CTEP P10080
CC 18-C-0033

TITLE: Phase I Study of Recombinant Interleukin 15 in Combination with Checkpoint Inhibitors Nivolumab and Ipilimumab in Subjects with Refractory Cancers

Abbreviated Title: IL-15 + Nivo + Ipi triplet

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NCI-Supplied Agent:
rhIL-15 (NSC 745101)
Nivolumab (NSC 748726)
Ipilimumab (NSC 732442)

IND #: 116180

IND Sponsor: DCTD, NCI

ClinicalTrials.gov Identifier: NCT03388632

Roles: [A]obtains information by intervening or interacting with living individuals for research purposes; [B]obtains identifiable private information about living individuals; [C]obtains the voluntary informed consent of individuals to be subjects; [D]makes decisions about subject eligibility; [E]studies, interprets, or analyzes identifiable private information or data/specimens for research purposes

PRÉCIS

Background:

- IL-15 is a stimulatory cytokine that activates the immune system, inducing proliferation of T lymphocytes and NK cells. Administration of recombinant human IL-15 (rhIL-15) has been shown to result in a dramatic increase of circulating CD8+T cells and NK cells; these changes in immune cell populations suggest potential for anti-tumor activity.
- Immune checkpoint inhibitors, including nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4), block the engagement of specific T-cell signaling pathways by tumor cells. These regulatory pathways typically act to downregulate T cell activity and are co-opted by tumors to allow the malignant cells to evade the immune response.
- The combination of rhIL-15 with two checkpoint inhibitor therapies has potential to lead to enhanced immune activation, resulting in anti-tumor T cell responses that are effective in refractory cancers.

Primary Objective:

- Determine the safety, toxicity profile, dose-limiting toxicity (DLT) and maximum tolerated doses (MTD) of subcutaneous administration of rhIL-15 given in combination with the anti-CTLA-4 antibody ipilimumab and the anti-PD-1 antibody nivolumab in patients with metastatic or treatment-refractory cancers.

Exploratory Objectives:

- Assess the clinical activity of rhIL-15, ipilimumab, and nivolumab combination therapy as characterized by RECIST 1.1 and immune RECIST (iRECIST) response rate of patients treated in this trial.
- Investigate the biological effects of this combination on circulating T cell subsets and on PD-1/ PD-L1 expression and immune cell activation in tumor tissue.

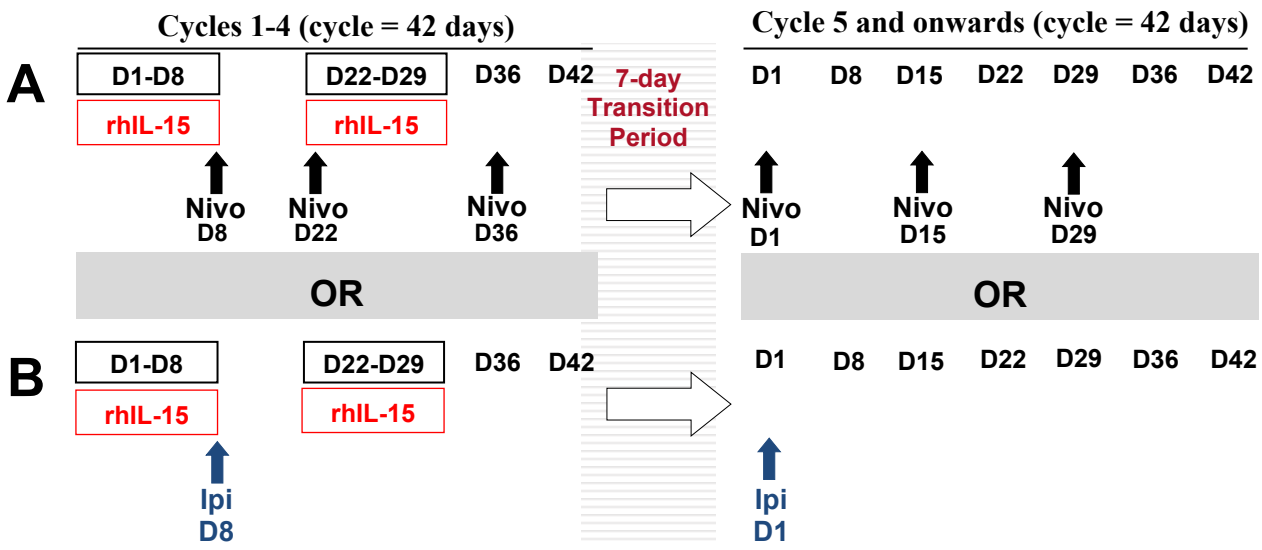
Eligibility:

- Patients $\geq$ 18 years of age with histologically confirmed solid tumor malignancy that is metastatic or treatment-refractory cancers

Study Design:

- The first 4-6 patients enrolling in the study will be placed into lead-in doublets with a combination of rhIL-15 and either nivolumab OR ipilimumab; once toxicity is cleared in both doublets (i.e., 2 patients enrolled on each doublet remain free of DLTs for 6 weeks) and a safety analysis is reviewed and approved by the IRB, new patients will be enrolled directly onto the triple agent combination.
- For the first four 42-day cycles on the triplet, patients will receive SC rhIL-15 on days 1-8 and 22-29, intravenous (IV) nivolumab on days 8, 22, and 36, and IV ipilimumab on day 8. Cycles 5 and onwards will not include treatment with rhIL-15
- Patients will be encouraged to report any and all adverse events, given the high likelihood of toxicities with the triplet combination therapy
- Blood for PD endpoints will be collected throughout the study and tumor biopsies will be collected pretreatment and on C1D42 (optional during the doublets and triplet escalation phase, mandatory during the triplet expansion phase)

SCHEMA: LEAD-IN DOUBLETS



The first 4-6 patients enrolling in the study will be placed into doublet A (2-3 patients) or doublet B (2-3 patients).

Doublet treatment cycle (cycles 1-4):
Doublet **A**:

rhIL-15 0.5 mcg/kg/day given SC days 1-8 and 22-29 (IL-15 doses are limited to first 4 cycles only)
Nivolumab (anti-PD1) 240 mg given IV on days 8, 22, and 36

OR
Doublet **B**:

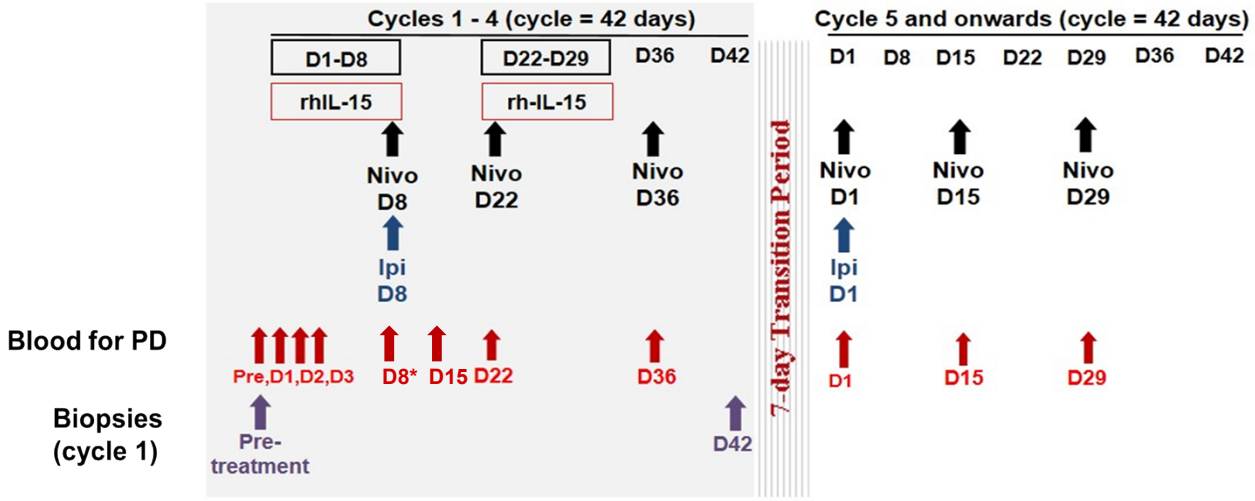
rhIL-15 0.5 mcg/kg/day given SC days 1-8 and 22-29 (IL-15 doses are limited to first 4 cycles only)
Ipilimumab (anti-CTLA-4) 1 mg/kg given IV on day 8

After completing 4 cycles, patients may continue onto single checkpoint inhibitor therapy for cycles 5 and onwards; they may not continue receiving rhIL-15 or enter the triplet cohort. A 1-week break (Transition Period) will be required between Cycle 4 and Cycle 5 to ensure a 2-week period between nivolumab doses.

CT scans for restaging will be performed every cycle (every 6 weeks) ± 1 week during cycles 1-4 and every 2 cycles (every 12 weeks) ± 1 week thereafter.

Blood and biopsy collection for assessment of PD endpoints will be optional (see Triplet Schema for timepoints).

SCHEMA: TRIPLET



New patients will be enrolled onto the triplet only after toxicity is cleared in both lead-in doublets (see Doublet Schema). Each doublet will enroll up to 3 patients. Toxicity is cleared once at least 2 patients enrolled on the doublet tolerate the treatment for 6 weeks (i.e., do not experience a DLT). If 1 patient on the doublet experiences a DLT, 1 or 2 more patients will be enrolled for a total of 3; if 2 of the 3 patients experience a DLT, enrollment into the triplet cohort will not occur, and the study will be halted and reevaluated.
As of Amendment C (10/3/18), toxicity has been cleared in both lead-in doublets. 3 patients were enrolled on Doublet A (rhIL-15 + nivolumab) and 2 patients were enrolled on Doublet B (rhIL-15 + ipilimumab); none of the 5 patients experienced a DLT in the 6-week period.

When nivolumab and ipilimumab are administered on the same day, nivolumab will be administered first followed by ipilimumab (Nivolumab Investigator Brochure 2016).

Cycles 1 through 4 (IL-15 doses are limited to first 4 cycles only**):**

rhIL-15 given SC days 1-8 and 22-29 based on dose level (DL 1 = 0.5 mcg/kg/day; DL 2 = 1 mcg/kg/day; DL 3 = 2 mcg/kg/day)
Nivolumab (anti-PD1) 240 mg given IV on days 8, 22, and 36
Ipilimumab (anti-CTLA-4) 1 mg/kg given IV on day 8
CT scans for restaging will be performed every cycle (every 6 weeks) ± 1 week

All subsequent cycles:

A 1-week break (Transition Period) will be required between Cycle 4 and Cycle 5 to ensure a 2-week period between nivolumab doses.

Nivolumab (anti-PD1) 240 mg given IV on days 1, 15, and 29
Ipilimumab (anti-CTLA-4) 1 mg/kg given IV on day 1
CT scans for restaging will be performed every 2 cycles (every 12 weeks) ± 1 week

Blood for flow cytometry assessments (mandatory) will be collected:

At baseline (pretreatment)
During cycles 1-4: day 1 to 3; day 8* (*before ipi + nivo), day 15 ± 2 days, day 22 ± 2 days; and day 36 ± 2 days
Cycle 5 and onwards: days 1, 15, and 29

Tumor biopsies (cycle 1 only) will be collected pretreatment and on C1D42 (optional during the escalation phase and mandatory during the expansion phase)

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 Determine the safety, toxicity profile, dose-limiting toxicity (DLT) and maximum tolerated doses (MTD) of SC rhIL-15 (rhIL-15), given in combination with the anti-CTLA-4 antibody ipilimumab and the anti-PD-1 antibody nivolumab in patients with metastatic or treatment-refractory cancers which are not curable or do not have known measures or treatments that are associated with a survival advantage

1.2 Exploratory Objectives

1.2.1 Assess the clinical activity of rhIL-15, ipilimumab, and nivolumab combination therapy as characterized by RECIST 1.1 and immune RECIST (iRECIST) response rate of patients treated in this trial

1.2.2 Investigate the biological effects of this combination on circulating T cell subsets and on PD-1/PD-L1 expression and immune cell activation in tumor biopsies

1.2.3 Perform genomic analysis on tumor biopsies in order to identify genomic alterations and gene expression changes associated with clinical response to rhIL-15, ipilimumab, and nivolumab combination therapy

2. BACKGROUND

2.1 Immunotherapy for Advanced Metastatic Solid Tumors

In the past several years, there have been very positive results obtained from clinical trials of immunotherapy treatments, including adoptive cellular therapies and immune checkpoint inhibitors [1-11]. Cellular therapies use autologous effector cells obtained from patients, such as tumor infiltrating lymphocytes (TILs), or genetically altered cells (chimeric antigen receptor cells, or CARs) to target malignant cells with a direct anti-tumor approach. However, even when an appreciable wave of these activated tumor antigen (Ag)-specific TILs can be generated, a prolonged immune response with the sustained production of stimulatory cytokines must be maintained for clinically significant anti-tumor activity [12-14].

