2015; Ranganath and Panella, 2015).

One important consideration for the proposed trial is balancing the potential safety concerns associated with immune checkpoint blockers with the potential benefits in this study population. The third most common cause of death among kidney transplant recipients is cancer (Rama and Grinyo, 2010). Thus, uncovering an effective anti-cancer strategy in this population—even at the cost of a functioning allograft—would have a profound impact on future practice. Because we are only including kidney transplant recipients, dialysis will be offered to patients in the case of allograft failure. Data from the United States Renal Data System (USRDS) suggest that survival for patients who start dialysis is approximately 10.5-11 years for patients aged 40-44 years and 5.5-5.7 years for those 60-64 years-of-age (Saran *et al.*, 2018). These data will be clearly explained to potential trial participants in the context of each patient's own risk of death from cancer.

The current study will illuminate the complex interactions between immune checkpoint molecules, allo-antigens, and cancer neoantigens, and provide critical insight into the contributions of immunoregulatory molecules in order to better understand how to selectively activate anti-tumor immunity while minimizing immune-related toxicities.

2.5 Correlative Studies Background

Correlative studies undertaken as part of this protocol will help elucidate the biology behind allograft rejection in the setting of immune checkpoint blockade, which may affect the design of future clinical trials for recipients of life-enhancing and life-sustaining transplanted organs including lung, heart, liver, and other organs.

2.5.1 Histopathological Analyses of Allograft in Setting of Rejection

Although the histopathological characteristics of allograft rejection in the general kidney transplant population have been well described, little is known about the features of allograft rejection in SOTRs receiving immune checkpoint blockade therapy. The rationale underlying this correlative analysis is based upon the need to uncouple the anti-tumor response from the anti-allograft response brought about by administration of anti-PD-1 therapy.

In the case described above (Lipson *et al.*, 2016), anti-allograft activity was thought to be T cell-mediated. Additionally, expression of PD-L1 was detected in both the tumor and the allograft, suggesting that the immunoregulatory pathway comprised of PD-1 and its ligands is active in both microenvironments. Thus, one approach to uncoupling anti-tumor and anti-allograft immuno-activation is to find immune checkpoints that are differentially expressed in the tumor and the kidney. To identify these pathways, immunostains for an extended array of

immunoactive markers including PD-L1, PD-1, PD-L2, LAG-3, TIM-3 and others will be performed.

2.5.2 Histopathological Analyses of Tumor

In addition to the analysis described above (interrogation of the tumor microenvironment to find immune checkpoints that are differentially expressed in the tumor and the kidney allograft), we are also interested in the histological characteristics of response in immunosuppressed patients (i.e., SOTRs). Thus, H&E stained slides of tumor (pre- and on-therapy) for each subject will be reviewed. IHC will be performed for both immune checkpoint molecules (PD-L1, PD-1, LAG-3) and immune cell subsets (CD3, CD4, CD8, and CD68).

2.5.3 Circulating dd-cfDNA

In the general kidney transplant population, the dd-cfDNA assay has been shown to be predictive of Banff Grade 1B and higher active acute cellular rejection, and of antibody-mediated rejection (Bloom *et al.*, 2017). However, the assay's utility in SOTRs receiving immune checkpoint blockade therapy is unknown. We hypothesize that an early sign of allograft rejection may allow for more rapid initiation of immunosuppression and avoidance of allograft loss. We plan to compare the ability of the dd-cfDNA assay to predict allograft rejection as measured by standard clinical metrics (see Section 7.2).

2.5.4 Serum and Peripheral Blood Mononuclear Cells (PBMCs)

We aim to analyze serum and PBMC to accomplish some or all of the following:

- Define new tumor antigens and their relevance to disease biology, and correlate antigen expression with immune responses and disease outcomes.
- Evaluate potential immune-related prognostic or treatment response indicators.
- Evaluate the causative mechanisms of immune-related toxicities in patients receiving cancer therapy with immune checkpoint blockade.
- Characterize factors and molecular pathways in the tumor immune microenvironment that lead to immune suppression, tolerance to tumor antigens, and cancer progression.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must be kidney transplant recipients with a functioning allograft who do not currently require dialysis.

3.1.2 Patients must have histologically or cytologically confirmed melanoma, basal cell carcinoma, Merkel cell carcinoma, cutaneous squamous cell carcinoma, or MSI-high cancers for which standard non-immunological medical, surgical, or radiation therapy would be insufficient (*i.e.*, patients who are not surgical candidates). This trial is not intended to provide therapy as a neoadjuvant approach.

3.1.3 Measurable disease as defined by RECIST 1.1 criteria, *i.e.*, at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, magnetic resonance imaging (MRI), or calipers by clinical exam is preferred, but not required. Patients with evaluable disease but no target lesions (*e.g.*, evaluable bone metastases) may be included after discussion with the Principal Investigator (PI). See Section 12 for detailed criteria.

3.1.4 Patients must have documentation, in consultation with the PI, that they received, refused, or were ineligible for the following non-immunologic therapies:

For patients with:	**Prior therapies include:**
BRAF-mutant melanoma	BRAF/MEK inhibitors
Merkel cell carcinoma	Platinum + VP-16
Basal cell carcinoma	Hedgehog pathway inhibitors
Cutaneous squamous cell carcinoma	Cetuximab
MSI colorectal carcinoma	FOLFOX

3.1.5 Patient's age must be ≥18 years. Because no dosing or AE data are currently available on the use of nivolumab and ipilimumab in kidney transplant recipients <18 years of age, children are excluded from this study, but may be eligible for future pediatric trials.

3.1.6 Patients must have ECOG performance status ≤2 (Karnofsky ≥60%), see Appendix A, Performance Status Criteria.

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

- leukocytes ≥2,000/mcL
- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL

- total bilirubin ≤1.5 × institutional upper limit of normal (ULN)
- AST(SGOT)/ALT(SGPT) ≤2.5 × institutional ULN
- serum creatinine ≤3 × ULN
  Note: patients with creatinine levels above 3 × ULN may be eligible after consultation with the study PI.

3.1.8 The effects of nivolumab and ipilimumab on the developing human fetus are unknown. For this reason, and because other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential (WOCBP) and men must agree to use adequate contraception (*e.g.*, hormonal or barrier methods of birth control, or abstinence) prior to study entry, for the duration of study participation, and for 31 weeks after the last dose of nivolumab or ipilimumab. Women who are not of childbearing potential (*i.e.*, who are postmenopausal or surgically sterile) as well as azoospermic men do not require contraception.

WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of beta-human chorionic gonadotropin [B-HCG]) during the screening period. Follow-up evaluations will include interval sexual/menstrual histories as needed.

Men who receive nivolumab or ipilimumab and are sexually active with WOCBP must use a contraceptive method with a failure rate of <1% per year for the duration of the study and for a period of 7 months after the last dose of nivolumab or ipilimumab.

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

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

3.1.9 Human immunodeficiency virus (HIV)-infected patients will be eligible for this trial if they are on effective antiretroviral regimens utilizing non-CYP-interactive agents and have an undetectable viral load.

If there is evidence of chronic hepatitis B virus (HBV) infection, HBV viral load must be undetectable on suppressive therapy, if indicated. If there is history of hepatitis C virus (HCV) infection, the patient must have been treated and have undetectable HCV viral load.

3.1.10 Patients must be able to understand and be willing to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients must not have received a liver, lung, heart, or pancreas transplant; or allogeneic stem cell transplant; or any kind of bone marrow transplant.

3.2.2 Patients must not be unwilling or unable to undergo dialysis.

3.2.3 Patients must not have prior evidence of HLA or non-HLA donor-specific antibodies (DSA). Patients with detectable DSA but negative dd-cfDNA may be eligible after consultation with the study PI.

3.2.4 Patients must not have a history of antibody- or cell-mediated allograft rejection within 3 months of study entry.

3.2.5 Patients must not have had chemotherapy or radiotherapy within 4 weeks of study entry or those who have not recovered from AEs due to agents administered more than 4 weeks earlier.

3.2.6 Patients must not have had prior treatment for their current cancer with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.

3.2.7 Patients must not be receiving any other investigational agents.

3.2.8 Patients must not have known central nervous system (CNS) metastases or leptomeningeal metastases because of poor prognosis and concerns regarding progressive neurologic dysfunction that would confound the evaluation of neurologic and other AEs. Patients with brain metastases are permitted to enroll if metastases have been treated and there is no MRI evidence of progression for 4 weeks after treatment is complete and no evidence of progression within 28 days prior to study entry.

3.2.9 Patients must not have a history of severe hypersensitivity reaction to any monoclonal antibody.

3.2.10 Patients must not have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to other agents used in study.

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

3.2.12 Pregnant women are excluded from this study because nivolumab and ipilimumab have the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for AEs in nursing infants secondary to treatment of the mother, breastfeeding should be discontinued if the mother is treated with nivolumab or ipilimumab. These potential risks may also apply to other agents used in this study.

3.2.13 Patients must not have active autoimmune disease, or history of autoimmune disease that might recur, which may affect vital organ function, and will only be eligible after consultation with the study PI.

This includes but is not limited to:

- immune-related neurologic disease,
- multiple sclerosis,
- autoimmune (demyelinating) neuropathy,
- Guillain-Barre (GB) syndrome,
- myasthenia gravis,
- systemic autoimmune diseases such as systemic lupus erythematosus (SLE),
- connective tissue diseases,
- scleroderma,
- inflammatory bowel disease (IBD; *e.g.*, ulcerative colitis or Crohn's disease),
- rheumatoid arthritis, and
- Sjögren's syndrome.

3.2.14 Patients must not have had evidence of active or acute diverticulitis, intra-abdominal abscess, GI obstruction and abdominal carcinomatosis which are known risk factors for bowel perforation should be evaluated for the potential need for additional treatment before coming on study.

3.3 Inclusion of Women and Minorities

National Institutes of Health (NIH) policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

Women and minorities will have the same opportunities as all others to participate in this study. This study is race and gender neutral. Subject selection is based solely on meeting the diagnosis specific eligibility criteria for this study. All patients aged 18 or older presenting to one of the above-referenced centers with an appropriate diagnosis (see inclusion criteria) will be assessed

for eligibility for the study. Although demographic distributions vary by institution, the gender and racial/ethnic composition of the patients seen at the Johns Hopkins Oncology Center is representative of the population of the Baltimore, MD metropolitan area. Specifically, in the past 5 years, patients enrolled on clinical trials of the Oncology program have consisted of approximately 50% male, 50% female, 30% African American, 5% Hispanic and 5% Asian American. With the exception of patients with skin cancers which primarily affect light-skinned individuals, we anticipate that the patient population from Hopkins will reflect the above estimates.

See Section 9.2 for more information about accrual of women and minorities.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to Oncology Patient Enrollment Network (OPEN), Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR: MD, DO, or international equivalent,
- NPIVR: advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD),
- AP: clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System [RUMS], OPEN, Rave,),
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
- Associate Basic (AB): individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster,
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN,
- Act as the site-protocol Principal Investigator (PI) on the IRB approval, and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance).

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 Site Registration

This study is supported by the NCI CTSU.

IRB Approval

Sites participating with the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol PI (i.e., the investigator on the IRB/REB approval) must meet the following five criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status,
- Rostered at the site on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating roster,
- If using NCI CIRB, rostered on the NCI CIRB Signatory record,
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile, and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federalwide Assurance (FWA) number,
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization, and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Regulatory Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Participating Organization on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on *Protocols* in the upper left of your screen
  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select *LAO-MD017*, and protocol number *10214*,
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

4.2.2 Requirements for Protocol 10214 Site Registration

- A Site initiation visit (SIV) is required for each participating site prior to activation. The local site PI must participate on the call as well as their research nurse, study coordinator, and pharmacist. To schedule a SIV, please email the Protocol Liaison and crocc@jhmi.edu and reference the protocol in the subject line of the email.
- Specimen Tracking System Training Requirement:
  - All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
  - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
  - The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. However, new versions of the Specimen Tracking System may require new training.
  - This training will need to be completed before the first patient enrollment at a given site.
  - Peter Clark and Diana Vulih are the main points of contact at Theradex for the training (PClark@theradex.com and DVulih@theradex.com, Theradex phone: 609-799-7580).

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal, log on to the CTSU members' website → Regulatory → Regulatory Submission.

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

4.2.4 Checking Site Registration Status

You can verify your site registration status on the members' section of the CTSU website.

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

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

4.3 Patient Registration

4.3.1 OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account.
- To perform enrollments or request slot reservations: Be on an LPO roster, ETCTN Corresponding roster, or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- If a DTL is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

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

- Patient has met all eligibility criteria within the protocol stated timeframes, and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with the registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

4.3.2 OPEN/IWRS Questions

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

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 609-619-7862 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.3.3 Patient Enrollment Instructions

This study will use the ETCTN Specimen Tracking System (STS).

- All biospecimens collected for this trial must be submitted using the ETCTN Specimen Tracking System (STS) unless otherwise noted.
- The system is accessed through special Rave user roles: "CRA Specimen Tracking" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the Biorepository.
- Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website under the Rave/DQP tab.
- **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Detailed instructions can be found in Section 5.3.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 28 days. Issues that would cause treatment delays should be discussed with the study PI. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Contact should be notified of cancellations as soon as possible.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Summary Table for Specimen Collection

Time Point	Specimen	Send Specimens To:
Archival		
	• Formalin-fixed paraffin-embedded (FFPE) tumor tissue block[1] (if available)	Tumor microenvironment Core at Johns Hopkins University
Baseline		
	• 2-3 punch biopsies of tumor tissue, at least 3-4 mm in size or 2-3 passes with a 1 cm 16-18-gauge core needle (if no archival tissue available) **(optional)**	Tumor microenvironment Core at Johns Hopkins University
	• ~20 mL whole blood in two SST tubes for serum analyses • ~100 mL whole blood in 10 CPT tubes for PBMC analyses	Topalian lab at Johns Hopkins University
Week 4		
	• 2-3 punch biopsies of tumor tissue, at least 3-4 mm in size or 2-3 passes with a 1 cm 16-18-gauge core needle **(optional)**	Tumor microenvironment Core at Johns Hopkins University
	• ~20 mL whole blood in two SST tubes for serum analyses • ~100 mL whole blood in 10 CPT tubes for PBMC analyses	Topalian lab at Johns Hopkins University
Immune-mediated adverse reaction (including allograft rejection)		
	• ~20 mL whole blood in two SST tubes for serum analyses • ~100 mL whole blood in 10 CPT tubes for PBMC analyses	Topalian lab at Johns Hopkins University
Allograft rejection		
	• One ~1 cm, ~18-gauge core needle kidney biopsy sample plus biopsy material leftover after standard-of-care analysis • 2-3 punch biopsies of tumor tissue, at least 3-4 mm in size or 2-3 passes with a 1 cm 16-18-gauge core needle **(optional)**	Tumor microenvironment Core at Johns Hopkins University

Time Point	Specimen	Send Specimens To:
Disease progression		
	• ~20 mL whole blood in two SST tubes for serum analyses • ~100 mL whole blood in 10 CPT tubes for PBMC analyses	Topalian lab at Johns Hopkins University
[1] For archival tissue, a copy of the corresponding anatomic pathology report must be sent with the tissue and uploaded to Rave. [2] For new biopsies, a copy of the radiology and operative reports from the tissue removal procedure must be sent with the tissue. When completed, upload the corresponding pathology reports to Rave.		