An extended immune response can be achieved by inhibiting “immune checkpoints”, such as CTLA-4 or PD-1, intrinsic regulatory mechanisms that exist to control the amplitude of the immune response and are co-opted by cancer cells to limit anti-tumor activity. Inhibiting immune checkpoint signaling releases the “brakes” on the immune system, allowing T cells to exhibit antitumor activity. From the beginning, the clinical experience with CTLA-4 blockade demonstrated the advantages of this therapeutic strategy. Clinical activity was observed in patients with metastatic melanoma, hormone-refractory prostate cancer, and renal cell carcinoma (RCC) [15].

Correlative laboratory studies have demonstrated that CTLA-4 blockade increases the number of tumor-specific CD8+ effector cells, shifts the spectrum of effector cells away from the terminally differentiated phenotype, and downregulates Treg function. Other reports suggest that anti-

CTLA-4 treatment can potentiate the tumor-specific activity of NK cells [12, 16]. There is evidence that elevation of absolute lymphocyte count or higher frequency of circulating CD4+ ICOS^{high} T-cells correlates with an improved clinical outcome, including improved survival, in anti-CTLA-4-treated patients. Anti-CTLA-4 treatments can also potentiate the biologic effects of other immunotherapies such as vaccines, high dose interleukin-2 (HDIL-2), and granulocyte macrophage colony stimulating factor (GM-CSF) [17-21]. Recent publications reporting the efficacy and adverse event (AE) profile for sequential or combination anti-CTLA-4 treatment with other immunotherapeutics has demonstrated the real potential for combination checkpoint inhibitor therapy [22-24]. In fact, anti-CTLA-4 treatment is routinely combined with therapies targeting PD-1.

Another key immune checkpoint, programmed death-ligand 1 (PD-l) is expressed on activated T cells, and receptor expression is sustained in states of chronic stimulation such as chronic infection or cancer [25, 26]. Ligation of PD-1 with its ligand PD-L1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or inhibition of T cells (Figure 1). PD-L1 expression is prevalent in many human tumors (e.g., lung, bladder, ovarian, melanoma, colon carcinoma), and its overexpression has been associated with poor prognosis in patients with several cancers (the other known ligand of PD-1, PD-L2, is primarily expressed in normal tissues) [27-30]. Aberrant expression of PD-L1 on tumor cells and tumor-infiltrating immune cells, such as macrophages and dendritic cells, has been reported to impede anti-tumor T-cell immunity and contribute to immune evasion [31, 32].

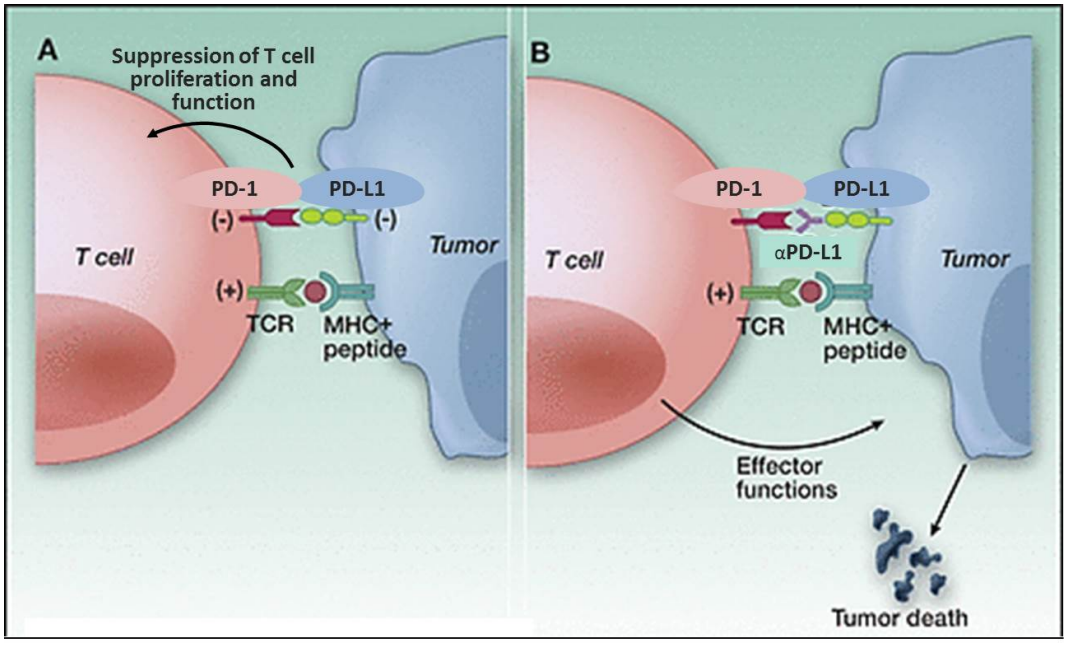


Figure 1. PD-1 and PD-L1 interaction and T cell responses. A) Binding of T-cell PD-1 by tumor PD-L1 results in the downregulation of T-cell proliferation and effector functions that destroy tumor tissue. B) Blockade of this pathway by an anti-PD-1 antibody prevents this downregulation, and allows T cells to maintain their antitumor response and ability to mediate tumor cell death. *Adapted from Sznol et al., 2013 [33].*

Given the inhibitory effects of PD-L1 signaling on T cell proliferation and activity, agents targeting PD-L1 pathways were developed with the intention of bolstering tumor-specific T-cell immunity. Indeed, the initial studies with anti-PD1 agents Nivolumab (Nivo) and Pembrolizumab (Pembro) demonstrated response rates in the 15 to 20% range for patients with relapsed refractory non-small cell lung cancer (NSCLC).

Early correlative laboratory results indicated that baseline (pretreatment) intratumoral PD-L1 expression was a key predictor of sensitivity to anti-PD1/PD-L1 therapy, identifying tumors to which the immune response could be positively modulated by interrupting the PD-1/PD-L1 axis. Subsequent publications have reported clinical activity for anti-PD1/PD-L1 agents in patients with (transitional cell) bladder cancer, Hodgkin's lymphoma (HL), non-Hodgkin's follicular lymphoma (FL) and squamous cell head and neck cancer (SCCH&N). The summated effect of this clinical data has led to the recognition that checkpoint inhibitor therapy may ultimately define a common treatment pathway for most metastatic relapsed/refractory malignancies [2, 5, 34-37].

Correlative analyses of cellular therapies have also led to recognition of neo-antigens (neoAgs) derived from tumor cells, resulting from mutations of various somatic genes, as superior targets for effector T cells. The importance of neoAgs as targets is most evident in the correction of the initial conclusion that colorectal (CRC) cancers were not sensitive to anti-PD1/PD-L1 treatment; actually, CRCs are responsive to checkpoint inhibitors when neoAgs stemming from microsatellite instability (MSI) or mismatch repair (MMR) deficiency are present [38, 39].

Overall, checkpoint inhibitor therapy represents a very promising avenue in cancer treatment. Two of the most extensively studied checkpoint inhibitors are ipilimumab, an anti-CTLA-4 antibody, and nivolumab, an anti-PD-1 blocking antibody.

2.1.1 Ipilimumab

Ipilimumab is an anti-CTLA-4 antibody approved by the FDA for the treatment of patients with unresectable or metastatic melanoma or adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy [40, 41]. Full dosing and administration information, as well as a more complete summary of the clinical experience with ipilimumab, can be found in the Yervoy® United States Package Insert [USPI] [41]. Discussion of adverse events and safety considerations can be found in Section 2.1.6 of the protocol.

2.1.1.1 Mechanism of Action

CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response [41].

2.1.1.2 Pharmacokinetics

The pharmacokinetics (PK) of ipilimumab was studied in 785 patients with unresectable or metastatic melanoma who received doses of 0.3, 3, or 10 mg/kg once every 3 weeks for 4 doses. The PK of ipilimumab is linear in the dose range of 0.3 to 10 mg/kg. Following administration of ipilimumab every 3 weeks, the systemic accumulation was 1.5-fold or less. Steady-state concentrations of ipilimumab were reached by the third dose; the mean C_{min} at steady state was 19.4 mcg/mL at 3 mg/kg and 58.1 mcg/mL at 10 mg/kg every 3 weeks. The mean value (percent coefficient of variation) based on population PK analysis for the terminal half-life (t1/2) was 15.4 days (34%) and for clearance (CL) was 16.8 mL/h (38%) [41].

2.1.1.3 Clinical Pharmacodynamics

Ipilimumab Effect on Circulating T Cells
CTLA-4 is a negative regulator of T-cell activation. By blocking CTLA-4, ipilimumab increases the percentage of peripheral activated T cells and central memory T cells (Investigator Brochure 2016). These changes are evidenced by Week 4 and generally remain sustained through Week 12 (Table 1). The sum of these changes in immune cell subsets may result in anti-tumor activity, as well as irAEs.

Table 1. Key T-cell Subsets from Studies CA184004 and CA184007

T-cell Population	**Study**	**Ipilimumab Dose (mg/kg)**	**Fitted Mean Relative Frequency (%) Mean (95% CI)**		
			Baseline[a]	Week 4[b]	Week 12[c]
Activated CD4+ / Total CD4+	CA184004	3	17.0 (13.4, 20.6)	25.2 (21.3, 29.2)	24.7 (21.0, 28.3)
		10	14.9 (11.2, 18.6)	24.8 (20.8, 28.8)	24.7 (20.5, 29.0)
Activated CD8+ / Total CD8+	CA184004	3	24.7 (18.9, 30.5)	31.1 (25.2, 37.1)	33.4 (27.5, 39.4)
		10	22.5 (16.5, 28.6)	25.7 (19.6, 31.9)	27.6 (21.0, 34.2)
Central memory CD4+ / Total CD4+	CA184007	10	54.5 (52.4, 56.7)	59.6 (57.5, 61.7)	62.0 (59.9, 64.1)
Central memory CD8+ / Total CD8+	CA184007	10	37.4 (33.8, 41.0)	41.0 (37.5, 44.6)	45.3 (41.7, 48.9)

[a] Baseline is defined as the predose measurement closest in time to first dose.
[b] Nominal Week 4 is defined as visits between study Days 8 and 42, inclusive.
[c] Nominal Week 12 is defined as visits between study Days 64 and 98, inclusive.

Preclinical data indicate that, in addition to increasing the number of tumor reactive T-effector cells that mobilize to mount an attack against tumor cells, CTLA-4 blockade can also reduce Treg function, which may lead to a further increase in anti-tumor immune response. Ipilimumab may selectively deplete Tregs at the tumor site, leading to an increase in the intratumoral T-effector/Treg cell ratio which drives tumor response leading to cell death [42].

Ipilimumab Effect on Absolute Lymphocyte Count
In clinical studies, ipilimumab increased absolute lymphocyte count (ALC) in peripheral blood. In 214 subjects with advanced melanoma in Study CA184022, ipilimumab increased ALC in a

dose-dependent manner, with the largest increase observed at 10-mg/kg dose (Figure 2).

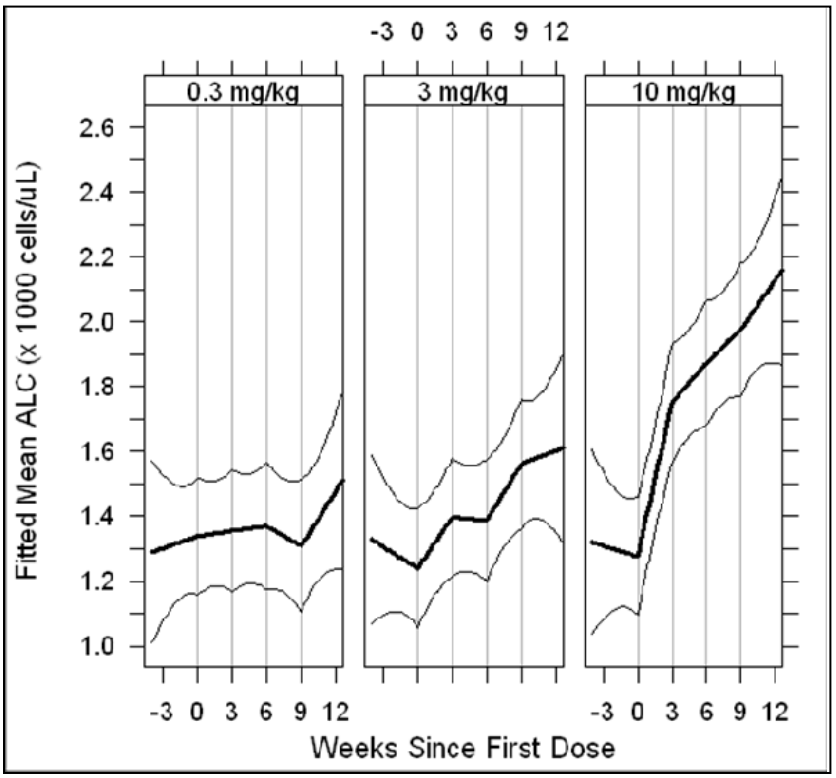


Figure 2. CA184022 Fitted Mean ALC versus Weeks since First Ipilimumab Dose, by Ipilimumab Dose

Interestingly, a unique checkpoint inhibitor phenomenon recognized early in the anti-CTLA-4 clinical trials was the potential for delayed response or response after initial early progression. This circumstance is now included in the decision algorithm for checkpoint inhibitor therapy and has been codified in the Immune Response Criteria Examination (ir-RC) that is now commonly applied in the response assessment for checkpoint inhibitor trials [43-45].