5.2 Specimen Procurement Kits and Scheduling

5.2.1 Specimen Shipping Kits

5.2.1.1 SST tubes and CPT tubes

Vacutainer SST and CPT tubes for serum and PBMC collection should be obtained from commercial sources.

5.2.2 Scheduling of Specimen Collections

Please adhere to the following guidelines when scheduling procedures to collect tissue:
- Tumor tissue specimens collected during biopsy procedures should be fixed (submerged) in formalin.
- Tissue can be stored at room temperature in formalin and should be shipped within approximately 72 hours for next-day delivery Monday through Friday.

Please adhere to the following guidelines when scheduling blood collection procedures:
- Fresh blood specimens may be collected Monday through Friday.
- Specimens collected Monday through Thursday should be shipped the same day as collection and shipped for next-day delivery Monday through Friday.
- Blood specimens collected on Friday should be processed as described in Section 5.4.5 and shipped frozen on dry ice within approximately a week following collection.

5.3 Specimen Tracking System Instructions

5.3.1 Specimen Tracking System Overview and Enrollment Instructions

For the ETCTN STS, the following information will be requested:
- Protocol Number
- Investigator Identification
  - Institution and affiliate name
  - Investigator's name

- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 3.
- Additional Requirements:
  - Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the portion of this protocol that uses the ETCTN Specimen Tracking System. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID), collection date, block number, and the IWRS-assigned UPID and patient study ID for this trial. For newly acquired biopsies, the radiology and operative report(s) must also be uploaded into Rave. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, initials, medical record number, and patient contact information from the institutional pathology report prior to submission.**

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tacking System, please contact the Theradex Help Desk at CTMSSupport@theradex.com.

A shipping manifest **must** be included with all sample submissions.

5.3.2 Specimen Labeling

5.3.2.1 Blood Specimen Labels

Include the following on blood specimens (including whole blood and frozen, processed blood products – like serum and plasma):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, blood, serum)
- Collection date and time (to be added by hand)

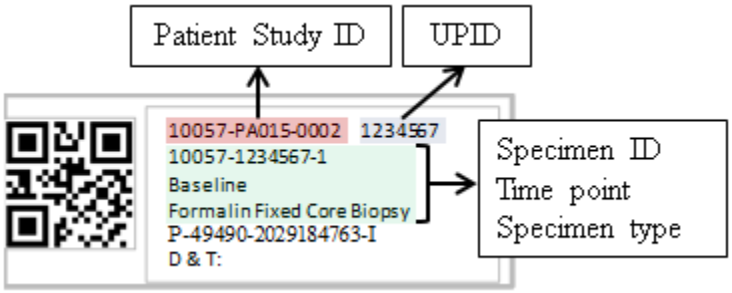
5.3.2.2 Tissue Specimen Labels

Include the following on all tissue specimens or containers (*e.g.*, formalin jar):

- Patient Study ID
- UPID
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, FFPE Block, Formalin Fixed Tissue, Fresh Tissue in Media, *etc.*)
- Tissue type (P for primary, M for metastatic, or N for normal)
- Surgical pathology ID (SPID) number
- Block number from the corresponding pathology report (archival only)
- Collection date and time (to be added by hand)

5.3.2.3 Example of Specimen Label

The following image is an example of a tissue specimen label printed on a standard Avery label that is 1 inch high and 2.625 inches wide.



The QR code in the above example is for the Specimen ID shown on the second line.

NOTE: The QR code label is currently under development at Theradex as of 31-Aug-2018; therefore, labels generated by the STS for this study may not include a QR code.

The second line item from the end includes four data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (e.g., for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. The last alpha-numeric code is protocol specific and is only included if the protocol requires an additional special code classification

The last line on the example label is for the handwritten date and optional time.

5.3.3 Overview of Process at Treating Site

5.3.3.1 OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN) system. OPEN communicates automatically with the Interactive Web Response System (IWRS) which handles identifier assignments, any study randomization, and any prescribed slot assignments. If specimen analysis is required to determine eligibility, the protocol will be setup with multi-step registration.

Registration without eligibility specimen analysis:

1. Site enters registration data into OPEN during one or more steps.
2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends all applicable registration data directly to Rave at the end of the final registration step.

Any data entry errors made during enrollment should be corrected in Rave.

5.3.3.2 Rave Specimen Tracking Process Steps

Step 1: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial clinical specimen data:

- **Specimen Tracking Enrollment** CRF: Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using report in EDC and collect specimen.

- Label specimen containers and write the collection date and time on each label.
- After collection, store labeled specimens as described in Section 5.4.
- Apply an extra specimen label to <u>each</u> report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Molecular Reports (up to four), Surgical (or Operative) reports and Pathology Verification form (when applicable). Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen). Uploaded reports should have protected health information (PHI) data like name, mailing address, medical record number or social security number (SSN) redacted. Do not redact SPID, block number or relevant dates, and include the UPID and patient ID on each document.

Step 3: Complete specimen data entry.

- **Specimen Transmittal** Form: Enter Collection date and time and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- **Shipping Status** CRF: Enter tracking number, your contact information, recipient, number of containers and ship date once for the 1st specimen in a shipment.
- **Copy Shipping** CRF: Select additional specimens to add to an existing shipment referenced by the tracking number.

Step 5: Print shipping list report and prepare to ship.
- Print two copies of the shipping list, one to provide in the box, the other for your own records.
- Print pathology or other required reports to include in the box. Be sure the printed copy includes the specimen label.

Step 6: Send email notification.
- For only one of the specimens in the shipment, click "Send Email Alert" checkbox on the **Shipping Status** CRF to email recipient.

Step 7: Ship the specimen(s).

5.4 Specimen Collection

5.4.1 General Methods

5.4.1.1 Tissue / tumor biopsies

Biopsies of tumor or other tissue should provide sufficient material for histologic examination of tissue architecture (i.e., core or punch biopsy rather than fine needle aspiration). Biopsy technique should be determined by the investigator based on the following guidance.
- Core needle sampling is frequently the preferred technique for obtaining tissue from lymph nodes and other internal tumors. It is recommended that at least **2-3 core biopsies,** 16-18 gauge in diameter and at least 1 cm in length, are obtained. Specimens should be placed immediately into buffered formalin and shipped to the Tumor Microenvironment Core at Johns Hopkins University (see Section 5.5).
- Punch biopsy sampling is frequently the preferred technique for obtaining tissue from cutaneous lesions and other externally accessible tumors. It is recommended that at least **2-3 biopsies,** each 3-4mm in diameter are obtained. Specimens should be placed immediately into buffered formalin and shipped to the Tumor Microenvironment Core at Johns Hopkins University (see Section 5.5).
- Endoscopic approaches are permitted if necessary in the opinion of the investigator.
- Excisional biopsies are permitted if necessary in the opinion of the investigator.
- Imaging-guided (e.g., ultrasound, CT) procedures are permitted if necessary in the opinion of the investigator.

5.4.1.2 Whole Blood

Whole blood should be collected according to local institutional standards. When collecting blood for multiple purposes, blood for serum analysis (SST tubes) should be collected first, then

blood for PBMC analysis (CPT tubes), and finally blood for dd-cfDNA (Cell-Free DNA BCT® tubes).

5.4.2 Archival Tumor Biopsy

If previously-collected formalin-fixed paraffin-embedded (FFPE) tissue will be submitted, then the following criteria must be met:

- Tissue must have been collected within 12 weeks prior to registration
- Formalin-fixed paraffin-embedded tumor tissue block(s) must be submitted. The optimal block is at least 70% tumor. Specimen size requirement is as follows:
  - Surface area: 25 mm^2 is optimal. Minimum is 5 mm^2.
  - Volume: 1 mm^3 optimal. Minimum volume is 0.2 mm^3.

If an existing block cannot be submitted, the following are requested, if available:

- One H&E slide,
- Five 4 µm unstained air-dried charged or uncharged slides

See Section 5.3.1 for labeling instructions.

5.4.3 Kidney Biopsy

If a patient shows markers of allograft rejection (see Section 7.2), a biopsy of their renal allograft should be obtained immediately. Patients may refuse biopsy and still remain on study. The biopsy should be performed according to local institutional standards. In addition, one ~1 cm, ~18-gauge core needle research biopsy sample should be procured, if possible. The research core sample plus biopsy material leftover after standard-of-care analysis should be provided to the Johns Hopkins team for research purposes. After collection, specimens will be formalin-fixed and paraffin-embedded per standard institutional protocol. Thereafter, samples should be sent as follows:

One H&E stained slide AND one unstained slide from every FFPE block from the standard-of-care surgical pathology specimens, or FFPE blocks if either of the above is not available. In addition, the research core sample should be embedded in paraffin and sent to the Tumor Microenvironment Core at Johns Hopkins University (see Section 5.5, below).

All slides and FFPE blocks can be sent at ambient temperature. Please ensure that each slide is labeled with the surgical pathology case number as well as the part number and block designation (number and/or letter, *e.g.*, 1A, 2A) to ensure that each slide can be matched to a particular block as outlined in the gross description on the pathology report.

See Section 5.3.1 for additional labelling instructions.

5.4.4 Fresh Tumor Biopsy

Patients will undergo optional baseline and on-treatment biopsies of tumor per the study calendar (See Section 5.1 and Section 11). The on-treatment biopsies should be obtained around Week 4,

and at the time of allograft rejection. The biopsy obtained at the time of allograft rejection should be obtained at the same time as the standard-of-care renal biopsy. Biopsy site(s), number of samples, and technique will be determined by the investigator. In general, the following techniques will yield tissue sufficient for meaningful correlative analysis:

- 2-3 punch biopsies of at least 3-4 mm in size or
- 2-3 passes with a 1 cm 16-18-gauge core needle

After collection, specimens will be formalin fixed and paraffin embedded per standard institutional protocol. Thereafter, samples should be sent as follows:

- One H&E stained slide AND 5 unstained slides from every FFPE block in the surgical pathology specimen, or FFPE blocks if either of the above is not available.

All slides and FFPE blocks can be sent at ambient temperature. Please ensure that each slide is labeled with the surgical pathology case number as well as the part number and block designation (number and/or letter, e.g. 1A, 2A) to ensure that each slide can be matched to a particular block as outlined in the gross description on the pathology report.

Sites should make every effort to either procure an archival specimen or to obtain a new biopsy prior to starting therapy but it is not an absolute requirement for joining the trial. If a biopsy will compromise the evaluability of a lesion for response (RECIST v1.1), the biopsy may be omitted.

See Section 5.3.1 for additional labelling instructions.

5.4.5 Blood Collection

5.4.5.1 Collection of Blood in SST Tubes

1. Label two 10 mL SST tubes according to Section 5.3.1.
2. Collect 10 mL of blood into each pre-labeled tube and gently invert to mix. **Note:** blood must be thoroughly mixed to ensure preservation of specimen.
3. If collection occurs Monday through Thursday, samples should be shipped overnight at room temperature. Specimens should be labeled according to Section 5.3.1.

If collected on a Friday, within 2 hours after collection, SST tubes should be processed as follows:

1. Centrifuge tubes at 25 °C for 10 minutes at 1290 × g in a swinging-bucket rotor. If using a fixed-angle rotor, centrifuge for 15 minutes.
2. Remove the hemogard closure by twisting and pulling simultaneously, until the tube stopper is loosened. Then, lift the closure off of the tube.
3. Transfer serum to a suitable sterile tube.
4. Fill up to four 1.8-mL cryovials, with ~1.2 to 1.6 mL of serum each. Dispense any additional serum in 3.6-mL cryovials.
5. Serum aliquots should be stored at -80 °C prior to shipping
6. Serum aliquots should be shipped frozen on dry ice. Specimens should be labeled according to Section 5.3.1.

5.4.5.2 Collection of Blood in CPT Tubes

1. Label 10 CPT tubes according to Section 5.3.1.
2. Collect 10 mL of blood into each pre-labeled tube and gently invert to mix.
3. If collection occurs Monday through Thursday, samples should be shipped overnight at room temperature. Specimens should be labeled according to Section 5.3.1.

If collected on a Friday, within 2-6 hours after collection, CPT tubes should be processed as follows:

1. Centrifuge tubes at 25 °C for 30 minutes at 1500 × g.
2. Gently invert tubes 5-10 times to resuspend the cells in the plasma, and then transfer entire plasma contents into a 50 mL conical tube. Avoid transferring red blood cells.
3. Add room temperature RPMI 1640 (Life Technologies) for a 1:3 dilution (Usually up to 45 mL for every two CPT tubes).
4. Spin tubes at 1500 rpm (470 × g) for 10 minutes at room temperature.
5. Aspirate off the supernatant without disturbing the cell pellet.
6. Resuspend in appropriate volume of RPMI 1640 and combine tubes to count. In general, resuspend combined cells in 5 mL RPMI per CPT, up to a total volume of 40 mL, (*e.g.*, for 10 CPT tubes, combine cells in a total volume of 40 mL).
7. Count cells and check platelet abundance.
    a. If there are ≤20 per high-power field (400×): spin at 1500 rpm for 10 minutes.
    b. If there are >20 per high-power field (400×): spin at 1000-1200 rpm for 10 minutes, then re-count. Expect some cell loss due to the slow spin.
8. Freeze cells in 90% FBS + 10% DMSO. There should be between 5×10^6 and 3×10^7 cells/mL per cryovial tube. Freeze at least 3 vials and up to 10 vials.
9. Store at -80°C prior to shipping.
10. PBMC samples should be shipped frozen on dry ice. Specimens should be labeled according to Section 5.3.1.

5.5 Shipping of Specimens from Clinical Site to Other Laboratories

5.5.1 Kidney and Tumor Biopsies

Kidney and tumor FFPE blocks or tumor tissue slides should be shipped at ambient temperature via overnight delivery to be received Monday through Friday to:

Janis Taube, M.D.
c/o Julie Stein, M.D.
Johns Hopkins University School of Medicine
Department of Dermatopathology
600 N. Wolfe Street – Blalock 907
Baltimore, MD 21287
Phone: +01-410-955-3484

5.5.2 Blood Samples for Serum and PBMC Analysis

Samples collected Monday through Thursday should be shipped at room temperature on the day of collection via overnight delivery to be received Monday through Friday. Samples collected on a Friday should be processed as described in Section 5.4.5 and shipped frozen on dry ice within approximately a week following collection.

Ship specimens to:

Tracee McMiller
Manager, Topalian Lab
Johns Hopkins Medicine
CRB II, Room 528
1550 Orleans Street
Baltimore, MD 21287
Phone: 410-502-8220
Fax: 410-502-1958

Send a 24-hour email notification to the Topalian lab's e-mail:

TopalianLab@lists.johnshopkins.edu

The subject line should specify "Study 10214 patient sample shipment," and the body of the e-mail should specify the patient ID(s) and date and time of draw.

5.6 Biomarker Plan

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Specimens and Time Points	Laboratory Performing Assay
1	Histopathological analysis of allograft in setting of rejection	Immuno-histochemistry CLIA: Y[a] / N[b]	Exploratory To characterize molecular mechanisms and pathogenesis of anti-PD-1-mediated allograft rejection.	M	FFPE kidney allograft biopsy After analysis of tissue from standard-of-care allograft biopsy at the time of rejection	Tumor microenvironment Core at Johns Hopkins University Lab PIs: Dr. Janis Taube and Dr. Serena Bagnasco PI emails: jtaube1@jhmi.edu sbagnas1@jhmi.edu
2	Histopathological analysis of tumor	Immuno-histochemistry CLIA: Y[a] / N[b]	Exploratory To characterize immunological changes in the tumor microenvironment (*e.g.*, changes in T-cell subset populations or expression of immune checkpoint molecules).	O	FFPE tumor biopsy block or 1 H&E and 10 unstained slides. Baseline, at week 4 ±7 days of treatment, and at the time of allograft rejection.	Tumor microenvironment Core at Johns Hopkins University Lab PIs: Dr. Janis Taube and Dr. Serena Bagnasco PI emails: jtaube1@jhmi.edu sbagnas1@jhmi.edu
3	Circulating donor-derived cell-free DNA (dd-cfDNA)	PCR-based CLIA: Y	Exploratory To investigate the utility of dd-cfDNA as an indicator of kidney injury in the study population	M	Whole blood Baseline (prior to immune-suppression adjustment), every 2 weeks for the first 12 weeks of nivolumab or nivolumab/ ipilimumab therapy, then every 4 weeks during every cycle after that, and in case of an immune-mediated adverse reaction or disease progression	CareDx, Inc., Brisbane, CA
4	Serum and PBMCs	Various	Exploratory Please see section 2.5.4 for details of analysis	M	Whole blood Baseline, Week 4, at time of progression, and in case of immune-mediated adverse reaction	Topalian lab at Johns Hopkins Lab PI: Dr. Suzanne Topalian PI email: stopali1@jhmi.edu

a: The lab doing immunostains for CD3, CD4, CD8, CD20, FoxP3 CD68, and CD163 is CLIA certified.
b: The lab doing immunostains for PD-L1, PD-1, PD-L2, and LAG-3 is not CLIA certified.

5.7 Exploratory/Ancillary Correlative Studies

5.7.1 Histopathological Analysis of Allograft in Setting of Rejection

5.7.1.1 Specimen Receipt and Processing at the Tumor microenvironment Core at Johns Hopkins University

Immunostains for CD3, CD4, CD8, CD20, FoxP3 CD68, and CD163 will be performed in a CLIA-certified lab using standard automated methods. Additional immunostains for an extended array of immunoactive markers including PD-L1, PD-1, PD-L2, and LAG-3 (Lipson *et al.*, 2017; Sunshine *et al.*, 2017), will be performed by the Tumor Microenvironment Core Laboratory at Johns Hopkins Hospital (JHH) as previously described (Taube *et al.*, 2014; Taube *et al.*, 2015; Yanik *et al.*, 2017). Specimens will be considered PD-L1-positive for either tumor cell or immune cell staining if membranous staining is present in more than 5% of the neoplastic cells or 5% of the immune cells, respectively (Taube, *et al.*, 2012).

5.7.1.2 Site Performing Correlative Study

Assays will be performed in the laboratories of the Johns Hopkins Department of Pathology by Dr. Serena Bagnasco and Dr. Janis Taube. Dr. Bagnasco is an Associate Professor of Pathology with expertise in kidney transplant pathology. She serves as director of the Hopkins Renal Pathology Service. Dr. Taube is an Associate Professor of Dermatology and Pathology and serves as the Director of the Division of Dermatopathology and as the Assistant Director of the Dermato-immunology Laboratory at the Johns Hopkins School of Medicine.

5.7.2 Histopathological Analysis of Tumor

5.7.2.1 Specimen Receipt and Processing at the Tumor microenvironment Core at Johns Hopkins University

Immunostains for CD3, CD4, CD8, CD20, FoxP3 CD68, and CD163 will be performed in a CLIA-certified lab using standard automated methods. Additional immunostains for an extended array of immunoactive markers including PD-L1, PD-1, PD-L2, and LAG-3 (Lipson *et al.*, 2017; Sunshine *et al.*, 2017), will be performed by the Tumor Microenvironment Core Laboratory at JHH as previously described (Taube *et al.*, 2014; Taube *et al.*, 2015; Yanik *et al.*, 2017). Specimens will be considered PD-L1-positive for either tumor cell or immune cell staining if membranous staining is present in more than 5% of the neoplastic cells or 5% of the immune cells, respectively (Taube, *et al.*, 2012).

5.7.2.2 Site Performing Correlative Study

Assays will be performed in the laboratories of the Johns Hopkins Department of Pathology by Dr. Janis Taube. Dr. Taube is an Associate Professor of Dermatology and Pathology and serves as the Director of the Division of Dermatopathology and as the Assistant Director of the Dermato-immunology Laboratory at the Johns Hopkins School of Medicine.

5.7.3 Circulating donor-derived cell-free DNA (dd-cfDNA)

5.7.3.1 Site Performing Correlative Study

CareDx, Inc., Brisbane, California (CLIA certified) will perform the study. Please refer to Appendix E for additional information regarding collection.

5.7.4 Serum and PBMC Analysis

5.7.4.1 Specimen Receipt and Processing at the Topalian Lab at Johns Hopkins University

Upon receipt, serum aliquots will be stored at -80 °C and PBMC samples will be stored in liquid nitrogen.

5.7.4.2 Site Performing Correlative Study

The laboratory of Dr. Suzanne Topalian at Johns Hopkins University will perform the assays. Samples will be analyzed to:

- Define new tumor antigens and their relevance to disease biology, and correlate antigen expression with immune responses and disease outcomes.
- Evaluate potential immune-related prognostic or treatment response indicators.
- Evaluate the causative mechanisms of immune-related toxicities in patients receiving cancer therapy with immune checkpoint blockade.
- Characterize factors and molecular pathways in the tumor immune microenvironment that lead to immune suppression, tolerance to tumor antigens, and cancer progression.

6. TREATMENT PLAN

6.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported AEs and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Prior to beginning nivolumab therapy, patients will have their immunosuppression medication adjusted to the following regimen:

Immunosuppression Regimen Description					
Agent	**Premedications and Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Tacrolimus	None	Dosed to achieve goal trough level of 2-5 ng/mL	PO	Twice daily	No more than 28 days
Prednisone	None	5 mg*	PO	Daily	
*Patients may remain on higher-dose prednisone if already taking. PO=orally					

Patients receiving the above protocol-specified immunosuppression regimen may participate on the study. These patients can register any time prior to starting the study immunotherapy regimen below.

The patient will be requested to maintain a medication diary of each dose of medication (see Appendix C). The medication diary will be returned to clinic staff for review. Once patients are on a stable immunosuppression regimen and the tacrolimus trough level (2-5 ng/mL) is reached, they may begin nivolumab therapy:

Nivolumab Regimen Description					
Agent	**Premedications and Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Nivolumab	None, except in the case of an infusion reaction (see Section 6.9)	480 mg	IV infusion over ~30 minutes	Day 1, Week 1	4 weeks
Tacrolimus*	None	Dosed to achieve goal trough level of 2-5 ng/mL**	PO	Twice daily	
Prednisone*	None	5 mg***	PO	Daily	
* Patients who experience PD on this regimen may reduce or discontinue the use of tacrolimus and prednisone as detailed in section 6.2.					

Nivolumab Regimen Description					
Agent	**Premedications and Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
** Tacrolimus trough levels should be monitored each cycle while receiving Nivolumab in order to maintain 2-5 ng/ml. *** Patients may remain on higher-dose prednisone if already taking. IV=intravenous, PD=progressive disease, PO=orally					

Patients whose tacrolimus trough level is not yet within the protocol-specified range of 2-5 ng/ml may start nivolumab after consultation with the Principal Investigator.

Patients will be assessed clinically every ~2 weeks and radiographically every ~8 weeks.

6.1.1 Nivolumab

Once patients have finished immunosuppression adjustment, they may begin nivolumab treatment. Nivolumab will be given by IV infusion every 4 weeks (+7 days) at a dose of 480 mg for 24 Cycles (96 weeks).

There will be no dose modifications allowed.

Nivolumab is to be administered as an approximately 30-minute IV infusion, using a volumetric pump with a 0.2-1.2 micron in-line filter. The drug can be diluted with 0.9% normal saline for delivery, but the total infusion volume should not exceed 160 mL. For patients weighing less than 40 kg, the total infusion volume must not exceed 4 mL per kg of patient weight. Nivolumab is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

6.1.2 Prednisone

Patients will take 5 mg prednisone PO once each day. Patients may remain on higher-dose (up to 10 mg daily) prednisone if already taking prior to study entry. Prednisone should be taken per the package insert/SOC instructions with or without food. Do not take another dose if vomiting occurs. A missed dose may be taken if more than 12 hours to the next expected dose. Prednisone should be taken in the morning approximately the same time each day and prior to infusion.

6.1.3 Tacrolimus

Tacrolimus will be dosed to achieve a trough level between 2-5 ng/mL. Higher doses are permitted if required for maintenance of the allograft. Patients who require tacrolimus trough levels >5-8 ng/mL should be discussed with the overall study PI. Sublingual tacrolimus (instead of oral) may be administered to patients if needed (*e.g.*, nausea/vomiting, inability to swallow, *etc.*). Tacrolimus should be taken approximately the same time each day and prior to infusion. Patients should be instructed not to eat 2 hours before taking tacrolimus and not to eat for 1 hour after taking tacrolimus. Missed doses can be taken within 6 hours of the expected dosing time. Vomited doses should not be made up.

Adjustments to tacrolimus dosing should be made under the guidance of each institution's transplant nephrologist. Typically, a reliable tacrolimus trough level can be measured within 2-4 days of starting the therapy. Many investigators recheck the trough level (prior to morning tacrolimus dose, 12 hours from the evening dose) 3 days later to ensure stability.

No formal washout period is required for patients who were previously taking other immunosuppressive agents (*e.g.*, sirolimus, mycophenolate mofetil) at the time of screening. The period of time that will be necessary to ensure that the tacrolimus level is correct will provide sufficient time to allow previous immunosuppressive agents to "wash out."

During the study, serum tacrolimus levels should be checked approximately weekly for the first ~4-6 weeks, then every ~2 weeks for ~4-6 weeks, then every ~4 weeks thereafter.

6.2 Week 16 Assessment

At 16 weeks, patients will be assessed for tumor response to therapy. Patients who experience SD, PR, or CR will be allowed to continue study therapy per Section 6.1 (nivolumab 480 mg IV every 4 weeks for up to 24 doses total). Patients whose disease demonstrates progression will be given 3 options:

1. Reduce or discontinue immunosuppression and continue nivolumab therapy (480 mg IV every 4 weeks for up to 24 total doses) per section 6.1. Dose reductions of immunosuppression will be performed on a case-by-case basis. This option likely increases the risk of allograft loss.
2. Transition to treatment with nivolumab 3 mg/kg IV every 3weeks for 4 doses + ipilimumab 1 mg/kg IV every 3 weeks for 4 doses, followed by 480 mg nivolumab every 4 weeks for 21 doses per Section 6.3. This option likely carries a higher risk of immune-mediated toxicity compared to nivolumab monotherapy.
3. Discontinue study treatment.

If a patient chooses either option 1 or 2 above, the other option may be used later (*i.e.*, if immunosuppression is decreased and the patient again experiences PD, ipilimumab could be added to therapy or if ipilimumab is added and the patient again experiences PD, immunosuppression could be decreased).

Ideally, patients should be assessed 16 weeks after initiation of nivolumab (regardless of the number of doses received) and complete at least 2 on-treatment scans with the second scan being completed at least 4 weeks after the first scan, before being declared to have PD to allow for the possibility of an immune-related tumor response. However, if, in the opinion of the investigator, a patient demonstrates unequivocal evidence of PD after, for example, 8 weeks of nivolumab therapy, the patient may transition at that time. Additionally, patients who experience delayed disease progression (*e.g.*, an initial objective response followed by PD) may transition at that time.

Patients should transition from nivolumab monotherapy to one of the above 2 options within ~28 days of determination of PD. Patients do not need to be re-screened.

Patients who have experienced allograft loss should discontinue tacrolimus regardless of treatment option chosen. Prednisone may be prescribed as needed.

6.3 Nivolumab with Ipilimumab

Patients who experience PD on single-agent nivolumab, or patients who have experienced allograft loss, may shift to a combination therapy with nivolumab and ipilimumab. During the initial induction period, nivolumab will be dosed at 3 mg/kg and ipilimumab will be dosed at 1 mg/kg. Each will be given by IV infusion over approximately 30 minutes once every 3 weeks for 4 cycles (12 weeks). After the 4th and final induction dose, there will be a six-week gap before beginning maintenance nivolumab therapy. This gap includes the 3 weeks in Cycle 4, thus Cycle 5 (the first cycle of the maintenance period) should begin 3 weeks after the end of Cycle 4. During the maintenance period, nivolumab will be dosed at 480 mg by IV infusion over approximately 30 minutes once every 4 weeks. This maintenance regimen may be continued for up to 21 cycles (84 weeks) regardless of the duration of nivolumab administration prior to transitioning to combination therapy.

Tacrolimus and prednisone administration will continue as described in Section 6.1. Patients who have experienced allograft loss should discontinue tacrolimus regardless of treatment option chosen. Prednisone may be prescribed as needed.

Dosing calculations should be based on the actual body weight. If the patient's weight differs by >10% from the weight used to calculate the original dose, the dose may be recalculated. All doses should be rounded to the nearest milligram. There will be no other dose modifications allowed.

Toxicity management for the combined agents follows the same template guidelines and algorithms that are provided in Section 7 and Appendix B for single agent nivolumab.

When both nivolumab and ipilimumab are to be administered on the same day, separate infusion bags and filters must be used for each infusion, there should be a 30-minute rest period between infusions, and nivolumab is to be administered first. Nivolumab is to be infused over approximately 30 minutes, promptly followed by a saline flush to clear the line of nivolumab and a 30-minute rest period before starting the ipilimumab infusion. Ipilimumab is to be infused over approximately 30 minutes, also followed by a saline flush.