2.1.1.4 Clinical Development

Bristol-Myers Squibb (BMS) and Medarex, Inc. (MDX, acquired by BMS in Sep-2009) have co-sponsored an extensive clinical development program for ipilimumab, encompassing more than 19,500 subjects (total number of subjects enrolled in ipilimumab studies) in several cancer types in completed and ongoing studies, as well as a compassionate use program. 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.

Phase 3 programs are ongoing in melanoma, prostate cancer, and lung cancer. In melanoma, 2 completed Phase 3 studies (MDX010-20 and CA184024) have demonstrated a clinically meaningful and statistically significant survival benefit in pretreated advanced melanoma and previously untreated advanced melanoma, respectively. The safety profile of ipilimumab is generally consistent across these trials with a) the majority adverse events (AEs) being inflammatory in nature, which is consistent with the proposed mechanism of action of ipilimumab; b) the same types of such immune-mediated events in the gastrointestinal (GI) tract, skin, liver, and endocrine system being reported; and c) most of these events being manageable with immune suppressive therapies. See Section 2.1.6 of the protocol or the Yervoy® United States Package Insert [USPI] for further details [41].

In melanoma, 2 BMS-sponsored Phase 3 studies are ongoing in subjects with high-risk Stage III melanoma (CA184029, with adjuvant immunotherapy) and pretreated and treatment-naïve advanced melanoma (CA184169, 3 mg/kg versus 10 mg/kg ipilimumab). The completed Phase 3 study (CA184043) evaluated ipilimumab in subjects with metastatic castration-resistant prostate cancer (mCRPC) who had progressed during or following treatment with docetaxel. Eligible subjects were randomized to a single dose of bone-directed radiotherapy (RT), followed by either ipilimumab 10 mg/kg or placebo (799 randomized: 399 ipilimumab, 400 placebo). This study did not meet its primary endpoint of overall survival (OS). The hazard ratio (HR) of 0.85 (95% confidence interval [CI]: 0.72, 1.00) for survival favored ipilimumab but did not reach statistical significance with a P value of 0.053. Planned sensitivity analyses favored ipilimumab, where the greatest benefit appeared to be in subgroups defined by good prognostic features and low burden of disease. Additional evidence of ipilimumab activity observed in the study included a reduced risk of disease progression relative to placebo (HR = 0.70), superior clinical outcomes compared to placebo in tumor regression, and declines in prostate specific antigen (PSA). The safety profile in this study was consistent with the previously defined AE profile at the same dose.

2.1.2 Nivolumab

Nivolumab is an FDA-approved PD-1 blocking antibody; it is approved for the treatment of patients with unresectable or metastatic melanoma, metastatic non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and classical Hodgkin lymphoma [46]. Full dosing and administration information, as well as a summary of the clinical experience with ipilimumab, can be found in the OPDIVO® United States Package Insert [USPI] [46]. Discussion of adverse events and safety considerations can be found in Section 2.1.6 of the protocol.

2.1.2.1 Mechanism of Action

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

2.1.2.2 Pharmacokinetics

Nivolumab pharmacokinetics were assessed using a population PK approach for both single-agent nivolumab and nivolumab with ipilimumab.

Nivolumab as a single agent: The PK of single-agent nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of Nivolumab every 2 or 3 weeks. Nivolumab clearance decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of approximately 24.5% (47.6%) resulting in a geometric mean steady state clearance (CLss) (CV%) of 8.2 mL/h (53.9%); the decrease in CLss is not considered clinically relevant. The geometric mean volume of distribution at steady state (Vss) (CV%) is 6.8 L (27.3%), and geometric mean elimination half-life (t1/2) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by approximately 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks.

Nivolumab with ipilimumab: The geometric mean (CV%) CL, Vss, and terminal half-life of nivolumab were 10.0 mL/h (50.3%), 7.92 L (30.1%), and 24.8 days (94.3%), respectively. When administered in combination, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab. When administered in combination, the clearance of nivolumab increased by 42% in the presence of anti-nivolumab antibodies. There was no effect of anti-ipilimumab antibodies on the clearance of ipilimumab.

2.1.2.3 Clinical Pharmacodynamics

The clinical pharmacodynamics (PD) were assessed for nivolumab monotherapy and for nivolumab in combination with ipilimumab.

The PD effects of nivolumab were studied by assessing receptor occupancy (RO), peripheral immune cell population modulation, systemic cytokine modulation, and change in absolute lymphocyte count (ALC) in studies MDX1106-03 and/or CA209009 (Investigator Brochure 2016). Results were as follows:

- Peripheral RO of PD-1 is saturated at doses ≥ 0.3 mg/kg dose levels as measured on CD3+ cells from frozen and fresh peripheral blood mononuclear cells (PBMCs).
- Nivolumab treatment had no clinically meaningful changes in activated T-cells in peripheral blood; no dose response was evident.
- Baseline measurements of select immune cell subsets were not associated with response to nivolumab.
- Mean ALC measured over time did not change at any nivolumab dose nor was it associated with response to nivolumab.
- Median percent increase from baseline to post-dose for CXCL9 and CXCL10 were consistent with demonstration of immunomodulatory activity of nivolumab on these chemokines.

To understand if the effect of nivolumab in combination with ipilimumab was distinct from that of either nivolumab or ipilimumab monotherapy, changes in immunomodulatory PD biomarkers with combination nivolumab and ipilimumab treatment was assessed in study CA209004. ALC, activated CD4+ and CD8+ T cells in the periphery, and levels of inflammatory cytokines were measured in blood and serum in CA209004. Results were as follows:

- No consistent rise in ALC was observed with combination nivolumab and ipilimumab therapy, similar to nivolumab monotherapy.
- Increases in activated CD4+ and CD8+ T cells were observed with the combination regimen, consistent with the pharmacodynamic effects of ipilimumab alone and distinct from the effects of nivolumab alone.
- Combination therapy resulted in increases in interferon-β induced serum cytokines, such as MIG (CXCL9) and IP-10 (CXCL10), which are also increased with single agent nivolumab.

2.1.2.4 Clinical Development

The PK, clinical activity, and safety of nivolumab have been assessed in approximately 70 clinical studies sponsored by BMS, ONO, or other partners. Across those studies, approximately 12,300 subjects have received nivolumab monotherapy in single- or multiple-dose Phase 1/2/3 studies or studies with nivolumab in combination with other therapeutics (ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies).

Nivolumab has demonstrated clinical activity in NSCLC, melanoma, RCC, and cHL (approved indications) and other tumor types as monotherapy or in combination with ipilimumab. The majority of responses were durable and exceeded 6 months. In randomized, controlled studies, nivolumab monotherapy demonstrated statistically significant improvement in overall survival over standard of care in subjects with advanced or metastatic melanoma, in subjects with advanced or metastatic NSCLC, and in subjects with advanced RCC. In randomized, controlled studies, nivolumab in combination with ipilimumab demonstrated statistically significant improvement in progression-free survival and objective response rate over ipilimumab monotherapy in subjects with advanced or metastatic melanoma.

All available data suggest that nivolumab monotherapy has a consistent AE profile across tumor types. There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. The safety profile of nivolumab in combination with ipilimumab was consistent with the mechanisms of action of nivolumab and ipilimumab. The nature of the AEs was similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs were increased with the combination. See Section 2.1.6 of the protocol or the OPDIVO® United States Package Insert [USPI] for further details [46].

2.1.3 Combination Treatments with Checkpoint Inhibitors

Fully engaging the immune system's anti-tumor potential with combination therapy is expected to produce even more striking clinical activity. Combination checkpoint inhibitor trials have indeed

demonstrated an increase in efficacy, although higher amounts of toxicity have been observed as well.

The studies that were first performed compared treatment with single agent ipilimumab (Ipi) or single agent nivolumab (Nivo) versus the combination [47, 48]. The initial trial evaluated six different dose levels between the 0.3 to 10 mg/kg dose range for each agent given in combination, compared to a smaller group of patients previously treated with Ipi who then received sequential Nivo 1 or 3 mg/kg in patients with refractory metastatic melanoma. While the safety profile and efficacy were similar among 3 dosing cohorts (3 mg/kg of Ipi [Ipi3] + 1 mg/kg of Nivo [Nivo1], Ipi1 + Nivo3, and Ipi3 + Nivo3), the Ipi3 + Nivo1 combination dosing was selected as optimal for the treatment of melanoma.

The subsequent Checkmate 067 was a randomized, double-blind phase III trial that compared this combination dose level to the licensed monotherapy regimens and confirmed significant improvement in response rate and median progression-free survival [47]. There was a higher incidence of AEs and CTC grade 3 or 4 events in the patients treated with the combination. These toxicities led to a greater number of patients discontinuing the therapy and a higher rate of treatment with "immune modulating" corticosteroid, but had no noticeable impact long term morbidity or mortality. Data from the more recent Checkmate 012 trial, which evaluated 4 different combination treatment doses and schedules given as first line therapy to metastatic NSCLC patients, demonstrated that Nivo 3 mg/kg with Ipi 1 mg/kg given every 6 or 12 weeks is probably a better treatment plan for advanced non-melanoma patients [49].

The considerable safety data from these trials has produced a good understanding of the toxicity profile and the relative contribution of each agent to AEs (see discussion of safety considerations in Section 2.1.6 of the protocol). Data from these trials also showed similar response rates for PD-L1^{pos} and PD-L1^{neg} patients treated with the combination treatment or Nivo, raising questions regarding the clinical consequences of intratumoral PD-L1 expression and highlighting the fact that there is still much to learn regarding modulation of the anti-tumor immune response. There are currently several ongoing clinical trials evaluating other checkpoint inhibitor combinations, as well as randomized trials comparing anti-PD-1 and anti-CTLA-4 treatment in combination versus monotherapy in patients with NSCLC, small cell lung cancer (SCLC) requiring maintenance treatment, and other melanoma subgroups.

2.1.4 Summary of Clinical Experience with Recombinant Human Interleukin 15 (rhIL-15)

IL-15 is a stimulatory cytokine that activates the immune system by inducing proliferation of T lymphocytes and NK cells. The first-in-human (FIH) phase I dose escalation clinical trial with rhIL-15 was performed at the NCI in patients with metastatic melanoma and renal cell carcinoma. Recombinant hIL-15 was given as a 30-minute infusion (IVB) once daily for 12 consecutive days [50]. Ultimately, dose escalation was limited by a constellation of post-infusional toxicities related to a concentrated wave of cytokine production, and the MTD was much lower than predicted by the non-human toxicology experiments. While resolution or shrinkage of some tumor deposits was seen in a number of patients' restaging scans, the best response was stable disease. At the same time this trial was being conducted, additional preclinical non-human

primate (NHP) experiments indicated that sustained-treatment rhIL-15 regimens (continuous intravenous infusion [CIV] and subcutaneous [SC] injection) were better immune activators, were less toxic, and had greater clinical potential than the IVB regimen [51]. Based on the NHP and other preclinical data, parallel clinical trials evaluating CIV treatment for 10 consecutive days and SC treatment given Monday through Friday for 2 consecutive weeks were opened [52, 53]. These nearly completed trials have shown general improvement in the toxicity profile and more pronounced immune activation than what was observed in the IVB trial (refer to the Investigator Brochure 2017 for more information).

There are several important observations and safety findings from these trials that directly affect design when considering combination rhIL-15 and checkpoint inhibitor treatment. While the most common AE with rhIL-15 treatment was anemia, autoimmune GI toxicity has also occurred (Table 2). However, more than a half dozen patients treated in the NCI rhIL-15 trials had previous significant auto-immunity, usually GI toxicity, during their prior ipilimumab treatment, and none of these patients demonstrated any flare or recurrence of these irAEs during their rhIL-15 treatment.

Table 2. Adverse Events ≥ Grade 2 Related to rhIL-15 Observed Between April 23, 2013 and April 22, 2014, on Study 10-C-0021 (Investigator Brochure 2017)

Adverse Event	Grade	Number of Events
Blood and lymphatic system disorders		
Anemia	2	34
Anemia	3	7
Cardiac disorders		
Pericardial effusion	2	1
Gastrointestinal disorders		
Ileus	2	1
Nausea	2	1
Vomiting	2	1

In addition to the common cytokine side effects of fevers, myalgias, and arthralgias, most patients treated at the higher dose levels in the CIV rhIL-15 trial had transient asymptomatic elevation of hepatic transaminases (ALT and AST), but this resolved spontaneously (even with continuation of the rhIL-15 treatment). As a result, transient grade 3 events were later excluded as DLTs.

Transient skin toxicities of pruritus, erythematous rashes and 2 unique cases of classic SLE butterfly-like rashes were seen in 2 CIV rhIL-15 patients. Neither patient had changes in their negative auto-antibody profile or arthropathy or auto-immune type findings and these rashes resolved completely after their treatment was finished. Transient grade 3/4 neutropenia was observed, but this likely reflected a redistribution of neutrophils from the circulation to the tissues rather than a depletion of neutrophils (Investigator Brochure 2017).