Nivolumab/Ipilimumab Regimen Description					
Agent	**Premedications and Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Nivolumab (Induction)	None, except in the case of an infusion reaction (see Section 6.9)	3 mg/kg	IV infusion over ~30 minutes	Day 1, Week 1 for 4 cycles (Four total doses)	3 weeks
Ipilimumab (Induction)	None, except in the case of an infusion reaction (see Section 6.9)	1 mg/kg	IV infusion over ~30 minutes	Day 1, Week 1 for 4 cycles (Four total doses)	
Nivolumab (Maintenance)	None, except in the case of an infusion reaction (see Section 6.9)	480 mg	IV infusion over ~30 minutes	Day 1, Week 1, starting six weeks after the last dose of ipilimumab	4 weeks
Tacrolimus*	None	Dosed to achieve goal trough level of 2-5 ng/mL**	PO	Twice daily	N/A
Prednisone*	None	5 mg**	PO	Daily	
* Patients who have experienced allograft loss may discontinue tacrolimus and prednisone. ** Tacrolimus trough levels should be monitored each cycle while receiving Nivolumab/Ipilimumab in order to maintain 2-5 ng/ml. *** Patients may remain on higher-dose prednisone if already taking. IV=intravenous, PO=orally					

6.4 Treatment Beyond Progression

A minority of subjects treated with immunotherapy may derive clinical benefit (*e.g.*, delayed response, stable disease, or increased OS) despite initial evidence of PD with nivolumab or combination treatment.

Patients may be permitted to continue treatment beyond initial RECIST 1.1-defined PD if, in the opinion of the investigator, they may benefit from doing so. In general, patients must be clinically stable with no change in performance status due to disease progression and there must be no indication for immediate alternative treatment.

6.5 Criteria to Resume Treatment

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

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

- An evaluation of endocrine, GI, hepatic, and pancreatic functions must be made prior to restarting to exclude any additional IMARs.
- Non-drug-related toxicity including hepatic or pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed.

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

A patient who is successfully treated for allograft rejection (*i.e.*, still has a functional kidney allograft) may restart study therapy after rescreening and consultation with the PI if the patient:

- Experienced an objective response or SD on study therapy,
- Experiences progressive or recurrent disease after having been off study therapy, and
- Has been off study therapy for at least 90 days but less than 1 year.

6.6 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of nivolumab or ipilimumab with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The study PI should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently updated medical reference for a list of drugs to avoid or minimize the use of.

6.7 Duration of Therapy

In the absence of treatment delays due to AE(s), treatment may continue for 24 cycles or until one of the following criteria applies:

- Complete radiographic response;
- Signs of allograft rejection (see Section 7 for further information);
- Disease progression (see Section 7 for further information);
- Intercurrent illness that prevents further administration of treatment;
- AEs which require permanently going off study treatment (see Section 7 and specific algorithms in Appendix B);
- Any dosing interruption lasting >6 weeks, with the following exceptions:
    - Dosing interruptions >6 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator. Prior to re-initiating treatment in a subject

with a dosing interruption lasting >6 weeks, the study PI must be consulted. Tumor assessments should continue according to the protocol even if dosing is interrupted;
- Patient decides to withdraw from the study;
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the Investigator;
- Patient non-compliance;
- Pregnancy:
  - All women of child-bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed, or late, menstrual period) at any time during study participation;
  - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study;
- Termination of the study by the study sponsor; or
- The drug manufacturer can no longer provide the study agents.

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

6.8 Duration of Follow Up

Follow-up visits should be scheduled as follows:
- All patients who receive study therapy will be monitored for SAEs and IMARs for 90 days after their last dose of nivolumab or ipilimumab. Patients will be followed via monthly phone calls.
- For patients except those who develop PD (*i.e.*, patients who complete 96 weeks of therapy or whose treatment is discontinued after a CR or drug toxicity): every 8 weeks (±14 days) during the year immediately following cessation of therapy, then every 12 weeks (±21 days) during the second year following cessation of therapy, then every 16 weeks (±21 days) during the third year following cessation of therapy, then every 24 weeks (±28 days) during the fourth year following cessation of therapy.
- Patients with documented PD will be contacted by telephone or other means (*e.g.*, email) every 12 weeks ±14 days to assess for survival. Survival follow-up will continue until death or 5 years from the date of trial registration, whichever occurs first.

6.9 Treatment of Nivolumab- or Ipilimumab-Related Infusion Reactions

Nivolumab- or ipilimumab-related infusion or hypersensitivity reactions are rare. However, when such reactions occur, symptoms/signs may include fever, chills, rigors, headache, rash, urticaria, angioedema, pruritis, arthralgias, hypo- or hypertension, bronchospasm, back pain, or other symptoms.

All grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 guidelines.

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

6.9.1 **Grade 1 symptoms:** Mild reaction, infusion interruption and/or intervention not indicated.

Infusion rate may be slowed or interrupted and restarted at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor the patient closely.

The following prophylactic medications are recommended for future infusions:

- Diphenhydramine 50 mg (or equivalent) and/or
- Paracetamol 325-1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations

6.9.2 **Grade 2 symptoms:** Moderate reaction that requires therapy or infusion interruption but responds promptly to symptomatic treatment (*e.g.*, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids).

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor patient until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor the patient closely. If symptoms recur, re-administer diphenhydramine 50 mg IV, and monitor the patient until resolution of symptoms. The amount of study drug infused must be recorded on the CRF. If symptoms recur, treatment medications may need to be continued for 24-48 hours, and no further nivolumab will be administered at that visit.

The following prophylactic medications are recommended for future infusions:

- Diphenhydramine 50 mg (or equivalent),
- Paracetamol 325-1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations, and
- Corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used, if necessary.

6.9.3 **Grade 3 or 4 symptoms**: Prolonged reaction (*i.e.*, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); hospitalization indicated for other clinical sequelae (*e.g.*, renal impairment, pulmonary infiltrates, etc.); life threatening; pressor or ventilatory support indicated.

- <u>Immediately discontinue nivolumab infusion.</u>
- Begin an IV infusion of saline and bronchodilators
- Epinephrine 0.2-1 mg diluted 1:1,000 for subcutaneous administration, or 0.1-0.25 mg diluted 1:10,000 for IV administration,

- Diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed.

Patient should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab should be discontinued permanently.

Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Monitor the patient until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (*e.g.*, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (*e.g.*, oral antihistamine, or corticosteroids). Additional treatment prior to next dose may be given according to the guidelines above.

Note: late occurring events including isolated fever and fatigue may represent the presence of systemic inflammation.

7. DOSING DELAYS/DOSE MODIFICATIONS

Note: If a patient experiences several AEs and there are conflicting recommendations, the investigator should use the recommended treatment modification for the most severe AE.

7.1 Nivolumab and Ipilimumab Dose Modifications

Below are dose modification tables for nivolumab and combination nivolumab with ipilimumab for the following adverse events. Please use as written and contact the drug monitor for any proposed changes.

Please refer to Appendix B, the Nivolumab Investigator's Brochure, or the Ipilimumab Investigator's Brochure for toxicity management algorithms which include specific treatment guidelines. These algorithms should be followed unless there are specific clinical circumstances for which the treating physician decides an alternative treatment approach is clinically appropriate. Consultation with the study PI or drug monitor is recommended.

In several places there are differences from the algorithms regarding protocol directed drug modifications and these are identified with (#). In these cases, please follow the protocol-specific guidelines in this section.

Generally, early evaluation while withholding drug, and appropriate treatment as indicated in the management tables and event specific guidelines is strongly encouraged.

- Any patient with grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to grade 1 severity within the re-treatment period OR that requires systemic treatment should go off protocol therapy
- Patients with any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued study drug dosing should go off protocol therapy.
- 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, or insulin therapy, or that does not require treatment **does not** require discontinuation of protocol therapy.
- If any kidney-related AEs (*e.g.* elevated serum creatine levels, development of DSA or non-HLA antibodies, or development of severe proteinuria [>1 g/day]) are observed, nivolumab should be held, a renal allograft biopsy should be obtained, and treatment for allograft rejection should be started immediately (see Section 7.2).

Skin Rash and Oral Lesions	Management/Next Dose for Nivolumab and Combination Nivolumab/Ipilimumab
≤ Grade 1	No change in dose*
Grade 2	Hold* until ≤ grade 1 (#). Resume at same dose level.
Grade 3	Hold* until ≤ grade 1. Resume at same level at investigator's discretion
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 Skin AE management guidelines.	

Liver Function AST, ALT, Bilirubin	Management/Next Dose for Nivolumab and Combination Nivolumab/Ipilimumab
≤ Grade 1	Hold, at investigator's discretion, until values return to ULN or baseline (#). Resume at same dose level.
Grade 2 (3 – 5 × ULN)	Hold until values return to baseline. Resume at same dose level.
Grade 3 (5 – 20 × ULN)	Hold until grade 1 (ULN – 3 x ULN) or baseline. Resume at same dose level, at investigator's discretion. If persistent (>7 days) or requires steroids, patients should go 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. Note: Grades for liver function follow multiples of ULN, rather than multiples of baseline.	
Recommended management: See Hepatic AE Management Algorithm.	

Diarrhea/Colitis	Management/Next Dose for Nivolumab and Combination Nivolumab/Ipilimumab
≤ Grade 1	Hold until baseline (#). No change in dose.
Grade 2	Hold until baseline. No change in dose.
Grade 3	Resume at same dose level, at investigator discretion, if resolved within 7 days without steroids and with no evidence of colitis. If persistent (>7 days), or requires steroids, patients should go off protocol therapy.
Grade 4	Off protocol therapy
See GI AE Algorithm for management of symptomatic colitis. Patients with Grade 2 symptoms but normal colonoscopy and biopsies may be retreated after resolution. Patients who require systemic steroids should be taken off study treatment. If possible without compromising acute care, evaluate pituitary function prior to starting steroids. Evaluation for all patients for additional causes includes *C. diff*, acute and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD.	
Recommended management: See GI AE Management Algorithm.	

Pancreatitis Amylase/Lipase	Management/Next Dose for Nivolumab and Combination Nivolumab/Ipilimumab
≤ Grade 1	Continue at same dose level, if asymptomatic, at investigator's discretion.
Grade 2	Continue at same dose level, if asymptomatic, at investigator's discretion. If symptomatic, resume at same dose level once resolved.
Grade 3	Continue at same dose level, if asymptomatic, at investigator's discretion. Patients should have imaging done when clinically indicated (*i.e.*, grade 3 pancreatitis) before resuming treatment. Patients who develop symptomatic pancreatitis or diabetes mellitus should go off protocol therapy.
Grade 4	Hold until grade 2. Resume at same dose level if asymptomatic. Patients should have imaging done before resuming treatment, and when clinically indicated. Patients who develop symptomatic pancreatitis or diabetes mellitus should go off protocol therapy.
Patients may develop symptomatic and radiologic evidence of pancreatitis as well as DM and diabetic ketoacidosis (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 re-treated. For treatment management of symptomatic pancreatitis please follow the Hepatic AE Management Algorithm.	

Pneumonitis	Management/Next Dose for Nivolumab and Combination Nivolumab/Ipilimumab
≤ Grade 1	Hold dose pending evaluation and resolution to baseline including baseline O2 saturation. Resume with no change in dose after pulmonary and/or infectious disease consultation excludes lymphocytic pneumonitis.
Grade 2	Hold dose pending evaluation. Resume with no change in dose after pulmonary and/or infectious disease consultation excludes ipilimumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Patients should go off protocol therapy if steroids are required.
Grade 3	Hold dose pending evaluation. Resume with no change in dose after pulmonary and/or infectious disease consultation excludes ipilimumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Patients should go off protocol therapy if steroids are required.
Grade 4	Off protocol therapy.
Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Patients with new lung nodules should be evaluated for sarcoid-like granuloma. Seasonal influenza killed vaccine should be recommended for all patients.	
Recommended management: See Pulmonary AE Management Algorithm.	

Other GI / Nausea and Vomiting	Management/Next Dose for Nivolumab and Combination Nivolumab/Ipilimumab
≤ Grade 1	No change in dose.
Grade 2	Hold pending evaluation for gastritis, duodenitis, and other immune AEs or other causes. Resume at same dose level after resolution to ≤ grade 1.
Grade 3	Hold pending evaluation until ≤ grade 1. Resume at same dose level. If symptoms do not resolve within 7 days with symptomatic treatment, patients should go off protocol therapy.
Grade 4	Off protocol therapy.
Patients with Grade 2 or 3 nausea or vomiting should be evaluated for upper GI inflammation and other immune related events.	

Fatigue	Management/Next Dose for Nivolumab and Combination Nivolumab/Ipilimumab
≤ Grade 1	No change in dose.
Grade 2	No change in dose.
Grade 3	Hold until ≤ grade 2. Resume at same dose level.
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, or hepatic; or muscle inflammation (as assessed by creatine phosphokinase levels).	

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

Endocrine Hypophysitis/Adrenal Insufficiency	Management/Next Dose for Nivolumab and Combination Nivolumab/Ipilimumab
≤ Grade 1	Hold pending evaluation, including consultation with an endocrinologist for evidence of adrenal insufficiency or hypophysitis. Patients with asymptomatic TSH elevation may continue treatment while evaluating the need for thyroid replacement.
Grade 2	Hold until patients are on a stable hormone replacement regimen. If treated with steroids, patients must be stable off steroids for 2 weeks. Resume at same dose level.
Grade 3	Hold until patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable off steroids for 2 weeks. Resume at same dose level.
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. Pituitary function should be evaluated before beginning steroid therapy or replacement therapy of any kind. *Note patients with thyroiditis may be retreated on hormone replacement therapy. Patients must be evaluated to rule out pituitary disease prior to initiating hormone replacement therapy.	
Recommended management: See Endocrine AE Management Algorithm	

Renal	Management/Next Dose for Nivolumab and Combination Nivolumab/Ipilimumab
≤ Grade 1	See Section 7.2
Grade 2	See Section 7.2
Grade 3	See Section 7.2
Grade 4	See Section 7.2

Infusion Reaction	Management/Next Dose for Nivolumab and Combination Nivolumab/Ipilimumab
≤ Grade 1	See Section 6.9
Grade 2	See Section 6.9
Grade 3	See Section 6.9
Grade 4	See Section 6.9

Fever	Management/Next Dose for Nivolumab and Combination Nivolumab/Ipilimumab
≤ Grade 1	Evaluate and continue at same dose level.
Grade 2	Hold until ≤ grade 1. Resume at same dose level.
Grade 3	Hold until ≤ grade 1. Resume at same dose level.
Grade 4	Off protocol therapy.
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever.	