2.1.5 Preclinical Experiments Evaluating the Triple Combination of Interleukin 15 (IL-15), anti-CTL-A4 and anti-PD-L1 Treatment

The combination of rhIL-15 with anti-CTLA-4 and anti-PD-1 treatment has potential to lead to enhanced immune activation, resulting in anti-tumor T cell responses that are effective in refractory cancers. IL-15 administration has been shown to increase PD-1 expression on CD8+ T cells, suggesting that combination with an anti-PD-1 antibody especially could increase effectiveness [54]. This hypothesis has led to the testing of this triple combination in 2 preclinical mouse tumor models [54, 55]. These experiments assessed the *in vivo* activity of single agent treatment with murine IL-15 (mIL-15), anti-PD-L1 (antibody 9B2), or anti-CTLA-4 (antibody UC10-4F10-11), as well as paired doublet and triplet combination therapy. Treatment was begun after intravenous (IV) injection of the colorectal cancer cell line CT-26 or subcutaneous (SC) injection of the prostate cancer cell line TRAMPC2. The mIL-15 treatment was administered intraperitoneally (IP) days 1-5, 8-12, and 15-19, analogous to the CIV and SCrhIL-15 already piloted in patients. The checkpoint inhibitors or isotype-matched IgG control antibodies were given IP twice weekly also for 3 weeks. As seen in Figure 3, treatment of CT-26 tumor-bearing mice with mIL-15 significantly increased PD-1 expression on CD8+ cells and CD8+CD44^{high} (memory) cells compared to control treatment, and T-cell PD-1 expression was reduced below the level seen in the control animals by co-administration of either anti-PD-L1 or the combination of anti-PD-L1 and anti-CTLA-4 [54].

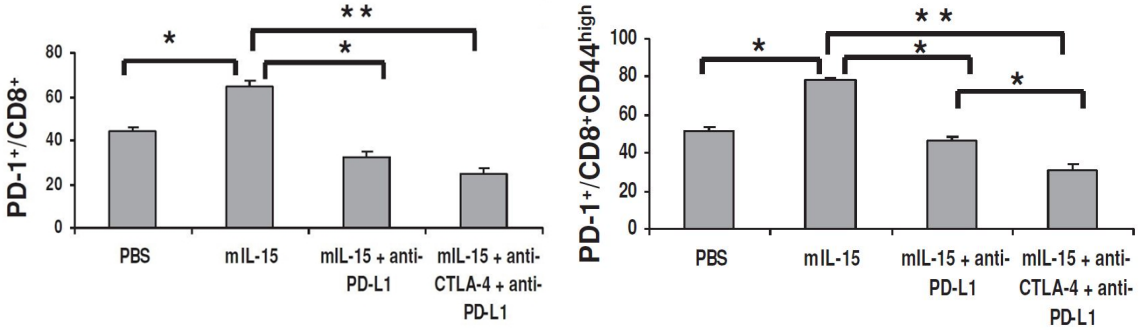


Figure 3. Flow cytometry analyzing PD-1 expression on splenic CD8$^+$ and CD8$^+$CD44^{high} T cells from CT26 tumor-bearing mice following treatment. Surface expression of PD-1 on CD8$^+$ T-cells was detected using APC-anti-CD8, PE-anti-PD-1 and isotype-matched IgG as a negative control. The figure is representative of 2 independent experiments wherein each group contained 3 to 5 animals. Statistical analysis was performed on the basis of PD-1 expression on CD8$^+$ and CD8$^+$CD44^{high} T cells. *, $P < 0.05$ and **, $P < 0.01$. *Adapted from Yu et al., 2010 [54].*

The triplet regimen resulted in significantly more production of the stimulatory IFNγ and less of the immunosuppressive IL-10, and it had greater cytotoxicity (lytic capacity) on a per cell basis than the control, mIL-15 or mIL-15 + anti-PD1 treatment groups (data not shown). Animals treated with the triplet regimen had fewer lung metastases (Figure 4A) and survived longer than animals treated with the three monotherapies or any paired combinations (Figure 4B) [54].

Similar data from experiments in the prostate cancer TRAMPC2 model system show that the triplet regimen increased the number of tumor-specific CD8+ T-cells and memory (CD44+) CD8+ T-cells assessed by tetramer analysis of stimulator of prostatic adenocarcinoma specific T-cells, or SPAS-1 (Figure 5A and B) [55]. This increase in the number of tumor-specific T-cells correlated with delayed tumor growth (Figure 6A) and improved overall survival (Figure 6B) for the triple therapy-treated group compared to the other treatment groups [55].

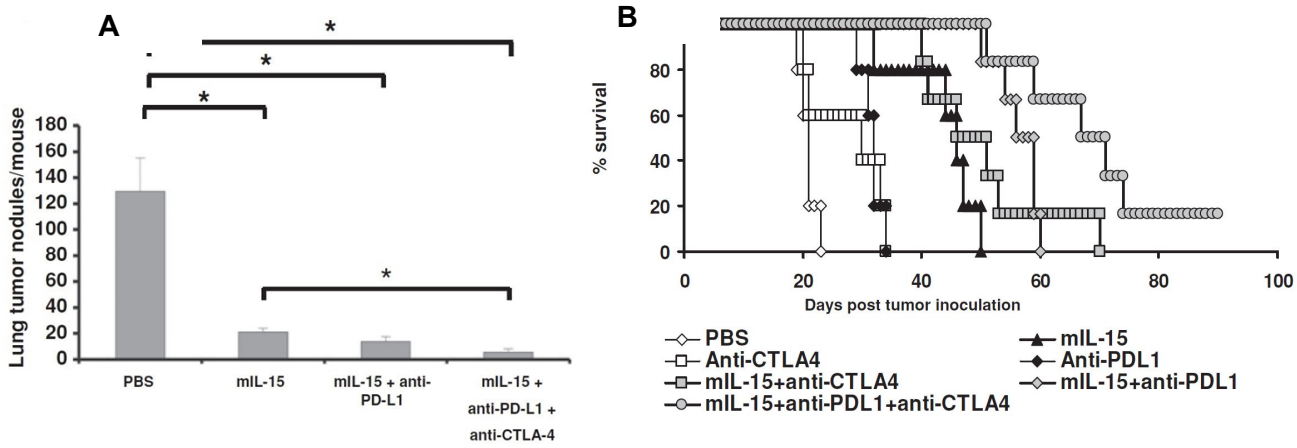


Figure 4. (A) IL-15 treatment reduced the number of tumor nodules in the lungs. Graph represents the number of CT-26 pulmonary metastases found on day 21. Each treatment group had 3 to 5 mice and the data is representative of 3 independent experiments. **(B)** IL-15 treatment in combination with multiple checkpoint inhibitors prolonged survival of CT26 tumor-bearing animals. Kaplan –Meier survival curves by treatment group. PBS control (open diamonds), anti-CTLA-4 (open squares), mIL-15 + anti-CTLA-4 (gray squares), mIL-15 (black triangles), anti-PD-L1 (black diamonds) and triple combination (gray circles). Data represent 3 independent experiments. *Adapted from Yu et al., 2010 [54].*

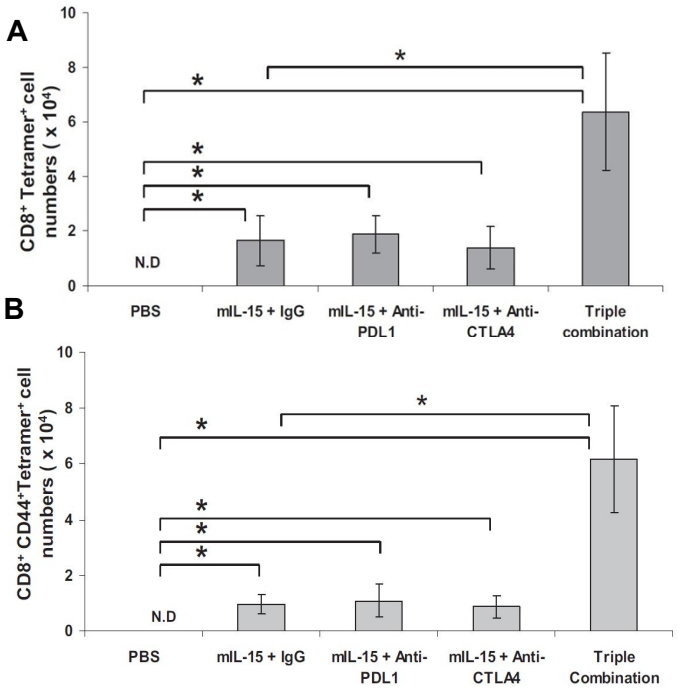


Figure 5. IL-15 given in combination with checkpoint inhibitors (anti-CTLA-4 and anti-PD-L1) was associated with an increase in SPAS-1 specific CD8+ and CD8+ memory cells. On day 21, splenocytes from tumor bearing mice that had undergone the various treatments were stained with PE-conjugated SPAS-1 tetramer. The absolute numbers of CD8+ T cells **(A)** and of CD8+CD44$_{high}$ T-cells **(B)** are shown, with data derived from 5 independent experiments. *Adapted from Yu et al. 2012 [55].*

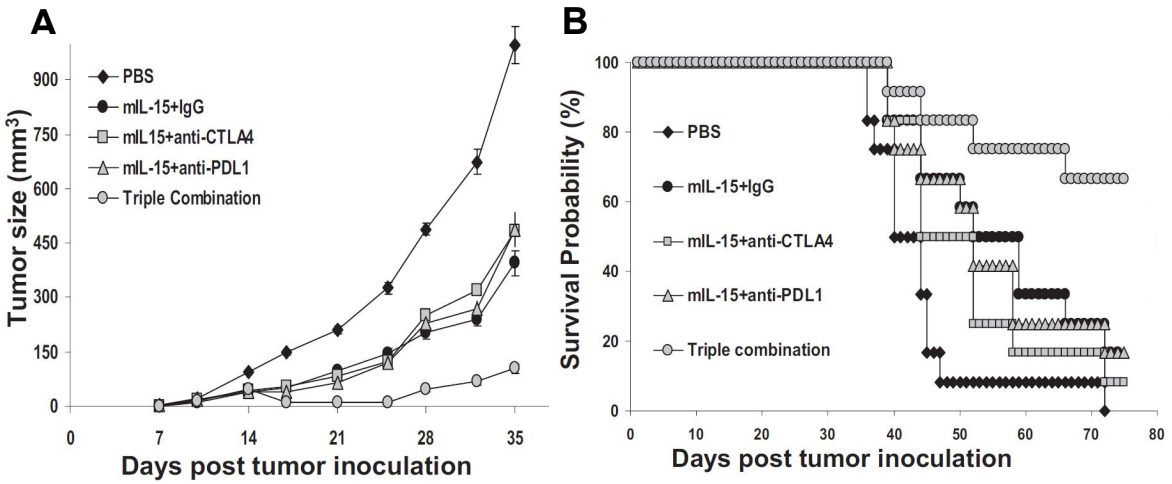


Figure 6. IL-15 given in combination with checkpoint inhibitors (anti-CTLA-4 and anti-PD-L1) protected against tumor growth and improved survival in TRAMPC2 tumor-bearing mice. **(A)** Tumor sizes are shown as mean ± SEM for 10 mice per treatment group. **(B)** Kaplan –Meier survival curves illustrate survivals of the mice for the respective treatments. *Adapted from Yu et al., 2012 [55].*

Finally, the roles of CD8+ and NK effector cells in this system were examined in subset depletion experiments with anti-CD8 or anti-NK-cell antibodies. As seen in Figure 7, depletion of CD8+ lymphocytes entirely negated the benefit of the triple therapy, allowing the tumors to grow to a similar size as in PBS control-treated mice [55].

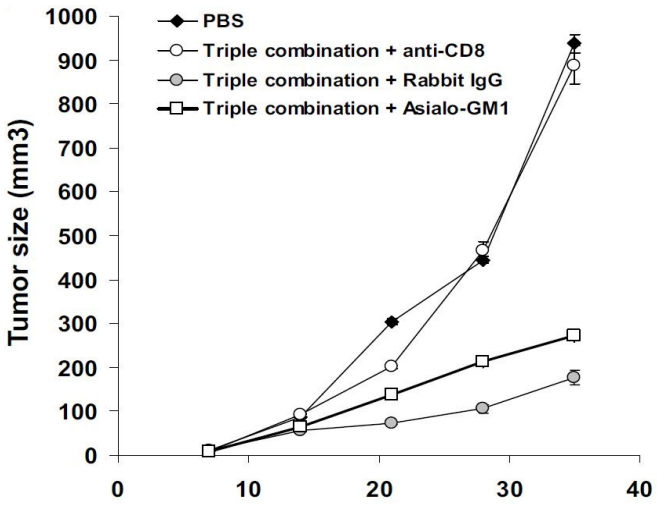


Figure 7. CD8+ T cells instead of NK cells involved in the antitumor response to TRAMP-C2 mediated by IL-15. Growth curves illustrate in vivo growth rates of TRAMP-C2 prostate tumors associated with mIL-15 **(A)** or triple combination **(B)** treatment. Selected groups of mice were administrated 50 mcL per mouse anti-asialo-GM1 or rabbit IgG to deplete NK cells on days 0 and 1, and then three times per week for 3 wk. Data represent two independent experiments. Tumor sizes shown represent means ± SEM, n = 8. *Adapted from Yu et al., 2012 [55].*

2.1.6 Adverse Events and Considerations for Clinical Safety

While these immunotherapeutic approaches have been shown to have tremendous benefit in various tumor types, the nature of these therapies—namely, activating the immune system—can lead to serious toxicities. Anti-CTLA-4 blockade, for example, demonstrates a rather unique spectrum of immune-related toxicities or adverse events (irAEs), including a potentially fatal pan-colitis that resembled inflammatory bowel disease (IBD). Other less problematic, but still clinically relevant, AEs caused by anti-CTLA-4 blockade include cutaneous inflammation, dysfunction of the pituitary gland (hypophysitis), and less commonly hepatitis, glomerulonephritis, pneumonitis, and neuropathies [15, 56-59].

Ipilimumab specifically has been shown to cause severe immune-mediated adverse reactions that include enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy (see Table 3). In clinical trials, the majority of these events initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab. Ipilimumab has also been shown to more commonly (in ≥5% of patients) cause fatigue, diarrhea, pruritus, rash, and colitis when administered at 3 mg/kg; at the higher 10 mg/kg dose, it commonly (in ≥5% of patients) causes nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, and insomnia. In the clinical trial evaluating ipilimumab at a dose of 3 mg/kg with or without an investigational gp100 peptide vaccine in patients with unresectable or metastatic melanoma, ipilimumab was discontinued for adverse reactions in 10% of patients. In the trial evaluating ipilimumab at a dose of 10 mg/kg versus placebo for adjuvant treatment of melanoma, ipilimumab was discontinued for adverse reactions in 52% of patients. Additional information regarding ipilimumab AEs can be found in the Yervoy® USPI [41].

Table 3. Summary of irAE Safety Data for 10 mg/kg Ipilimumab in Melanoma

	Total	**Low-grade (Grade 1 - 2) (%)**	**High-grade (Grade 3 - 4) (%)**	**Median Time to Resolution Grade 2 - 4 irAEs (weeks)**
All irAEs	72.3	46.2	25.2	-
Skin (*e.g.*, rash, pruritus)	52.0	49.2	2.8	6.14
GI (*e.g.*, colitis, diarrhea)	37.2	24.9	12.3	2.29
Liver (*e.g.*, LFT elevations)	8.0	0.9	6.8	4.0
Endocrine (*e.g.*, hypophysitis, hypothyroid)	6.2	3.7	2.5	20.1

Therapies targeting the PD-1/PD-L1 axis are associated with similar toxicities. Across all nivolumab studies conducted to date, drug-related AEs due to immune-related inflammation have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, GI toxicity, dermatologic toxicity (including rash), and hepatotoxicity (Investigator Brochure 2016). When nivolumab was given to patients with advanced melanoma,

NSCLC, castration-resistant prostate cancer, or renal-cell or colorectal cancer [9], serious adverse events (SAEs) occurred in 32 of 296 patients (11%). In a trial evaluating nivolumab at a dose of 3 mg/kg in patients with unresectable or metastatic melanoma, 26% of patients receiving nivolumab had a drug delay for an adverse reaction, and nivolumab was discontinued for adverse reactions in 9% of patients. A maximum tolerated dose (MTD) of nivolumab was not defined [46].

In a trial evaluating the combination of nivolumab and ipilimumab, the most frequent (≥10%) serious adverse reactions in the nivolumab plus ipilimumab arm and the nivolumab arm, respectively, were diarrhea (13% and 2.6%), colitis (10% and 1.6%), and pyrexia (10% and 0.6%). Serious adverse reactions (73% and 37%) and adverse reactions leading to permanent discontinuation (43% and 14%) or to dosing delays (55% and 28%), and all occurred more frequently in the combination relative to the nivolumab single agent arm [46]. 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 (Investigator Brochure 2016).

In the nivolumab clinical trials, GI and hepatic AEs were managed with treatment interruption or corticosteroids, and endocrine AEs were managed with replacement therapy as necessary, following algorithms similar to those developed for management of ipilimumab immune-related AEs [33]. Additional information regarding nivolumab AEs can be found in the OPDIVO® USPI [46].

Treatment with rhIL-15 carries serious autoimmune risks as well. While significant gastrointestinal (GI) toxicity was not common in the first 3 rhIL-15 trials, there was one very significant and striking incident of GI toxicity. The second patient treated at the 4 mcg/kg dose level in the CIV trial had grade 5 visceral arterial ischemia manifested as patchy infarction of the entire stomach, small and large bowel considered probably related to study treatment. The event occurred in the face of grade 2 then 3 diarrhea initiated by a change in enteric feeding formula and worsened after initiation of empiric ampicillin/sulbactam treatment classically associated with antibiotic associated diarrhea (Investigator Brochure 2017). The confounding or contributing factors make this event hard to interpret in the absence of a postmortem, but this incident alone weighs strongly against the safety profile of rhIL-15.

Overall, the AE profiles for rhIL-15, anti-PD1, and anti-CTLA-4 treatment have important overlaps for GI, hepatic, and cutaneous toxicities that raise concern for synergistic toxicities when combining these 3 agents. The possibility of synergistic toxicity must be considered in the design and the treatment plan when proposing this triplet therapeutic regimen. Evaluating each rhIL-15 checkpoint inhibitor combination first as a doublet, beginning with rhIL-15 administration alone, will help in deconstructing each individual agents' contributions to the AE spectrum, improving the risk-benefit equation for this treatment.

Another important factor in the design of the treatment plan is integrating the prior safety experience of the individual agents into the complete (dose adjustment, dosing delay or interruption, and resumption) treatment algorithm. Combination therapy has consistently led to a higher rate of treatment discontinuation due to adverse events than the rates seen with either

ipilimumab or nivolumab monotherapy. A previously reported phase I-II dose escalation trial examining the combination of the anti-CTLA-4 antibody MDX-010 with a different stimulatory cytokine, high dose IL-2, in 36 melanoma patients had 5 patients (14%) develop grade III/IV auto-immune toxicities [18], highlighting the ability of checkpoint inhibitor therapy to potentiate autoimmune effects caused by cytokine-induced T cell activation. A dose adjustment algorithm for the combination of Ipi/Nivo has been developed by the industry sponsors based on the appreciable clinical experience, previous AE findings, and the criteria for initiation of immunosuppressive treatment for particular Immune Related Adverse Events (irAE).

Immune-related AEs, including those affecting the skin and mucosal membranes, GI tract, liver, and kidney, can be managed with corticosteroid treatment, as mentioned above [60]. Indeed, updated results from the Checkmate and Keynote combination trials have shown that 50 to 75% of patients treated with the combination anti-PD-1 anti-CTLA-4 regimens received corticosteroid or other remitting agents. Furthermore, many patients had uninterrupted therapy for only short periods (median number of Ipi doses 3 and Nivo 3 to 4 doses Checkmate 218) [61-64]. The high rate of AEs, premature discontinuation of treatment, and initiation of immunosuppressive "immune modulatory agents" (IMM) that occurred in the combination-treated patients was not found to have a negative impact on efficacy. However, there is no prior clinical experience to assess the impact of concurrent corticosteroid treatment on patients who are receiving rhIL-15 treatment. The possibility of interruptions in treatment and the occasional addition of IMM corticosteroid therapy for substantial lengths of time are problematic for this proposal because the presumption must be that corticosteroids will substantially reduce or ablate the positive effects of rhIL-15.

2.2 Rationale

Immune checkpoint inhibition, in particular, PD-1/PD-L1 and CTLA-4 blockade, has had a broad but significant impact on the outcome of patients with several different types of cancer. Combining these agents, which act on different stages of T cell activation, with rhIL-15 is expected to dramatically enhance the anti-tumor immune response by causing T cell expansion, differentiation, and cytotoxic activity.

Regarding dosing, in the initial clinical trials with the Bristol Myers Squibb (BMS) anti-PD-1 agent Nivo, treatment was administered every 3 weeks, and this schedule was continued in the trial which evaluated combination treatment with Ipi [48]. The well-established treatment schedule for Ipi is also every 3 weeks for a maximum of 4 doses. In part due to the clinical experience with Merck's anti-PD1 agent Pembro, which has an every-other-week treatment schedule since first introduced, Nivo is now more commonly administered every other week when given in combination with Ipi. This new combination schedule led to a very complicated week 1, 2, 3, 4, and 5 treatment schedule for the 6-week treatment cycle in the randomized double-blind phase III trial comparing combination treatment with Ipi plus Nivo to single agent Nivo or Ipi (and to the appropriate placebos to preserve treatment blinding [47]. Recent changes have been made in the dose and schedule for Nivo and Ipi to improve or simplify these treatments. Nivo is now typically given at an unadjusted dose of 240 mg (although there are exceptions; see package insert [46]) and Ipi is administered every 3 weeks for the first 4 doses and every 12 weeks thereafter [41]. In the NCI-sponsored trials, rhIL-15 has been administered

for 10 to 12 usually consecutive days each 28 or 42-day cycle [49-52].

Given the established treatment regimens for rhIL-15, Nivo, and Ipi, it was not possible to devise a dosing schedule for the combination of these 3 agents that did not require some adaptation of the prior schedules. We have maintained the Nivo dosing schedule at every other week, as is commonly done when Nivo is administered in combination with Ipi. Ipi will be administered every 6 weeks (42 days) throughout the study, rather than being given less frequently after the initial treatment period, as is typically done. If there are concerns about toxicity after the completion of 4 cycles, patients may discontinue ipilimumab.

To further prevent toxicity in later cycles, rhIL-15 doses are being limited to the first 4 cycles. The initial triplet therapy cohorts will receive rhIL-15 at the lowest dose that has demonstrated appreciable immunologic activity in the prior trials and the current Nivo and Ipi recommended phase 2 doses and schedule. Evaluating each checkpoint inhibitor in combination with rhIL-15 as a doublet—before administering triple combination therapy to any patients—will help ensure safety, while also revealing the individual agents' contributions to the AE profile.

Furthermore, an 8-day run-in period with rhIL-15 alone before the addition of either checkpoint inhibitor is the optimal treatment schedule in terms of both safety and efficacy. Preclinical experiments have demonstrated that IL-15 treatment increases PD-1^+ lymphocyte infiltration [65], and a delay before administration of Nivo and Ipi ensures adequate time for the T cell population to undergo expansion and priming for an anti-tumor immune response, making inhibition of the PD1 and CTLA-4 checkpoint pathways much more effective. Results from the ongoing CIV rhIL-15 clinical trial have also generated findings indicating treatment-related inflammation at sites of tumor in a number of patients treated at the higher tolerable dose levels, suggesting sequential administration of rhIL-15 followed by Nivo with lower incidence of irAEs and then Ipi is the optimal treatment sequence. While in prior trials rhIL-15 has been administered for 10 to 12 consecutive days, we expect the 8-day period to be similarly effective in inducing T cell proliferation and have carefully chosen this length of treatment to fit with the dosing schedules of Nivo and Ipi.

2.3 Correlative Studies Background

Although checkpoint inhibitory agents have been shown to have clinical activity, there is as yet no predictive biomarker for this class of agent. Blocking PD-L1:PD-1 interactions with nivolumab and CTLA-4 signaling with ipilimumab may release the immune checkpoint blockade, allowing tumor infiltrating lymphocytes (TILs), myeloid-derived suppressor cells (MDSCs), M2 macrophages, and N2 neutrophils to mount an immune response [66, 67]. From the pharmacodynamic perspective, a relationship between extent of mutational load and molecular response of the T-cell receptor in CD8+ TILs should be expected following immune checkpoint therapy in cases that are expressing immune checkpoint molecules (i.e., in cases with a high likelihood that immune checkpoint pathways are preventing an immune response against neo-antigens). The "negative control" is that this should not occur in tumors not utilizing the checkpoints being inhibited by therapy, as evidenced by PD1/CTLA-4 TIL phenotyping.

One of the challenges of developing assays to measure the effects of immunotherapeutic agents

is that the target is an immune cell rather than a tumor. It is therefore necessary to measure primary effects on immune cells and secondary effects on the cancer cells, as well as the interactions between these two populations (Figure 6.2). Experimental models with an intact immune system are required for this, thereby excluding immunodeficient xenograft models and tumor cell lines.