Cardiac*	Management/Next Dose for Nivolumab and Combination Nivolumab/ Ipilimumab
≤ Grade 1	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of congestive heart failure, ischemia, arrhythmia, or myositis. Obtain history, EKG, and CK (for concomitant myositis) and CK-MB tests. Repeat troponin and CK tests, and EKG every 2-3 days. If troponin and labs normalize without evidence of myocarditis, the patient may resume therapy. If labs worsen or symptoms develop then treat as below.
≥ Grade 2 with suspected myocarditis	Hold dose.** Admit to hospital and consult with a cardiologist. Rule out MI and other causes of cardiac disease, and begin cardiac monitoring. Obtain an echocardiogram and consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone and immune suppression as clinically indicated. If no improvement is seen within 24 hours consider adding either infliximab, ATG, or tacrolimus. Patients may 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.
*Including congestive heart failure, LV systolic dysfunction, myocarditis, or elevated levels of phosphocreatine kinase and/or troponin. **Patients with evidence of myositis without myocarditis may be treated according to "All Other Events," below. Given the heightened risk for cardiac AEs, troponin should be monitored with each dose of nivolumab for the first two months to detect any early evidence of myocarditis. Baseline troponin should be obtained on study, after tacrolimus adjustment. Evaluation of cardiac function, including troponin and CPK levels, EKGs, and echocardiograms as clinically indicated, is recommended for any patients with a history of congestive heart failure or who are at risk because of underlying cardiovascular disease or previous exposure to cardiotoxic drugs. **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.**	

All Other Events	Management/Next Dose for Nivolumab and Combination Nivolimab/Ipililmumab
≤ Grade 1	No change in dose.
Grade 2	Hold until ≤ grade 1 or baseline (exceptions as noted below).
Grade 3	Hold until ≤ grade 1 or baseline and patient no longer on steroid treatment, if initiated (exceptions as noted below). Patients should go off protocol therapy for events with a high likelihood of morbidity or mortality with recurrent events.
Grade 4	Off protocol therapy.
Recommended management: As clinically indicated	

Patients requiring high-dose steroid treatment for autoimmune or inflammatory AEs should go off study treatment except for short courses of tapering steroids for infusion reactions, skin rash, or endocrine events.

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

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

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

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

Patients may be dose-delayed for evaluation and restarted depending on results.

Any patient started on corticosteroids who is later determined to not require steroid treatment for an autoimmune AE may resume therapy after a 2-week observation period without further symptoms at the discretion of the study PI or Investigator.

7.2 Prednisone and Tacrolimus Dose Modifications for Allograft Rejection

Given the potential for rejection due to the administration of nivolumab and ipilimumab in this study, patients should be monitored closely for signs of rejection.

Markers of allograft rejection may include the following:

- Unexplained ≥20% increase in serum creatinine over baseline,
- Development of donor-specific antigen (DSA) or non-HLA antibodies,
- Development of severe proteinuria (>1 g/day),
- Persistent increase in dd-cfDNA.

Serum creatinine (included in the comprehensive metabolic panel) will be monitored according to the schedule outlined in the treatment calendars (Section 11).

Donor-specific and non-HLA antibodies should be checked as clinically indicated at the direction of the institution's transplant nephrologist. Patients should be encouraged to report possible symptoms of rejection, including elevated temperature, elevated blood pressure, graft tenderness, and blood in the urine. Although experimental in this setting, dd-cfDNA levels (see Section 2.5.3 and the Biomarker Plan, Section 5.6) may be useful to monitor for signs of rejection.

Dipstick urinalysis should be performed per the schedule outlined in the treatment calendars. If 2+ or greater, a urine protein/creatinine ratio (spot or 24-hour) should be assessed at the direction of the institution's transplant nephrologist.

If rejection is suspected based on the above analyses, the following interventions will be triggered:

1. Hold or discontinue nivolumab (and ipilimumab, if applicable)
2. Immediately biopsy the renal allograft
    a. If cell-mediated rejection: Increase the tacrolimus dose (target trough level = 5-10 ng/mL) and administer 500 mg IV methylprednisolone daily for 3 days, with a prednisone taper thereafter. If no improvement, administer 5 mg/kg infliximab.
    b. If antibody-mediated rejection: Increase the tacrolimus dose (target trough level = 5-10 ng/mL), perform plasmapheresis, and administer IV immunoglobulin (Ig) per institutional protocol plus 500 mg IV methylprednisolone daily for 3 days with a prednisone taper thereafter.

A patient who experiences clinical benefit from the above regimen and still has a functional kidney allograft may restart study therapy after re-screening and consultation with the PI if the patient:

- Experienced an objective response or SD on study therapy,
- Experiences progressive or recurrent disease after having been off study therapy, and
- Has been off study therapy for at least 90 days, but less than 1 year.

Patients who experience allograft loss should begin dialysis and may resume nivolumab monotherapy or nivolumab plus ipilimumab combination therapy, as appropriate.

Dose modifications of tacrolimus and prednisone should be done per standard of care.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational and commercial agents administered in this study can be found in Section 10.1.

8.1 CTEP IND Agent(s)

8.1.1 Nivolumab (NSC 748726)

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

Other Names: nivolumab, MDX1106

Classification: Anti-PD-1 MAb

M.W.: 146,221 Daltons

Mode of Action: Nivolumab targets the PD-1, 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, PD-L1 and 2 PD-L2, results in the down-regulation of lymphocyte activation. Nivolumab inhibits the binding of PD-1 to PD-L1 and PD-L2. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

Description: Nivolumab Injection is a clear to opalescent, colorless to pale yellow liquid; light (few) particulates may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), 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).

How Supplied: Nivolumab is supplied by Bristol-Myers Squibb and distributed by the Pharmaceutical Management Branch (PMB), 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.

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 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.

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

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.

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 at 2-8 °C (36-46 °F) and a maximum of 8 hours of the total 24 hours can be at room temperature (20-25 °C, 68-77 °F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

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

Route of Administration: Intravenous infusion over 30 minutes. Do not administer as an IV push or bolus injection.

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

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 or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction.

Patient Care Implications: 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.

Availability: Nivolumab is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. Nivolumab is provided to the NCI under a Collaborative Agreement between Bristol-Myers Squibb and the DCTD, NCI (see Section 13.4).

8.1.2 Ipilimumab

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

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

Classification: Human monoclonal antibody

M.W.: 147,991 Daltons

Mode of Action: Ipilimumab is specific for the CTLA4 antigen expressed on a subset of activated T-cells. CTLA4 interaction with the B7 molecule, one of its ligands expressed on professional antigen presenting cells, can down-regulate T-cell response. Ipilimumab is thought to act by blocking the interaction of CTLA4 with the B7 ligand, resulting in a blockade of the inhibitory effect of T-cell activation.

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

How Supplied: Ipilimumab is supplied by Bristol-Myers Squibb and distributed by the PMB, CTEP/DCTD/NCI. Ipilimumab for injection, 200 mg/40 mL (5 mg/mL), is formulated as a clear to slightly opalescent, colorless to pale yellow, sterile, nonpyrogenic, single-use, isotonic aqueous solution that may contain particles.

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

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

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

Preparation: Ipilimumab is given undiluted or further diluted in 0.9% NaCl Injection, USP or 5% Dextrose Injection, USP in concentrations between 1 mg/mL and 4 mg/mL. Ipilimumab is stable in a polyvinyl chloride (PVC), non-PVC/non DEHP (di-(2-ethylhexyl) phthalate) IV bag or glass container up to 24 hours refrigerated at 2-8 °C (36-46 °F) or at room temperature/ room light.

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

Storage: Store intact vials refrigerated at 2-8 °C (36-46 °F), protected from light. Do not freeze.

Stability: Shelf-life surveillance of the intact vials is ongoing. Solution as described above is stable up to 24 hours refrigerated at 2-8 °C (36-46 °F) or at room temperature/ room light.

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

Route of Administration: Intravenous infusion over 30 minutes. Do not administer ipilimumab as an IV push or bolus injection.

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

Patient Care Implications: Monitor patients for immune-related adverse events, *e.g.*, rash/vitiligo, diarrhea/colitis, uveitis/episcleritis, hepatitis and hypothyroidism.

8.1.3 Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, 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 participating investigator at that institution.

Sites can request a 5-vial starter supply of nivolumab. Ipilimumab should not be requested until there is an active patient at the site.

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, a “current” password, and active person registration status. 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.

8.1.3.1 Agent Inventory Records

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.

8.1.3.2 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.1.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: https://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: https://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.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)

8.2 Commercial Agent(s)

8.2.1 Prednisone

Product description: Prednisone, a synthetic glucocorticoid, is a white crystalline powder. It is available as 1 mg, 2.5 mg, 5 mg, 20 mg, and 50 mg tablets, and as an oral solution. Tablets are available in immediate and delayed release formulations..

Route of administration: Prednisone is administered orally once each day. Delayed release tablet formulations should not be crushed or chewed. Prednisone may be taken with our without food.

Agent Ordering: Oral prednisone will be obtained from commercial sources.

See prednisone package inserts for more information.

8.2.2 Tacrolimus

Product Description: Tacrolimus, (FK506) is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. Tacrolimus appears as white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform. Tacrolimus inhibits T lymphocyte activation, although the exact mechanism of action is not known. Tacrolimus binds to FKBP-12, an intracellular protein. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin is inhibited. This effect may prevent the generation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (interleukin-2, gamma interferon). The net result is the inhibition of T lymphocyte activation (*i.e.*, immunosuppression). Refer to the package insert for more information.

Availability: Tacrolimus is available for oral administration as capsules containing the equivalent of 0.5 mg, 1 mg, or 5 mg of anhydrous tacrolimus. Inactive ingredients include lactose, hydroxypropyl methylcellulose, croscarmellose sodium, and magnesium stearate.

Storage and Handling: Tacrolimus capsules should be stored at room temperature (15-30 °C, 59-86 °F). Tacrolimus for injection should be stored at 5-25 °C (41-77 °F).

Administration: Capsules should be taken by mouth every 12 hours without food. Immediate-release and extended-release oral formulations are not interchangeable. If a patient cannot take oral capsules, please use sublingual tacrolimus.

Potential drug interactions: Tacrolimus is extensively metabolized by the cytochrome P450 (CYP) system, primarily CYP3A4. Drugs that may increase tacrolimus blood concentrations include: calcium channel blockers (*e.g.*, diltiazem, nicardipine, nifedipine, verapamil), antifungal agents (*e.g.*, ketoconazole, clotrimazole, fluconazole, itraconazole), macrolide antibiotics (*e.g.*, clarithromycin, erythromycin, troleandomycin), gastrointestinal prokinetic agents (*e.g.*, cisapride, metoclopramide), and/or other drugs (*e.g.*, bromocriptine, cimetidine, cyclosporine, danazol, ethinyl estradiol, omeprazole, nefazodone, HIV-protease inhibitors. Drugs that may decrease tacrolimus concentrations include: anticonvulsants (*e.g.*, carbamazepine, phenobarbital, phenytoin), antibiotics (*e.g.*, rifabutin, rifapentine), and/or herbal preparations (*e.g.*, St. John's Wort [hypericum perforatum]). Grapefruit and grapefruit juice should be avoided. Refer to an updated reference for current information about drug-drug interactions with calcineurin inhibitors.

Agent Ordering: Tacrolimus will be obtained from commercial sources.

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

9.1.1 Overview

A "success" rate (CR/PR/SD without allograft loss at 16 weeks) of 15% or lower (null hypothesis) would be considered insufficient for further study in this population, while a "success" rate of 40% or higher (alternative hypothesis) would be considered worthy of further investigation. This trial will be performed using a modified Simon's two-stage minimax design (Simon, 1989). In the first stage, nine patients will be enrolled. To minimize risk to patients, accrual will be paused after the ninth patient is enrolled until a decision is made to continue the trial. If one or no patients experience CR/PR/SD without allograft loss at 16 weeks, the study will be temporarily closed to accrual for futility. Otherwise, 7 additional patients will be enrolled for a total of 16. The null hypothesis will be rejected if 5 or more patients experience CR/PR/SD without allograft loss. This design yields a type 1 error rate of 0.074 and power of 0.8 to distinguish between the null hypothesis and the alternative hypothesis.

9.1.2 Primary Endpoint

The percentage of kidney transplant recipients with selected advanced cancers for whom standard medical, surgical or radiation therapy would be insufficient who experience CR/PR/SD without allograft loss at 16 weeks after administration of nivolumab, tacrolimus, and prednisone.

9.1.3 Secondary Endpoints

- Objective response (CR or PR) rate (ORR) based on RECIST 1.1 criteria, and immune-related objective response rate (irORR) using immune-related response criteria (iRECIST);
- Allograft rejection rate;
- Duration of response among patients who experience CR or PR;
- Progression-free survival;
- Overall survival;

9.2 Sample Size/Accrual Rate

A minimum of 9, and up to 16, patients will be recruited for this study. Estimated accrual is approximately one patient every eight weeks.

The study population is expected to comprise 50% men and 50% women, but because this protocol involves a small number of patients recruited across multiple institutions with geographically, racially, and culturally diverse populations, we cannot estimate the racial composition of the cohort.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native					
Asian	1	1			**2**
Native Hawaiian or Other Pacific Islander					
Black or African American	2	2			**4**
White	4	4	1	1	**10**
More Than One Race					
Total	**7**	**7**	**1**	**1**	**16**

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9.3 Stratification Factors

N/A

9.4 Analysis of Primary Endpoints

The percent of kidney transplant recipients who experience CR/PR/SD at 16 weeks and do not experience allograft loss after administration of nivolumab, tacrolimus, and prednisone will be calculated, along with the corresponding exact 95% CI. A minority of subjects treated with immunotherapy may derive clinical benefit and experience a delayed response, stable disease, or increased OS despite initial evidence of PD with nivolumab or combination treatment. Subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed PD at the time of the initial progression event but may be later designated as delayed responses for purposes of determining CR/PR/SD and counted as responses for this study.

The evaluable population for the primary endpoint is all subjects who receive at least one dose of nivolumab and undergo tumor response assessments and graft assessments at ~8 and ~16 weeks. Patients who experience allograft loss within 16 weeks of receiving nivolumab will be evaluable for the primary endpoint even if tumor response assessments cannot be performed. Patients who, in the opinion of the investigator, experience PD (with or without allograft failure) prior to 16 weeks will also be evaluable.

9.5 Analysis of Secondary Endpoints

Renal allograft rejection rate will be estimated as the proportion of subjects who experience markers of allograft rejection as defined in Section 7.2.

Allograft loss is defined as allograft rejection leading to complete, permanent, and irreversible loss-of-function of the renal allograft. All patients who receive at least one dose of nivolumab will be evaluable for allograft rejection.

Objective response rate (ORR) is defined as the proportion of subjects whose best overall response from baseline is either a CR or PR, based on RECIST 1.1 criteria. ORR will be estimated along with 95% exact CI. A minority of subjects treated with immunotherapy may derive clinical benefit and experience a delayed response, stable disease, or increased OS despite initial evidence of PD with nivolumab or combination treatment. Subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed PD at the time of the initial progression event but may be later designated as delayed responses for purposes of determining ORR and counted as responses. The analysis of ORR will be performed on the response-evaluable population, defined as those subjects who have measurable disease at baseline, receive at least one dose of nivolumab, and undergo response assessments at ~8 and ~16 weeks. Patients who, in the opinion of the investigator, experience PD prior to 16 weeks will also be evaluable. Immune-related ORR based on immune-related response criteria (iRECIST) will also be summarized using the same method.

Among the patients who experience CR or PR, DOR is measured from the time criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent disease or PD is documented. DOR will be summarized using the Kaplan-Meier method. All patients who experience CR/PR will be evaluable for DOR.

Overall survival (OS) is the time from the first dose of nivolumab to the date of death from any cause. A subject who has not died will be censored at last known date alive. Progression-free survival (PFS) is defined as the time from the first dose of nivolumab to the date of the first documented tumor progression or death due to any cause, whichever occurs first. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Kaplan-Meier curves will be used to summarize OS and PFS. OS and PFS analyses will be performed for all patients who receive at least one dose of nivolumab.

Because the number of patients who change over to nivolumab + ipilimumab or continue nivolumab with reduction in their immunosuppressive regimen after disease progression on nivolumab monotherapy will be small and unpredictable, data from these patients will be considered investigative and potentially hypothesis-generating.

9.6 Reporting and Exclusions

9.6.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with tacrolimus and prednisone.

9.6.2 Evaluation of Tumor Response

All patients enrolled in the study will be assessed for response to treatment. Tumor responses will be assessed according to RECIST and iRECIST criteria.

9.6.3 Evaluation of Allograft

Allograft rejection will be reported as 1) rejection without loss; 2) rejection with loss; or 3) no rejection.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

AE monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

10.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

10.1.1 CAEPR for Nivolumab

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

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

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

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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]		

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%)**	
	Hypophysitis[3]		
	Hypothyroidism[3]		
EYE DISORDERS			
		Blurred vision	
		Dry eye	
		Eye disorders - Other (diplopia)[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]	
		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)***

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 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		
		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]	

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%)**	
		Renal and urinary disorders - Other (immune-mediated nephritis)	
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.

10.1.2 CAEPR for Ipilimumab

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for

Ipilimumab (MDX-010, NSCs 732442 and 720801)

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

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

Version 2.10, 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			

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%)**	
	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		
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			

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%)**	
		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		
		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		
	Guillain-Barre syndrome[2]		
	Headache		

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%)**	
	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	
		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)***

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%)**	
	Skin and subcutaneous disorders - Other (Sweet's syndrome)		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
	Urticaria		
VASCULAR DISORDERS			
	Hypotension		

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

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

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

[4]Complications including hyperacute graft-versus-host disease (GVHD), may occur in patients 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 (MDX-010) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.1.3 Adverse Event List for Prednisone

Common adverse reactions for corticosteroids include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite, and weight gain. See a prednisone package insert for more information.

10.1.4 Adverse Event List for Tacrolimus

The most common adverse reactions (≥15%) were abnormal renal function, hypertension, diabetes mellitus, fever, CMV infection, tremor, hyperglycemia, leukopenia, infection, anemia, bronchitis, pericardial effusion, urinary tract infection, constipation, diarrhea, headache, abdominal pain, insomnia, paresthesia, peripheral edema, nausea, hyperkalemia, hypomagnesemia, and hyperlipemia. See a tacrolimus package insert for more information

10.2 Adverse Event Characteristics

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

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 10.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

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

10.3 Expedited Adverse Event Reporting

10.3.1 Rave-CTEP-AERS Integration

The Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline AEs entered in Rave to determine whether they

require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. The Clinical Research Associate (CRA) will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Event form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

The reporting period (course/cycle) is correct, and AEs are recorded and complete (no missing fields) and the form is query-free (fields added to the form during study build do not need to be query-free for the integration call with CTEP-AERS to be a success).

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence that 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 that was phoned in must be entered immediately into CTEP-AERS using the deep link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents > Education and Promotion, and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information > User Guides.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

10.3.2 Distribution of Adverse Event Reports

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

10.3.3 Expedited Reporting Guidelines

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

Note: A death on study requires <u>both</u> routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression; clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 90 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **<u>MUST</u>** immediately report to the sponsor (NCI) **<u>ANY</u>** 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 **<u>ANY</u>** of the following outcomes:

- Death;
- A life-threatening adverse event;
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- 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).

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

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

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.

<u>Expedited AE reporting timelines are defined as:</u>

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

[1]Serious adverse events that occur more than 90 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 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

10.4 Routine Adverse Event Reporting

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

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

10.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

10.6 Secondary Malignancy

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

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

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

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

10.7 Second Malignancy

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

11. STUDY CALENDARS

11.1 Nivolumab Monotherapy

Nivolumab monotherapy	Screening	Immuno-suppression adjustment[A]	Treatment (cycle length = 28 days[B])												Follow-up	Immune-mediated Adverse Reaction[C]	Disease Progression
			Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycles 6+				
	Within 28 days of registration	Day -28 to Day 0	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	See Section 6.8		See Section 6.2
Medication administration																	
Nivolumab (480 mg IV)			X		X		X		X		X		X				
Tacrolimus		X	Continue twice daily oral dosing													X	X
Prednisone		X	Continue daily oral dosing													X	X
Patient medication diary review (Appendix C)		X	X		X		X		X		X		X				
Administrative Assessments																	
Informed consent / HIPAA[D]	X																
Pathology review	X																
Inclusion / Exclusion	X																
Medical History	X																
Record concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical Assessments																	
Physical examination[E]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG performance status	X		X		X		X		X		X		X		X	X	
Review of adverse events			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead EKG and echocardiogram[F]	X[F]																
Efficacy Assessments																	
CT scans: chest / abdomen / pelvis plus additional areas as appropriate	X						X				Day 1 every other cycle (Cycles 5, 7, 9, *etc.*)				X		
Clinical color photographs with scale ruler of tumors, as appropriate[G]	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Brain imaging[H]	X																
Standard-of-care Laboratory Assessments (Note: Day 1 assessments for each cycle may be ±3 days from scheduled timepoint)																	
CBC w/ differential	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
CMP[I]	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Dipstick urinalysis[J]	X	X[K]	X	X	X	X	X	X	X		X		X			X	
Pregnancy test[L]	X																
PT/PTT	X																

Nivolumab monotherapy	Screening	Immuno-suppression adjustment[A]	Treatment (cycle length = 28 days[B])												Follow-up	Immune-mediated Adverse Reaction[C]	Disease Progression
			Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycles 6+				
	Within 28 days of registration	Day -28 to Day 0	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	See Section 6.8		See Section 6.2
serum TSH, free T4	X		X		X		X		X		X		X		X		
Troponin and CPK		X[K]	X		X												
dd-cfDNA collection[O]	X		X	X	X	X	X	X	X		X		X			X	X
Tacrolimus trough level[R]			X		X		X		X		X		X				
Correlative studies																	
Serum collection[M]			X		X										X	X	X
PBMC collection[N]			X		X										X	X	X
Tumor biopsy[P]	X				X											X	
Allograft biopsy[Q]																X[Q]	

A: Immunosuppression adjustment will last no more than 28 days.
B: The cycle length may be extended by 7 days, except in the case of a drug toxicity, in which case treatment may be delayed up to 6 weeks, then resumed if appropriate in the opinion of the Investigator. Nivolumab is not be administered less than every 28 days. Laboratory assessments scheduled for treatment days (*i.e.*, Day 1 of a cycle) may be ±3 days from the scheduled timepoint.
C: Patients who experience allograft rejection should stop nivolumab treatment and a biopsy of the renal allograft should be obtained.
- If cell-mediated rejection: Increase tacrolimus dose (target trough level: 5-10 ng/mL), administer methylprednisolone 500 mg IV daily for 3 days, with prednisone taper thereafter. If no improvement, administer infliximab 5 mg/kg.
- If antibody-mediated rejection: Increase tacrolimus dose (target trough level: 5-10 ng/mL), perform plasmapheresis, and administer IV Ig plus methylprednisolone 500 mg IV daily for 3 days, with prednisone taper thereafter.

Note: Donor-specific and non-HLA antibodies should be checked as clinically indicated at the direction of the institution's transplant nephrologist.
D: Informed consent form and HIPAA authorization are to be provided before initiation of any screening assessments and may be obtained before Day -28.
E: Required on days when blood draws occur. To include vital signs (e.g., temperature, blood pressure, pulse).
F: All patients must have an EKG and echocardiogram at baseline screening. Additional EKGs and cardiac imaging should be performed as clinically indicated.
G: Biopsy may be performed when response assessment is confounded by the presence of ulceration, cyst(s), scarring/fibrosis, etc. See tumor biopsy instructions in protocol section 5.2.2.1.
H: MRI preferred; CT acceptable for patients unable to undergo MRI.
I: To include albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, AST, ALT, sodium.
J: If 2+ or greater, UPCR (spot or 24-hour) should be assessed at the direction of the institution's transplant nephrologist.
K: Baseline should be obtained after immunosuppression adjustment.
L: For women of childbearing potential.
M: Two 10 mL SST tubes; Day 1 collection should be prior to administration of nivolumab and the second collection should be during Week 4.
N: Ten 10 mL CPT tubes; Day 1 collection should be prior to administration of nivolumab and the second collection should be during Week 4.
O: Two 10-mL cfDNA BCT tubes. Samples should be collected every 2 weeks. If levels are stable at 12 weeks, testing may decrease to every 4 weeks. Standard of Care. Research based off of sample results
P: If safe and feasible in the investigator's opinion. Pre-treatment biopsy may be omitted if sufficient archival tumor tissue exists, procured within 12 weeks of enrollment without intervening therapy. The on-treatment biopsies should be obtained during Week 4, and if the patient experiences allograft rejection. A biopsy should not be obtained for immune-mediated adverse reactions with no renal involvement. Patients may refuse biopsy and still remain on study. If a biopsy will compromise the evaluability of a lesion for response (RECIST 1.1), it may be omitted. See Section 5.4.
Q: Patients who experience allograft rejection should stop nivolumab therapy and a biopsy of the renal allograft should be obtained. An allograft biopsy should **only** be obtained if allograft rejection is suspected, and is not necessary for immune-mediated adverse reactions with no renal involvement.
R: Tacrolimus trough levels should be monitored each cycle while receiving Nivolumab in order to maintain 2-5 ng/ml.
ALT=alanine aminotransferase, AST=aspartate aminotransferase, BCT=Blood collection tube, BUN=blood urea nitrogen, CBC=complete blood count, CPK=phosphocreatine kinase, CMP=comprehensive metabolic panel, CPT=cell preparation tube, CT=computed tomography, EKG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, HIPAA= Health Information Portability and Accountability Act, Ig=immunoglobulin, IV=intravenous, PBMC=peripheral blood mononuclear cells, PT=prothrombin time, PTT=partial thromboplastin time, RECIST=response evaluation criteria in solid tumors, SST=serum separating tube, T4=thyroxine, TSH=thyroid stimulating hormone, UPCR=urine protein/creatinine ratio

11.2 Nivolumab-Ipilimumab Combination Therapy

Nivolumab + Ipilimumab	Induction (cycle length = 21 days[A])												3-week gap[B]			Maintenance (cycle length = 28 days[A])				Follow-up	Immune-mediated Adverse Reaction[C]	Disease Progression
	Cycle 1			Cycle 2			Cycle 3			Cycle 4[B]						Cycle 5		Cycles 6+				
	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1	Day 15			See Section 6.2
Medication administration																						
Nivolumab (3 mg/kg IV)	X			X			X			X												
Ipilimumab (1 mg/kg IV)	X			X			X			X												
Nivolumab (480 mg IV)																X		X				
Tacrolimus	Continue twice daily oral dosing																				X	X
Prednisone	Continue daily oral dosing																				X	X
Patient medication diary review (Appendix C)	X			X			X			X			X			X		X				
Administrative Assessments																						
Record concomitant medications	X			X			X			X						X	X	X	X	X	X	
Clinical Assessments																						
Physical examination[D]	X			X			X			X			X			X	X	X	X	X		
ECOG performance status	X																					
Review of adverse events	X			X			X			X			X			X	X	X	X	X	X	
12-lead EKG and echocardiogram[E]	X																					
Standard-of-care Laboratory Assessments (Note: Day 1 assessments for each cycle may be ±3 days from scheduled timepoint)																						
CBC with differential	X			X			X			X			X			X	X	X	X			
CMP[F]	X			X			X			X			X			X	X	X	X			
Dipstick urinalysis[G]	X			X			X			X			X			X		X				
Pregnancy test[H]	X																					
serum TSH, free T4	X			X			X			X			X			X		X				
Troponin and CPK	X			X			X			X												
Whole blood for dd-cfDNA[L]	X			X			X			X			X			X		X			X	X
Tacrolimus trough level[O]	X			X			X			X			X			X		X				
Efficacy Assessments																						

Nivolumab + Ipilimumab	Induction (cycle length = 21 days[A])												3-week gap[B]			Maintenance (cycle length = 28 days[A])				Follow-up	Immune-mediated Adverse Reaction[C]	Disease Progression
	Cycle 1			Cycle 2			Cycle 3			Cycle 4[B]						Cycle 5		Cycles 6+				
	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1	Day 15			See Section 6.2
CT scans: chest / abdomen / pelvis plus additional areas as appropriate													X			Day 1 every other cycle, beginning with Cycle 6.						
Clinical color photographs with scale ruler of tumors as appropriate[I]	X			X			X			X			X			X	X	X	X			
Correlative studies																						
Serum collection[J]	X			X									X							X	X	X
PBMC collection[K]	X			X									X							X	X	X
Tumor biopsy[M]				X																	X	
Allograft biopsy																					X[N]	

Nivolumab + Ipilimumab	Induction (cycle length = 21 days[A])												3-week gap[B]			Maintenance (cycle length = 28 days[A])				Follow-up	Immune-mediated Adverse Reaction[C]	Disease Progression
	Cycle 1			Cycle 2			Cycle 3			Cycle 4[B]						Cycle 5		Cycles 6+				
	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1	Day 15			See Section 6.2

A: Cycle length may be extended by 7 days, except in the case of a drug toxicity, in which case treatment may be delayed up to 6 weeks, then resumed if appropriate in the opinion of the Investigator. Nivolumab/Ipilimumab is not to be administered less than every 21 days during induction or less than 28 days during maintenance. Laboratory assessments scheduled for treatment days (*i.e.*, Day 1 of a cycle) may be ±3 days from the scheduled timepoint.

B: After nivolumab (3 mg/kg IV) and ipilimumab (1 mg/kg IV) administration on Cycle 4, Day 1, there should be a six-week gap before beginning Cycle 5 and nivolumab (480 mg IV) maintenance therapy. This gap includes the 3 weeks in Cycle 4, thus there should be a 3-week gap between the end of Cycle 4 and the beginning of Cycle 5.