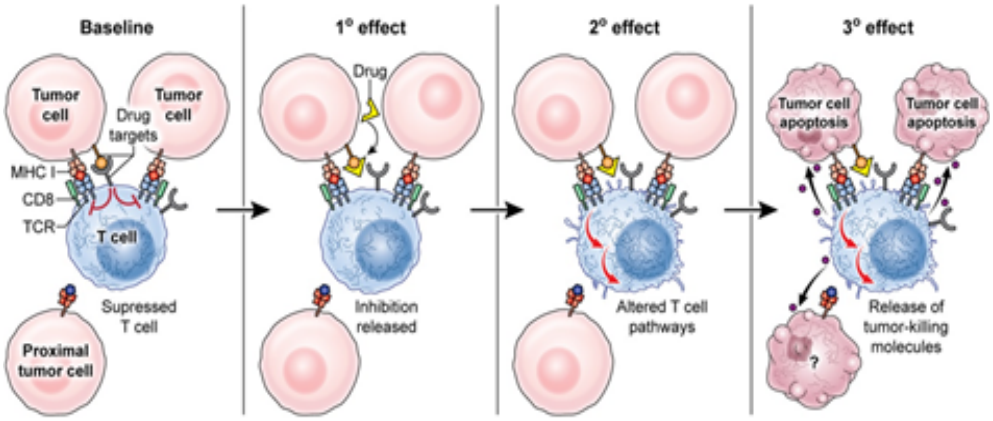


Figure 6.2. Immunoassays to measure the PD effects of checkpoint blockade agents can encompass effects on the immune cell-tumor cell interface, the T cell, and adjoining tumor cells (*adapted from Parchment et al [68]*).

The Pharmaceutical Assay Development and Implementation Lab (PADIS) at Frederick National Laboratory for Cancer Research (FNLCR) is currently developing a slide-based multiplex immunofluorescent assay to evaluate response to immune checkpoint inhibitors. Multiplexing allows geographical interpretation of tumor-immune cell interactions such that the location of TILs and T helper cells, expression of PD-L1 and PD1, and finally consequence of drug effect (e.g., apoptosis) within a tumor region of interest can be superimposed. Experimental methods using mixed cell cultures, including activated T cells, tumor cell targets, and supporting mesenchymal cells, are being used to validate measurement of PD-1 signaling in T-cells; for these assays, suitable antibodies against key signaling components have been commercially sourced, and new antibodies have been developed.

Detection of the activation of SHP-1, SHP-2, CD3zeta, and ZAP70, as well as the presence of PD1, PDL1, Ki67, and T cell phenotyping markers, has been validated in these systems and in TMAs. The following biomarkers can be imaged in formalin-fixed paraffin embedded sections (Figures 7.2-12); multiplex image capture and image analysis algorithms to quantify the biomarker staining are in development:

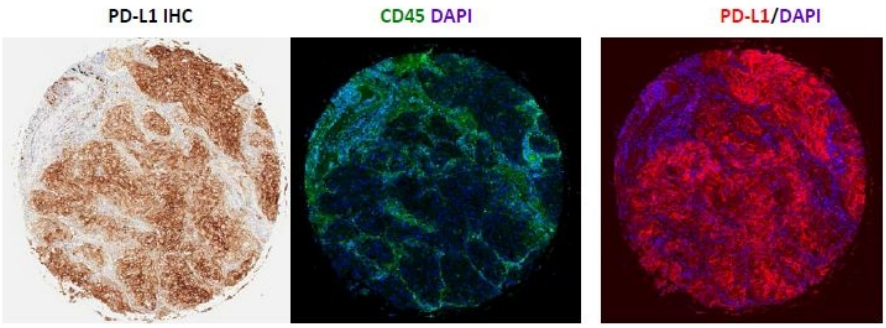


Figure 7.2. Two-plex IF. PD-L1 and CD45 common leukocyte antigen in a TMA of NSCLC cases.

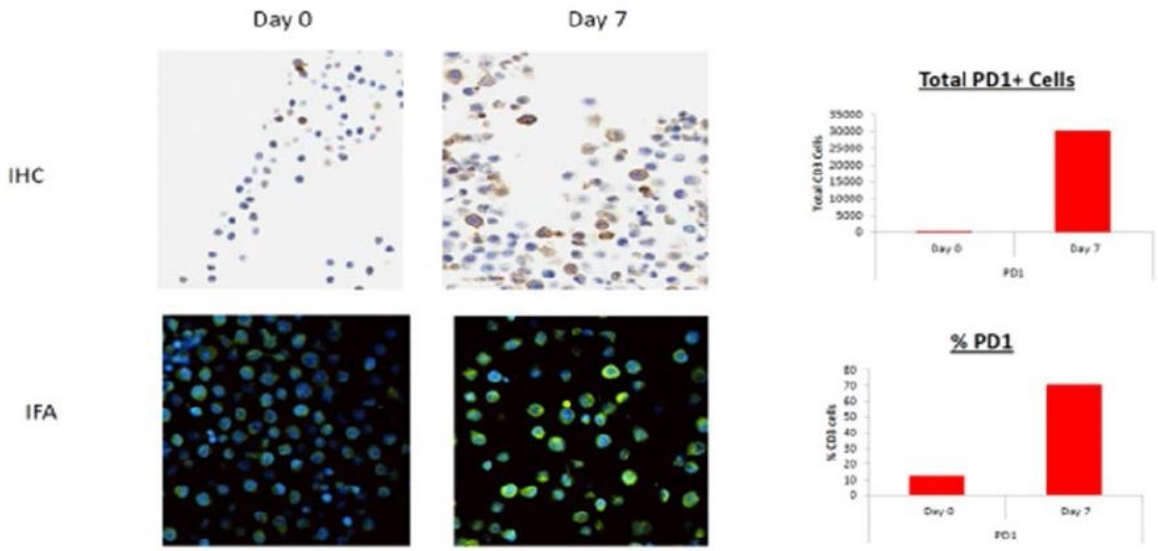


Figure 8. IHC and IFA analyses of PD-1 in FFPE sections of pelleted CD3/CD28-stimulated human T cells *in vitro*.

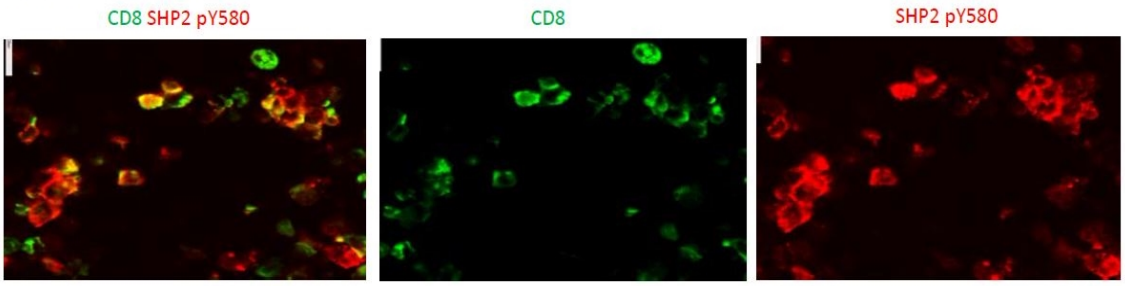


Figure 9. Two-plex IFA of CD8 (CTL)-restricted analysis of PD-1 signaling via pY580SHP2 in CD3/28/137-stimulated human T cells *in vitro*.

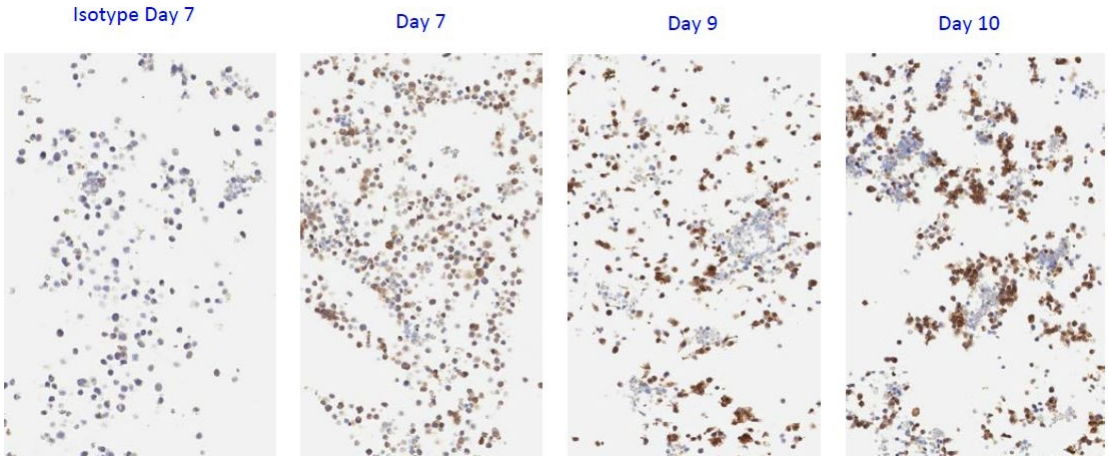


Figure 10. IHC analysis of pY580SHP2 in FFPE sections of pelleted CD3/28/137-stimulated human T cells *in vitro*.

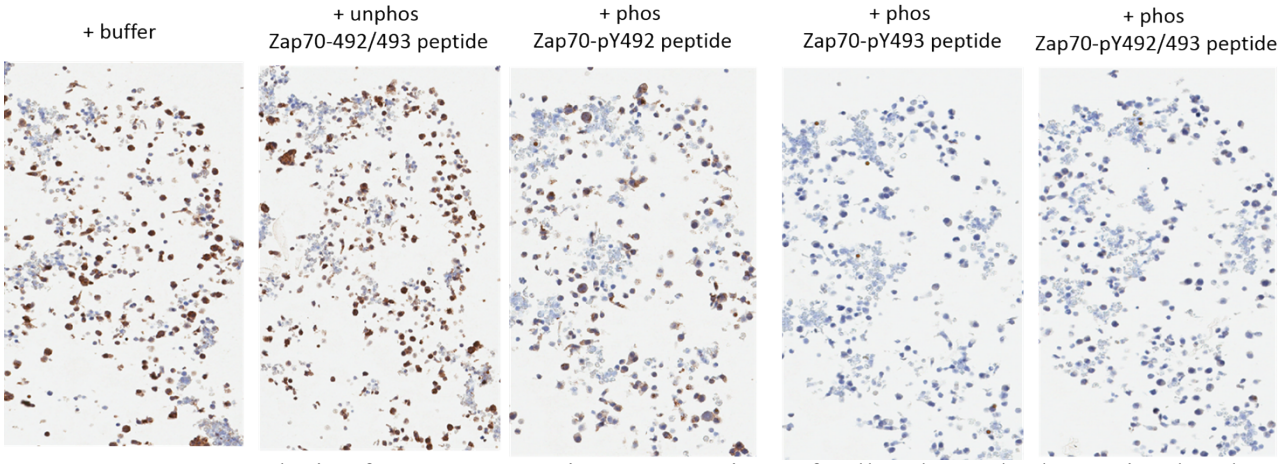


Figure 11. IHC analysis of pY493ZAP70 in FFPE sections of pelleted CD3/28/137-stimulated human T cells *in vitro*. The antibody to Zap70-pY493 is specific for pY493 epitope, as it can be blocked by incubation with the Zap70-pY493 peptide and not with the Zap70-pY492 peptide.

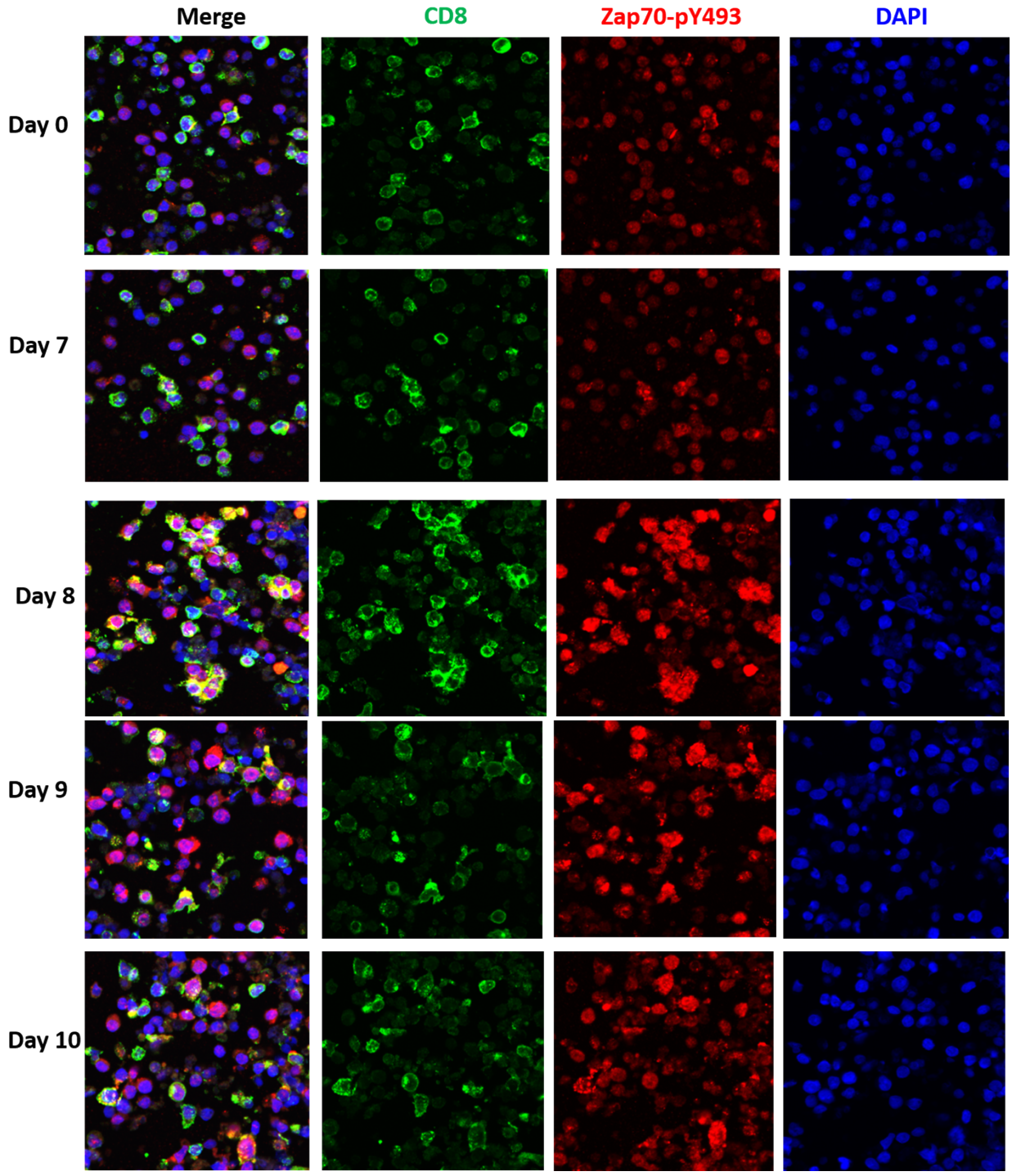


Figure 12. Zap70-pY493 staining of RDP 0707 CD3 cells stimulated with anti-CD3, CD28 and CD137 beads. Co-staining with CD8 is also shown. Zap70-pY493 signal will be thresholded based on positive and negative T cell controls and patient data can be reported as % CD8 with net positive or negative phospho-Zap70 pY493 signal.

Samples for correlative studies will be collected from the triplet cohorts only.

Paired biopsies (optional during the doublets and triplet escalation phase, mandatory during the triplet expansion phase) will be collected pretreatment and once at the end of cycle 1 (between days 40-42). Biopsy samples will be analyzed for:

- Status of PD1/PD-L1 checkpoint signaling
  - PD-1, PD-L1, PD-L2 (IHC)
  - pPD-1, phosphorylated cytoplasmic tail (qIFA)
    - For evidence of disruption of PD-L1 binding
  - pY^{536}SHP1, and possibly pY^{542}SHP2/ pY^{580}SHP2
- Tumor content of Tregs, CTLs, and myeloid-derived suppressor cells (MDSCs)
  - CD8, CD4, and Ki67 expression
  - CD69, TIM-1 and LAG-3
    - For immune cell activation
- Status of TCR activation
  - Activated T-cell receptor (TCR), specifically phosphorylated Zeta chain (pζ TCR) (qIFA)
    - For evidence of tumor immunity; TCR recognition of tumor antigen/T cell activation is a prerequisite for obtaining clinical benefit with immune checkpoint blockade
  - Activated ZAP70 (phosphorylated ZAP70-pY493) (qIFA)
    - For net balance between stimulatory and inhibitory signals
- Activation of intrinsic apoptosis signaling, using a validated, clinically suitable multiplexed immunoassay [69]
- Endothelial CAM expression
- JAK/STAT pathway analysis to further assess immune signaling: Nuclear phosphoSTAT3 and phosphoSTAT5 levels

Priority will be given to assays analyzing the status of PD1/PD-L1 checkpoint signaling and T cell activation, specifically Zap70-pY493. As Zap70 is the integration point between stimulatory (TCR) and inhibitory (immune checkpoint) signaling, phosphorylation on Y493 indicates that, as a result of immune checkpoint blockade, the net signaling has resulted in a T cell response. The other proposed assays will be performed if sufficient tissue is available.

Blood samples (optional during the doublets, mandatory during the triplet escalation/expansion phases) will also be collected throughout the triplet study (See Section 9.3) and will be analyzed for:

- Activation status of peripheral T cell subsets based on intracellular phosphomarkers (TCAP1) by flow cytometry
- Investigation of the expansion of NK cells and Gamma Delta-T cells (TCAP1-NK) by flow cytometry

T cell activation panel 1 (TCAP1) is a phospho-flow assay and the TCAP1-NK assay panel is a similar flow cytometric assay validated at PADIS using healthy donor PBMCs. Similarly to the IFA assay for biopsies discussed above, the TCAP1 assay allows the measurement of phosphorylation status of proteins related to T cell activation on circulating CD4+ and CD8+ T cells. The TCAP1-NK assay detects NK cells and Gamma Delta-T (γδ) cells and these immune cells are being investigated further to assess IL-15 impact on NK cells given that the Thomas Waldmann phase 1 trial with IL-15 (administered by continuous intravenous infusion) showed an IL-15-mediated expansion of NK-cell subsets [70]. The full TCAP1 and TCAP1-NK staining panel can be seen in Table 4 below.

Table 4. TCAP1 and TCAP1-NK Flow panel

	Target	Fluorochrome
Gating	CD3	PE-Cy7
	CD4	BV421
	CD8	BB700
	CD45	PE-CF594
	CD33	BV786
Analysis	CD279 (PD-1)	BV650
	Lck (pTyr505)	BV605
	Zap70 (pTyr493)	AF647
	SHP-2 (pTyr542)	PE
	CD3z (pTyr142)	AF488
	CD274 (PD-L1)	BV711
	CD56 (TCAP1-NK)	NCAM16.2
	CD16 (TCAP1-NK)	3G8
	TCR γδ1 (TCAP1-NK)	TS8.2
	TCR γδ2 (TCAP1-NK)	B6

2.3.1 Exploratory Laboratory Analyses

Exploratory genomic analysis may be performed on tumor biopsy samples from patients that respond to treatment. At the PI's discretion, patients on the triplet escalation/expansion phases that have baseline biopsy samples available (archival or collected on study) may be asked to undergo an additional optional biopsy at the time of confirmed response (patients that have already given two biopsies on study would not be eligible for this optional time-of-response biopsy, as the maximum number of biopsies per patient on this study is two). These biopsy samples will be used for whole exome (WES) and whole transcriptome (RNASeq) genomic analysis to enable the assessment of genomic alterations and gene expression changes associated with response (additional assays may be performed at the PI's discretion if an adequate amount of tumor tissue is collected). These data will be compared to data from germline blood to identify somatic variants. Comparison of the baseline sample to the post-treatment sample would reveal genomic changes that occur in the tumor with treatment over time and potentially shed light on the mechanisms of response to rhIL-15, ipilimumab, and nivolumab combination therapy. Genes of interest would include those involved in the immune response and antigen presentation (JAK/STAT pathway, TGFβ pathway, HLA genes) [71]. WES data would also be

used to determine tumor mutational burden (TMB), a biomarker previously shown to be associated with better survival after checkpoint inhibitor therapy [72, 73]. These exploratory sequencing results would not be shared with patients.

2.3.2 Genetic Sequencing Research Ethics

This trial may collect identifiable genetic data from patients enrolled after **Amendment G** (3/4/20) for exploratory studies to examine genomic alterations and gene expression patterns potentially associated with sensitivity to treatment. As patient clinical response data will be required for comparison to sequencing results, de-identifying the samples is not feasible. Designing the study therefore poses challenging questions about informed consent, the privacy of the patient and the patient's family, the researchers' obligation to disclose genetic information to the patient, and the use and storage of research data [74-76]. In the vast majority of cases, we do not know the medical significance of genetic variants [77, 78]. These challenges will continue to be evaluated to maintain the rigor and integrity of the study and the well-being of our patients. A Certificate of Confidentiality has been obtained from the NIH to help protect the privacy of all study participants.

The informed consent document for this protocol after **Amendment G** (3/4/20) contains language informing patients about the performance of genetic studies, and patients will have the option to choose whether they wish to take part in these studies.

Whole-exome sequencing (performed for research purposes; non-CLIA) of tumor and blood can detect non-ambiguous germline variants, which may raise health and privacy implications for the patient and his or her family. WES will not be validated for clinical use, and no clinical decisions can be made based on its results (see Section 9.5).

This study does not meet the criteria specified by the NIH Genomic Data Sharing (GDS) Policy and therefore a GDS plan has not been included in this protocol.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Subjects must have histologically confirmed solid tumor malignancy that is metastatic or treatment refractory cancers which are not curable or do not have known measures or treatments that are associated with a survival advantage (as defined by the subject or the physician Investigator). Enrollment of subjects with tumors that can be safely biopsied is encouraged.

3.1.2 Subjects must have evaluable, or measurable disease defined as ≥1 lesion that can be accurately measured in ≥1 dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with a spiral computed tomography (CT) scan.

3.1.3 Subjects must have recovered to ≤ grade 1 NCI Common Terminology Criteria for Adverse Events (CTCAE) or stabilized from toxicity of prior chemotherapy or biologic therapy administered more than 4 weeks or 5 half-lives earlier, whichever is shorter.

3.1.4 Subjects on bisphosphonates/denosumab for any cancer or on hormone therapy for prostate cancer may continue this therapy. However, subjects with prostate cancer must have confirmed metastatic disease that has progressed despite hormonal therapy or refused or is intolerant of hormonal therapy.

3.1.5 Age ≥18 years.

3.1.6 ECOG performance status ≤2 (Karnofsky or Lansky ≥70%, see Appendix A).

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

- leukocytes ≥2,000/mm3
- absolute neutrophil count (ANC) ≥1,500/mm3
- platelets ≥100,000/mm3
- total bilirubin ≤1.5× institutional upper limit of normal (ULN) (≤3 × upper limit of normal in the presence of documented Gilbert's syndrome)
- AST/ALT ≤1.5 × institutional upper limit of normal (ULN) or if liver metastasis, ≤2.5 x ULN
- Serum creatinine ≤1.5 × institutional ULN, OR Creatinine clearance ≥50 mL/min/1.73 m2 for subjects with serum creatinine levels >1.5 × higher than institutional normal

3.1.8 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

3.1.9 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

3.1.10 Subjects with inactive central nervous system (CNS) metastasis are eligible. Inactive CNS metastasis is defined as: no symptoms of brain metastases after successful definitive treatment of brain metastases (surgical resection, whole brain irradiation, stereotactic radiation therapy, or a combination of these) with stable or improved radiographic appearance on magnetic resonance imaging (MRI) scan at least 1 month after completion of treatment.

3.1.11 Subjects may have previously progressed on treatment with one of the 3 agents being used in this trial or treatment with other checkpoint inhibitors, as long as they have recovered from previous toxicity. Subjects that previously progressed on treatment with a combination of any 2 of the 3 agents being used in this trial are eligible for the triplet cohort only.

3.1.12 The effects of ipilimumab, nivolumab, and rhIL-15 on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, during the treatment portion of the study, and for a minimum for 5 months (women) and 7 months (men) after the last dose of study drug. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.1.13 Ability to understand and the willingness to sign a written informed consent

document.

3.1.14 Willingness to provide blood and biopsy samples for research purposes if on the expansion phase of the study.

3.2 Exclusion Criteria

3.2.1 Subjects who have received any prior cytotoxic therapy, immunotherapy, major surgery, antitumor vaccines or monoclonal antibodies in the 4 weeks or 5 half-lives, whichever is shorter, prior to C1D1 (6 weeks prior for checkpoint inhibitors such as anti-CTLA-4 or anti-PD1/PD-L1 and for nitrosoureas or mitomycin C). Subjects must not have received radiotherapy in the 2 weeks prior to C1D1. Subjects who had serious grade ≥3 irAE (excluding endocrinopathies) during previous treatment with one of the checkpoint inhibitors are excluded from the trial; subjects who had grade ≥1 irAE (including serious AEs) that have resolved to grade 1 are eligible at the discretion of the PI.

3.2.2 Subjects with primary brain cancers or active CNS metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events (See Eligibility Criterion 3.1.10).

3.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to any of the agents on this trial.

3.2.4 Concurrent anticancer therapy (including other investigational agents) with the exception of hormone therapy for breast or prostate cancer. Patients that have received treatment for a different cancer previously and have been disease-free for less than one year are excluded.

3.2.5 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, cognitive impairment, active substance abuse, or psychiatric illness/social situations that, in the view of the Investigator, would preclude safe treatment or the ability to give informed consent and limit compliance with study requirements.

3.2.6 Inability or refusal to practice effective contraception during therapy or the presence of pregnancy or active breastfeeding. Because there is no significant preclinical information regarding the risk to a fetus or newborn infant, pregnant or breastfeeding women will be excluded from participation in this trial.

3.2.7 Documented HIV infection or positive serology. Since rhIL-15 treatment stimulates the subjects' immune system to attack their tumor, the defective immune systems of subjects with HIV makes responses to this treatment much less likely to provide benefit and these subjects are not eligible for this trial.

3.2.8 History of severe asthma (subjects with a history of mild asthma that are on or can be switched to non-corticosteroid bronchodilator regimens are eligible).

3.2.9 Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids, should be excluded. The use of inhaled corticosteroids is allowed.

3.3 Screening Evaluation

3.3.1 History and physical examination: Complete history and physical examination (including height, weight, vital signs, and ECOG performance score) will be conducted within 8 days prior to enrollment.