C: Patients who experience allograft rejection should stop nivolumab and ipilimumab treatment and a biopsy of the renal allograft should be obtained (Section 7.2).

- If cell-mediated rejection: Increase tacrolimus dose (target trough level: 5-10 ng/mL), administer methylprednisolone 500 mg IV daily for 3 days, with prednisone taper thereafter. If no improvement, administer infliximab 5 mg/kg.
- If antibody-mediated rejection: Increase tacrolimus dose (target trough level: 5-10 ng/mL), perform plasmapheresis and administer IV Ig plus methylprednisolone 500 mg IV daily for 3 days, with prednisone taper thereafter.

Note: Donor-specific and non-HLA antibodies should be checked as clinically indicated at the direction of the institution's transplant nephrologist.

D: Required on days when blood draws occur. To include vital signs (*e.g.*, temperature, blood pressure, pulse).

E: After obtaining a 12-lead EKG and echocardiogram at Cycle 1, additional EKGs and cardiac imaging should be performed as clinically indicated.

F: To include albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, AST, ALT, sodium.

G: If 2+ or greater, UPCR (spot or 24-hour) should be assessed at the direction of the institution's transplant nephrologist.

H: For women of childbearing potential.

I: Biopsy may be performed when response assessment is confounded by the presence of ulceration, cyst(s), scarring/fibrosis, *etc.* See tumor biopsy instructions in Section 5.4.

J: Two 10 mL SST tubes; Day 1 collection should be prior to administration of nivolumab/ipilimumab and the second collection should be during Week 4.

K: Ten 10 mL CPT tubes; Day 1 collection should be prior to administration of nivolumab/ipilimumab and the second collection should be during Week 4.

L: Two 10-mL cfDNA BCT tubes. Samples should be collected every 3 weeks. If levels are stable at 12 weeks, testing may decrease to every 4 weeks starting with Cycle 5. Standard of Care. Research based off of sample results

M: If safe and feasible in the opinion of the investigator. The on-treatment biopsies should be obtained during Week 3, and if the patient experiences allograft rejection. A biopsy should not be obtained for immune-mediated adverse reactions with no renal involvement. Patients may refuse biopsy and still remain on study. If a biopsy will compromise the evaluability of a lesion for response (RECIST 1.1), the biopsy may be omitted. See tumor biopsy instructions in Section 5.2.2.1.

N: Patients who experience allograft rejection should stop nivolumab and ipilimumab therapy and a biopsy of the renal allograft should be obtained (Section 7.2). An allograft biopsy should **only** be obtained if rejection is suspected, and is not necessary for immune-mediated adverse reactions with no renal involvement.

O: Tacrolimus trough levels should be monitored every cycle while receiving Nivolumab/Ipilimumab in order to maintain 2-5 ng/ml.

ALT=alanine aminotransferase, AST=aspartate aminotransferase, BCT=blood collection tube, BUN=blood urea nitrogen, CBC=complete blood count, CPK=phosphocreatine kinase, CMP=comprehensive metabolic panel, CPT=cell preparation tube, CT=computed tomography, ECOG=Eastern Cooperative Oncology Group, Ig=immunoglobulin, IV=intravenous, PBMC=peripheral blood mononuclear cells, PT=prothrombin time, PTT=partial thromboplastin time, RECIST=response evaluation criteria in solid tumors, SST=serum separating tube, T4=thyroxine, TSH=thyroid stimulating hormone, UPCR=urine protein/creatinine ratio

12. MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response approximately every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained about 8 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised RECIST guideline (version 1.1) as well as by irRECIST. Both criteria will be used at each evaluation. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1.1 Definitions

12.1.1.1 Evaluable for Toxicity

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

12.1.1.2 Evaluable for Objective Response:

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

12.1.1.3 Evaluable Non-Target Disease Response

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

12.1.2 Disease Parameters

12.1.2.1 Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area may only be considered measurable if interval growth has occurred after administration of radiotherapy.

12.1.2.2 Malignant Lymph Nodes

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

12.1.2.3 Non-measurable Disease

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

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

12.1.2.4 Target Lesions

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

12.1.2.5 Non-target lesions

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

12.1.2.6 Clinical Lesions

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

12.1.3 Methods for Evaluation of Measurable Disease

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

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

12.1.3.1 Conventional CT and MRI

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

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

12.1.3.2 Positron Emission Tomography (PET)-CT

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

12.1.3.3 Ultrasound

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

12.1.3.4 Endoscopy, Laparoscopy

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

12.1.3.5 Tumor markers

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

12.1.3.6 Cytology and Histology

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

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

12.1.3.7 Fluorodeoxyglucose (FDG)-PET

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

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT,

additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

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

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

12.1.4 Response Criteria

12.1.4.1 Evaluation of Target Lesions

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

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

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

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

12.1.4.2 Evaluation of Non-Target Lesions

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

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

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

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

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

12.1.4.3 Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	≥4 wks. Confirmation**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Confirmatory scans should be obtained at least 4 weeks following initial documentation of response.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

12.1.5 Duration of Response

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

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

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

12.1.6 Progression-Free Survival

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

12.2 Other Response Parameters

Tumor responses will also be assessed using immune-related response criteria (Seymour *et al.*, 2017). Other endpoints can be found in Section 9.1.

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

AE lists, guidelines, and instructions for reporting can be found in Section 10, Adverse Events: List and Reporting Requirements.

Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

13.1 Study Oversight

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

All decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol PI through the CTMS/IWRS. In addition, the Protocol PI will have at least monthly, or more frequent, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, AEs, and unanticipated problems. Decisions to proceed to the second stage will require sign-off by the Protocol PI and the Protocol Statistician.

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

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

13.2 Data Reporting

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account, and
- Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.
    - To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type,
    - To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR, and
    - To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

Upon initial site registration approval for the study in Regulatory Support System (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 staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the accept link in the upper right-corner of the iMedidata page. Site staff 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. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the

CTSU members' website in the Data Management > Rave section 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.

13.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

13.2.2 Responsibility for Data Submission

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

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 4 weeks. Baseline data should be entered within 2 weeks of registration and Cycle 1, Day 1 data should be entered within 2 weeks of Cycle 2, Day 1. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 8 weeks past due.

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

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D) and a description of any DLTs. CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with

CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

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

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

13.3 CTEP Multicenter Guidelines

N/A

13.4 Collaborative Agreements Language

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

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

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

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

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

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

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

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

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

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

Email: ncicteppubs@mail.nih.gov

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

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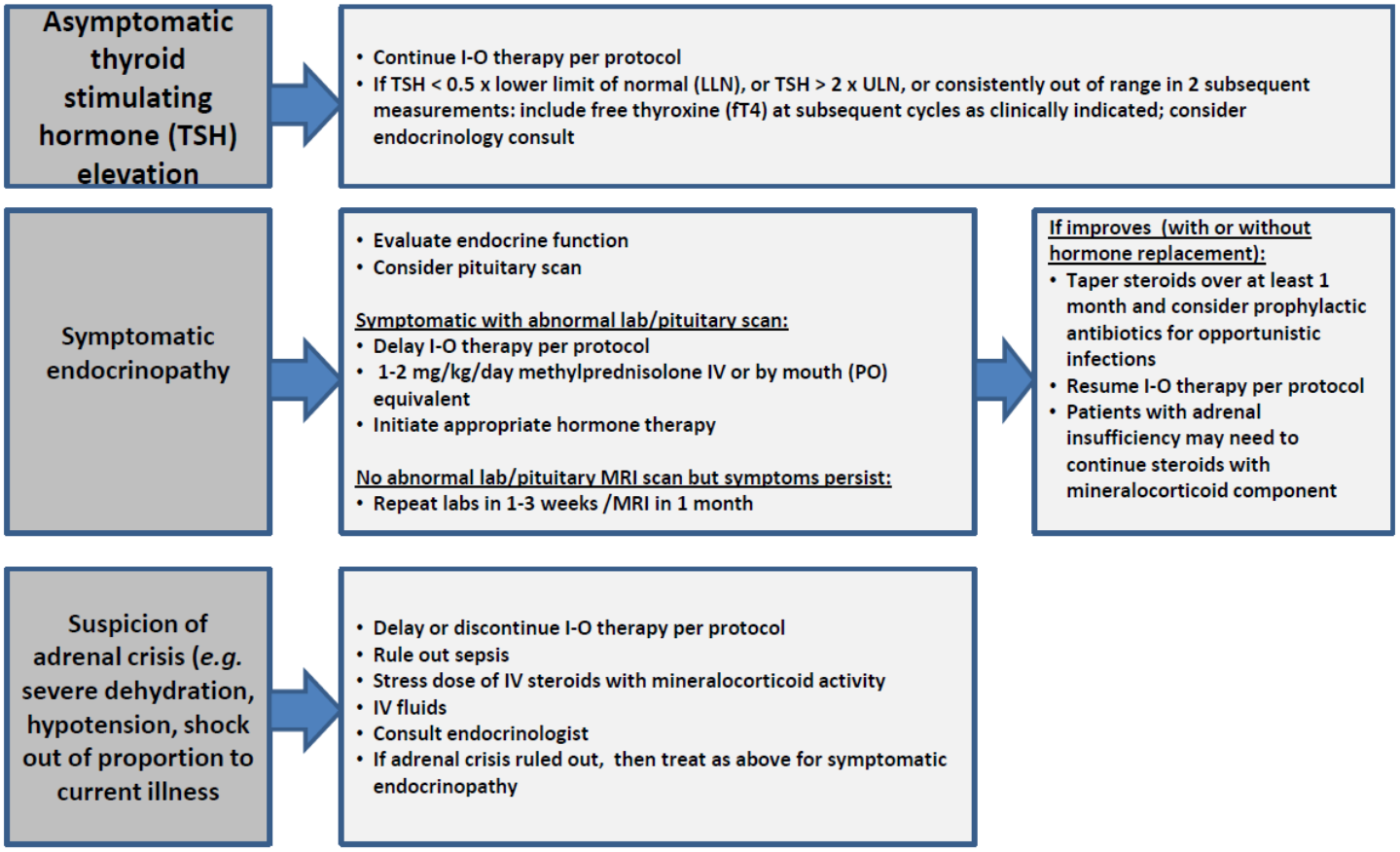
APPENDIX A. PERFORMANCE STATUS CRITERIA

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

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

Endocrinopathy Management Algorithm

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



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

GI Adverse Event Management Algorithm

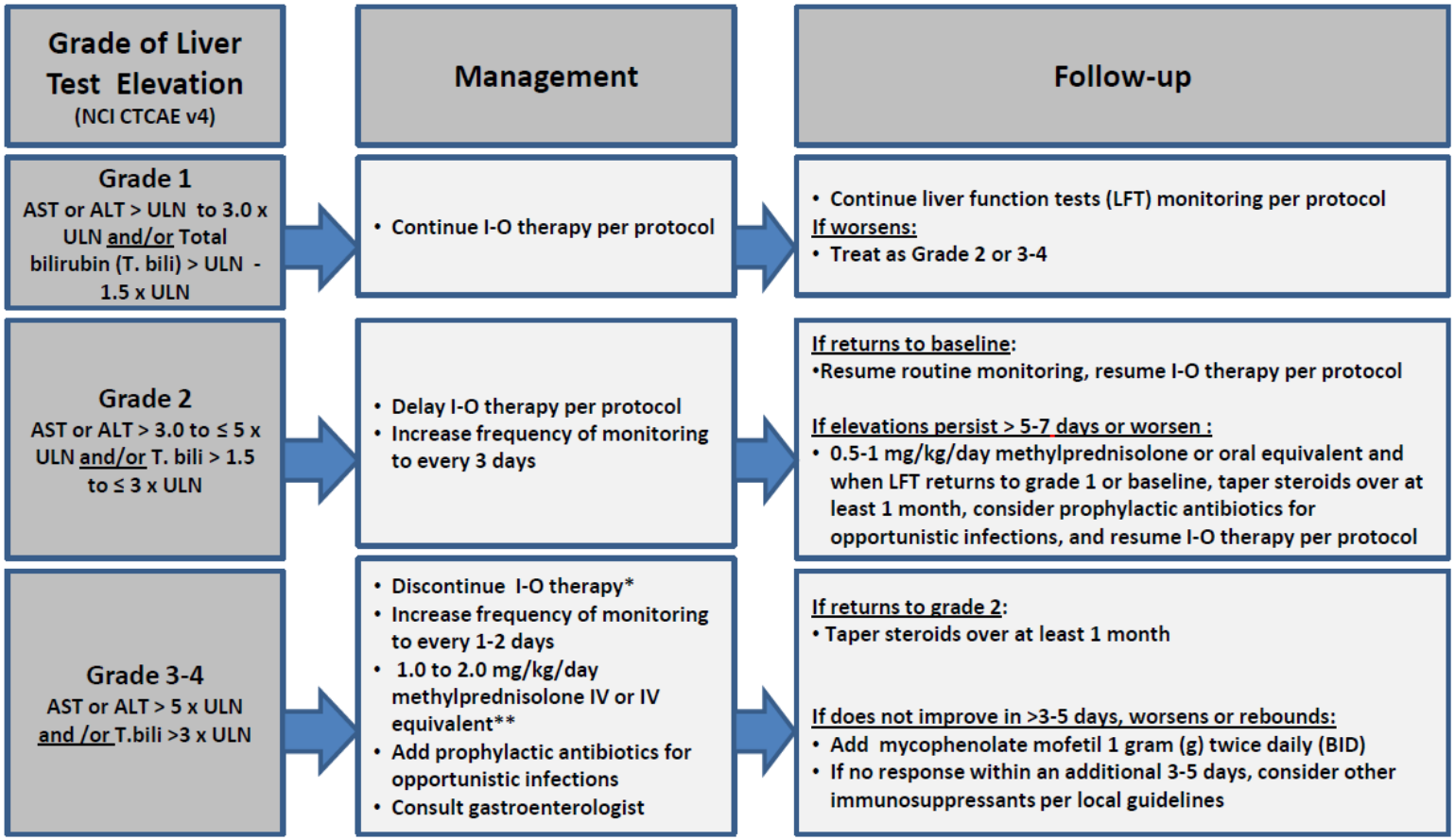
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

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.



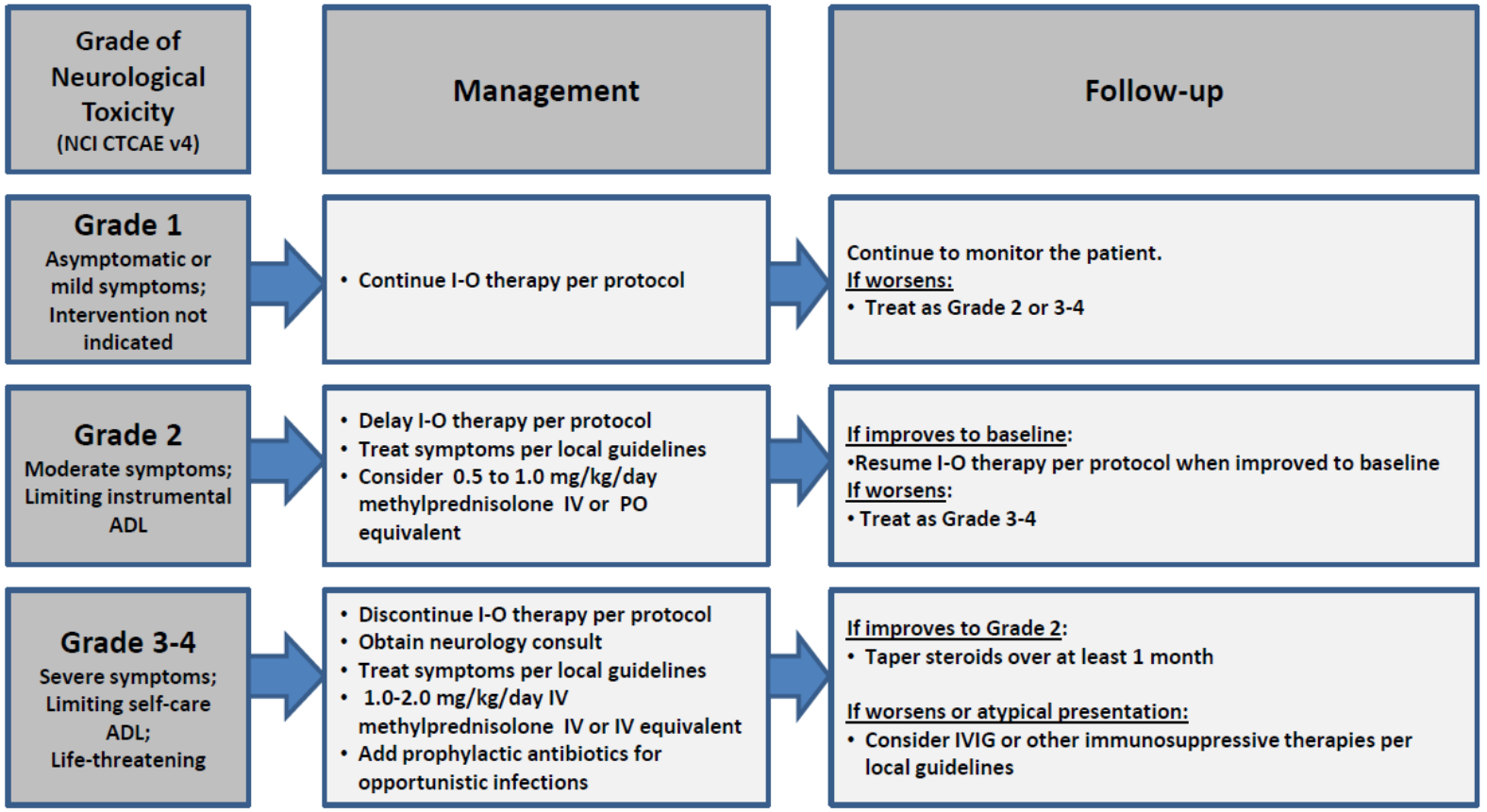
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Neurological Adverse Event Management Algorithm

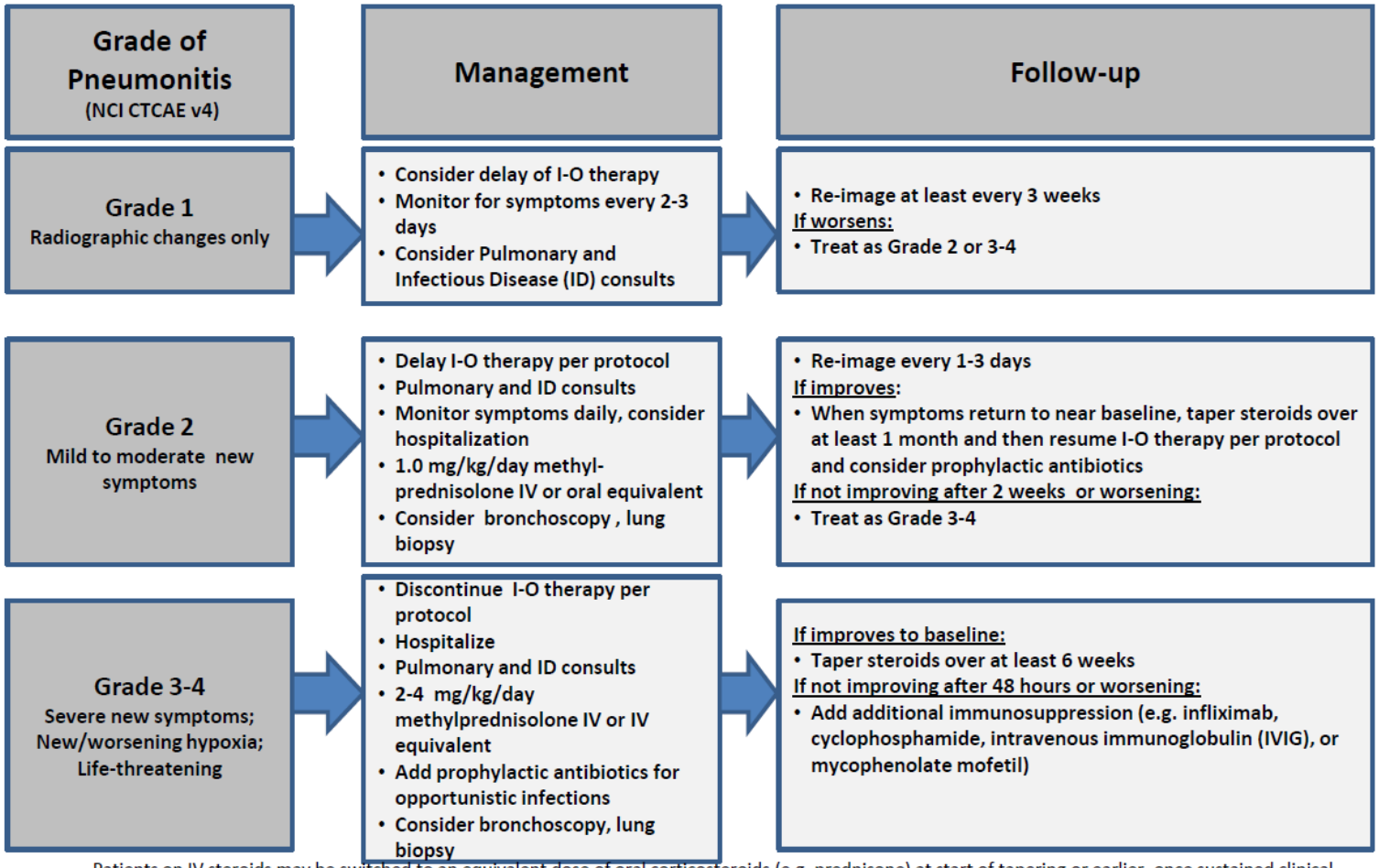
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

Pulmonary Adverse Event Management Algorithm

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



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

Renal Adverse Event Management Algorithm

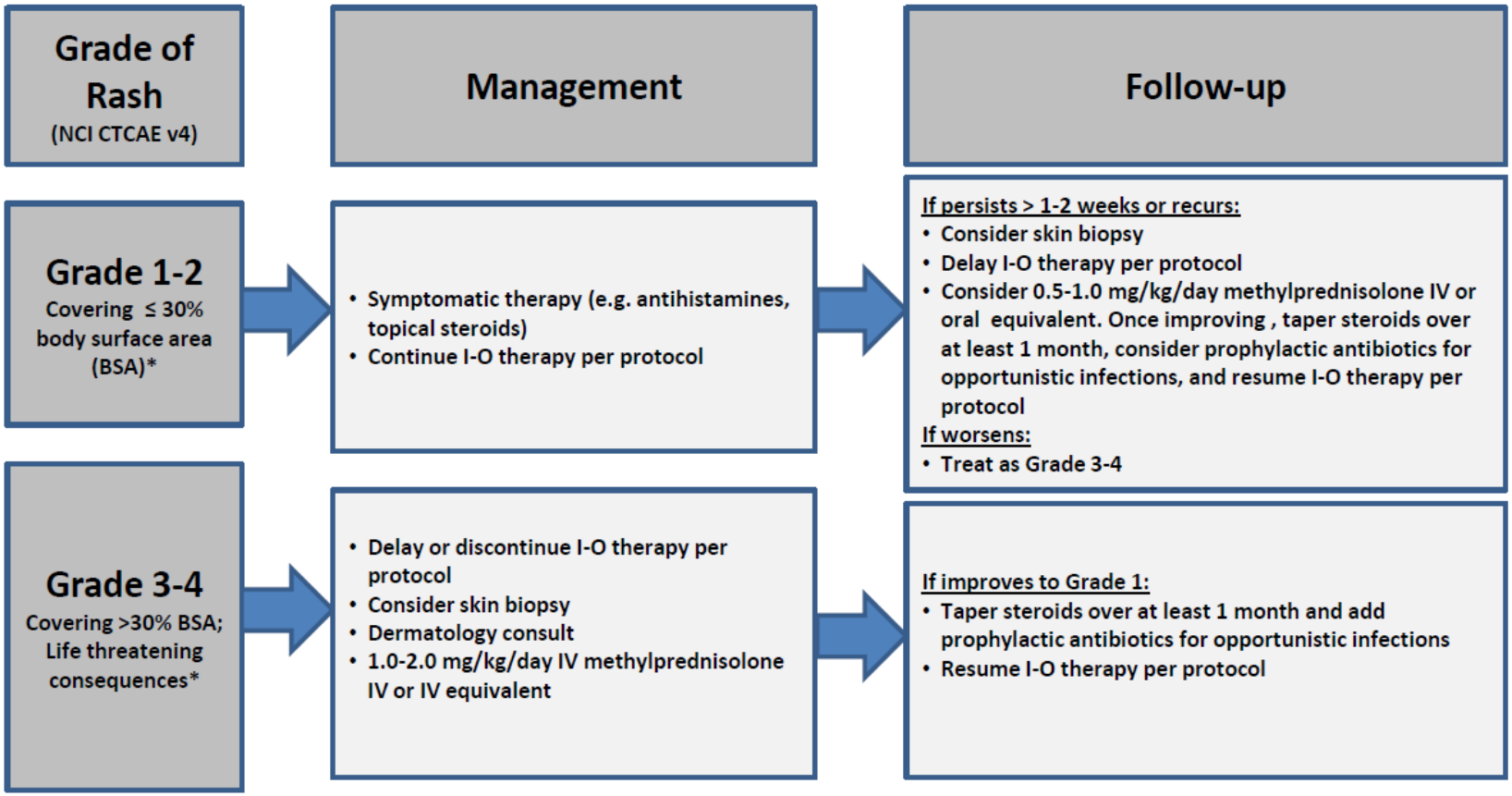
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > upper limit of normal (ULN) and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	<u>If returns to baseline</u>: •Resume routine creatinine monitoring per protocol <u>If worsens:</u> •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy	<u>If returns to Grade 1:</u> •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol <u>If elevations persist > 7 days or worsen:</u> •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	<u>If returns to Grade 1</u> : Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

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

Skin Adverse Event Management Algorithm

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



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

APPENDIX C. MEDICATION DIARIES

C.1 Medication Diary for Tacrolimus

CTEP-assigned Protocol # 10214
Local Protocol # ETCTN10214

PATIENT'S MEDICATION DIARY

Today's date: _____ **Agent: Tacrolimus**
Patient Name: _____(*initials acceptable*) **Patient Study ID:** _____

INSTRUCTIONS TO THE PATIENT:
1. Complete one form for each month.
2. You will take ___ ___-mg capsule(s) each day, ___ in the morning and ___ in the evening. You should take the capsules 12 hours apart, and at the same time each day. You should take the capsules with 8 oz. of water and without food.
3. Record the date, the number of capsules you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please return the forms to your physician when you go for your next appointment.

Day	Date	Time of morning dose	# of capsules taken	Time of evening dose	# of capsules taken	Comments
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
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21						
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26						
27						
28						
29						
30						
31						

Physician's Office will complete this section:
1. Date patient started protocol therapy: _____
2. Date patient was removed from study: _____
3. Patient's planned total daily dose: _____
4. Total number of pills taken this month: _____
5. Physician/Nurse/Data manager's signature: _____

Patient's Signature: _____

C.2 Medication Diary for Prednisone

CTEP-assigned Protocol # 10214
Local Protocol # ETCTN10214

PATIENT'S MEDICATION DIARY

Today's date: _____ **Agent: Prednisone**
Patient Name: _____(*initials acceptable*) **Patient Study ID:** _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month.
2. You will take your dose of prednisone each day in the morning. You will take ___ 5-mg tablet(s) every day with or without food. You should take prednisone at the same time each day and you should swallow the tablets whole. **Do not chew**.
3. Record the date, the number of tablets of each size you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please return the forms to your physician when you go for your next appointment.

Day	Date	What time was dose taken?	# of tablets taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
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Physician's Office will complete this section:

1. Date patient started protocol therapy: _____
2. Date patient was removed from study: _____
3. Patient's planned total daily dose: _____
4. Total number of pills taken this month: _____
5. Physician/Nurse/Data manager's signature: _____

Patient's Signature: _____

APPENDIX D. PATIENT CLINICAL TRIAL WALLET CARD

NIH NATIONAL CANCER INSTITUTE

CLINCIAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:	
Diagnosis:	
Study Doctor:	
Study Doctor Phone #:	
NCI Trial #:	10214
Study Drugs:	Nivolumab Ipilimumab Tacrolimus Prednisone

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

APPENDIX E. cfDNA COLLECTION

In addition to standard clinical monitoring, this study will investigate whether the cfDNA levels can serve as an early indicator of allograft rejection in the study population. The collection is standard of care (SOC).

Streck Cell-Free DNA BCT Tubes

Streck Cell-Free DNA BCT® Tubes for dd-cfDNA should be ordered as part of the Allosure® test kit directly from the CareDx® web portal: https://www.caredxinc.com/results-portal. This kit includes materials for collection and shipping.

Collection of Blood in cfDNA BCT® Tubes

1. Label two 10 mL cfDNA Streck tube according to the instructions in Section 5.3.1.
2. Collect 10 mL of blood into each pre-labeled tube and gently invert to mix. **Note:** blood must be thoroughly mixed to ensure preservation of specimen.
3. **After collection, blood in cfDNA BCT tubes should never be refrigerated**, as this will compromise the specimen. Blood collected in cfDNA BCT tubes is stable at room temperature.
4. Specimens should be shipped at room temperature on the day of collection

Blood Samples for Donor Derived Cell-Free DNA

Samples should be shipped at room temperature on the day of collection via overnight delivery to CareDx®. The Allosure® collection kits will include packing instructions and shipping labels.