3.3.2 Imaging Studies: Scans for tumor measurements must be done within 28 days prior to enrollment.

3.3.3 Laboratory Evaluation: within 8 days prior to enrollment:

- Hematological Profile: CBC with differential, platelets
- Biochemical Profile: ACTH, albumin, alkaline phosphatase, amylase, total bilirubin, BUN, bicarbonate, calcium, chloride, cortisol (a.m.), creatinine, glucose, LDH, lipase, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, TSH
- Fasting lipid profile
- Urinalysis: protein/creatinine ratio
- Serum or urine pregnancy test (B-HCG) for female participants of childbearing potential

3.3.4 Cardiac evaluation:

- Creatine phosphokinase (CPK), troponin I: within 8 days prior to enrollment
- EKG: within 8 days prior to enrollment
- ECHO: within 28 days prior to enrollment

3.3.5 HIV and hepatitis screening evaluation - within 28 days prior to enrollment:

- Hepatitis B Surface Antigen, Hepatitis B Surface Antibody, Hepatitis B Core Antibody, Hepatitis C Core Antibody
- HIV 1/2 serologies.

Eligibility history, physical examination, laboratory evaluations, urinalysis, and CPK/troponin I are to be conducted within 8 days prior to enrollment. As noted in Section 5, if protocol therapy is started within 8 days of these eligibility screening evaluations, values from the screening evaluations may be used as baseline measurements; if >8 days have passed since the screening evaluations, the medical history, physical examination, laboratory evaluations, urinalysis, and CPK/troponin I must be repeated prior to starting protocol therapy. The eligibility imaging scan must be done within 28 days prior to enrollment; to serve as the baseline scan, it must be done within 28 days prior to the start of protocol therapy.

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) 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 such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges,
- 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 acting as the Site-Protocol PI (Investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the Clinical Investigator (CI) on the DTL must be rostered at the enrolling site with a participating organization.

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 Cancer Trials Support Unit (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 email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation,
- IRB-signed CTSU IRB Certification Form, and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

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 (PO), and
- Compliance with all protocol-specific requirements (PSRs).

Submitting Regulatory Documents

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

To access the Regulatory Submission Portal, log on to the CTSU members' website, go to the Regulatory section, and select 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.

Checking Site Registration Status

Site's registration status may be verified on the CTSU website.

- Click on *Regulatory* at the top of the screen,
- Click on *Site Registration*, and
- Enter the site's 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

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 LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN or IWRS 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: Must be on an LPO roster, ETCTN corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.
- If a DTL is required for the study, the registrar must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for the 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. IWRS system also sends an email confirmation of the registration. You may 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 or the IWRS 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.

General Guidelines

Following registration, patients should begin protocol treatment within 14 days.
* Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

4.3 Patient Registration Process

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates, found here:
https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825

Cohorts:

Cohort 1: Adult

Arms:

Arm 1: Doublet A

Arm 2: Doublet B

Arm 3: Triplet

5. TREATMENT PLAN

This is a phase I study testing the subcutaneous (SC) administration of rhIL-15 in combination with intravenous (IV) administration of the checkpoint inhibitors nivolumab and ipilimumab in adults with refractory cancers. Doses and drug administration are defined in Section 5.1.

Reported adverse events and potential risks for rhIL-15, nivolumab, and ipilimumab are described in Section 7. Patients will be encouraged to report any and all adverse events, given the high likelihood of toxicities with the triplet combination therapy.

The first 4-6 patients enrolling in the study will be placed into lead-in safety doublets and will receive a combination of rhIL-15 and either nivolumab OR ipilimumab; once toxicity is cleared in both doublets and a safety analysis is reviewed and approved by the IRB, new patients will be enrolled directly onto the triple agent combination.

In order to allow for an appropriate observation period between patients, only 1 patient per week may begin treatment on any given dose level on either the doublet or triplet combination.

Doublet treatment plan: Each treatment cycle is 42 days long (cycle can start up to 7 days late due to scheduling conflicts; day 1 is the first day treatment is administered); patients will receive rhIL-15 given SC on days 1-8 and 22-29 and either nivolumab given IV on days 8, 22, and 36 OR ipilimumab given IV on day 8 (see Section 5.1.1 for doses). After completing 4 cycles, patients may continue onto single checkpoint inhibitor therapy for cycles 5 and onwards; they may not continue receiving rhIL-15 or enter the triplet cohort (see Doublet Schema). In cycles 5 and onwards, patients will receive nivolumab on days 1, 15, and 29 OR ipilimumab on day 1. A 1-week break (Transition Period) will be required between Cycle 4 and Cycle 5 to ensure a 2-week period between Cycle 4's third nivolumab dose and Cycle 5's first nivolumab dose. CT scans for restaging will be performed cycle ± 1 week (every 6 weeks) during cycles 1-4 and every 2 cycles ± 1 week (every 12 weeks) thereafter. Documentation must be provided for patients removed from study for progressive disease.

Triplet treatment plan: Each treatment cycle is 42 days long (cycle can start up to 7 days late due to scheduling conflicts; day 1 is the first day treatment is administered); patients will receive rhIL-15 given SC on days 1-8 and 22-29, nivolumab given IV on days 8, 22, and 36, and ipilimumab given IV on day 8 (see Section 5.1.2 for doses). Cycle 5 and onwards will not include treatment with rhIL-15 (see Triplet Schema). In cycles 5 and onwards, patients will receive nivolumab on days 1, 15, and 29 and ipilimumab on day 1. A 1-week break (Transition Period) will be required between Cycle 4 and Cycle 5 to ensure a 2-week period between Cycle 4's third nivolumab dose and Cycle 5's first nivolumab dose. When nivolumab and ipilimumab are administered on the same day, administer nivolumab first, followed by ipilimumab using separate infusion bags and filters for each infusion.

If there are concerns about toxicity during cycles 5 and onwards, patients may discontinue ipilimumab and continue receiving nivolumab monotherapy.

Throughout the course of treatment, treatment administration can be +3 days for resolution of

toxicities or +/- 3 days for patient scheduling purposes. There must be a minimum of 12 days between nivolumab doses.

Patient evaluations will be performed throughout the study as described below. Baseline history, physical examination, laboratory evaluations, and urinalysis are to be conducted within 8 days prior to the start of protocol therapy. If protocol therapy is started within 8 days of these eligibility screening evaluations (see Section 3.3), values from the screening evaluations may be used as baseline measurements; if >8 days have passed since the screening evaluations, the medical history, physical examination, laboratory evaluations, and urinalysis must be repeated prior to starting protocol therapy. Baseline imaging scans must be done within 28 days prior to the start of protocol therapy.

After baseline CT scans, CT scans for restaging will be performed every 6 weeks ± 1 week (every cycle) during the first 4 cycles and every 12 weeks ± 1 week (every 2 cycles) during cycle 5 and onwards. Documentation must be provided for patients removed from study for progressive disease.

In the doublet cohorts and triplet cohort (cycles 1-4), physical examination/vital sign measurements and labs (CBC with differential; serum chemistries; urinalysis) will be performed at baseline, weekly during cycles 1 and 2, and within 7 days prior to the start of every subsequent cycle (or more frequently per physician discretion). Fasting lipid profile will be obtained at baseline and within 7 days prior to the start of every subsequent cycle. HIV/hepatitis screening and pulmonary function tests will be performed as part of the screening evaluation. CPK/troponin I measurements will be performed at baseline and within 7 days of the start of every cycle. EKG and echocardiogram will be performed as part of the screening evaluation and then as clinically indicated.

Blood samples and research biopsies for correlative research studies will be collected as described in Section 9.2 and Section 9.3. Biopsies are optional on the doublets and triplet dose escalation cohort and will be collected whenever feasible; they are mandatory on the triplet expansion cohort.

Patients with tumors known to have tumor markers (PSA, CEA, CA125) will have the serum level of these markers assessed at the time of their radiographic restaging to gain further insight into the potential efficacy of rhIL-15 treatment. If tumor markers are initially above the upper limit of normal, they must normalize for the subject to be considered a complete response. Specific guidelines for serum tumor markers previously reported (CA125 and PSA) will be used to assess responses to rhIL-15 treatment.

5.1 Agent Administration

Treatment will be routinely administered on an outpatient basis. rhIL-15 will be given through SC injections, and nivolumab and ipilimumab will be administered through IV infusion (nivolumab over 30 minutes and ipilimumab over 90 minutes). IL-15 will be prepared in D5W/0.1% HSA or normal saline at no less than 100 mcg/mL in sterile borosilicate vials prior to being loaded in the syringes. Nivolumab can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose, USP to concentrations no less than 0.35

mg/mL. 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. See Section 8 for more details about study agent administration.

Administration of study drugs will be performed in a setting with emergency management capabilities and staff who are trained to monitor for and respond to medical emergencies. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

Reported adverse events and potential risks are described in Section 7. Patients will be encouraged to report any and all adverse events, given the high likelihood of toxicities with the triplet combination therapy. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.1.1 Lead-In Doublets

The first 4-6 patients enrolling in the study will be placed into one of two lead-in doublets (nonrandomized; investigator's choice): rhIL-15 + nivolumab (2-3 patients) or rhIL-15 + ipilimumab (2-3 patients). rhIL-15 will be given on days 1-8 and 22-29 in combination with either nivolumab (days 8, 22, and 36) or ipilimumab (day 8). Doses are shown below.

	Dose
rhIL-15 (first 4 cycles only)	0.5 mcg/kg/day SC
Nivolumab	240 mg IV (over 30 min)
Number of pts	3

OR

	Dose
rhIL-15 (first 4 cycles only)	0.5 mcg/kg/day SC
Ipilimumab	1 mg/kg IV (over 90 min)
Number of pts	3

Doublets are for evaluation of safety only, and assessment of toxicities will take place during and after the first cycle. Each doublet will enroll up to 3 patients; a doublet will be considered as clearing toxicity once at least 2 patients enrolled on the doublet tolerate the treatment for 6 weeks (i.e., do not experience a DLT). If 1 patient on the doublet experiences a DLT, 1 or 2 more patients will be enrolled for a total of 3; if 2 of the 3 patients experience a DLT, enrollment into the triplet cohort will not occur, and the study will be halted and reevaluated.

rhIL-15 administration will be limited to the first 4 cycles of treatment. After completing 4 cycles, patients in a doublet cohort may continue onto single checkpoint inhibitor therapy for cycles 5 and onwards; they may not continue receiving rhIL-15 or enter the triplet cohort.

After completion of the doublet phase, the trial will be halted and a safety analysis will be submitted to the IRB. The triplet phase will not be opened to enrollment until a review of the safety and efficacy data is conducted.

5.1.2 Triplet Cohort Dose Levels

New patients will be enrolled onto the triplet dose escalation cohort only after toxicity is cleared in both lead-in doublets and a safety analysis is reviewed by the IRB (see Section 5.1.1).

As of Amendment C (10/3/18), toxicity has been cleared in both lead-in doublets. 3 patients were enrolled on Doublet A (rhIL-15 + nivolumab) and 2 patients were enrolled on Doublet B (rhIL-15 + ipilimumab); none of the 5 patients experienced a DLT in the 6-week period. The IRB has approved enrollment onto the triplet cohort.

The dose escalation design, which has 3 planned dose levels, was based on the prior clinical experience with each of the 3 investigational agents with the intent to define the MTD for the combination treatment.

Dose levels cohorts	**1**	**2**	**3**
rhIL-15 (mcg/kg/day SC)	0.5	1	2
Nivolumab (mg; IV over 30 min)	240	240	240
Ipilimumab (mg/kg; IV over 90 min)	1	1	1
Number of patients	3 to 6	3 to 6	3 to 6

5.1.2.1 Standard 3+3 Dose Escalation Phase

Three patients will be treated at each new dose level. Dose escalation will be based on DLTs observed during the first cycle of treatment. If none of the 3 patients develop DLT at the dose administered, escalation will continue in cohorts of 3 patients each. If a DLT during the first cycle is observed in any of the 3 patients, then the cohort will expand up to 6 patients. If a second DLT is observed during cycle 1, then up to a total of 6 patients will be enrolled to the next lower dose level cohort. If no more than 1 in 6 patients in a dose level have DLT during the first cycle, dose escalation is permitted. DLTs seen after the first cycle will not affect the dose escalation decisions.

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.

≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

The MTD will be based on the assessment of DLTs, and will be defined as the dose level at which less than one-third of patients (0/3 or 0-1/6 patients) treated experience a DLT, with the next higher dose level demonstrating a one-third or greater number of patients (≥ 2 patients) having DLT. A DLT is defined as an AE that is felt to be related (possibly, probably, or definitely) to administration of study drugs, and meets prespecified criteria (see Section 5.2). If a subject did not experience DLT and did not finish 1 cycle of treatment (42 days), he or she will not be evaluable for determination of the MTD and will be replaced in the dose level.

Patients will be encouraged to report any and all adverse events, given the high likelihood of toxicities with the triplet combination therapy. Monitoring of AEs will continue during subsequent cycles to determine the safety and feasibility of the treatment regimen over time and to discern whether there is any need to make changes to the protocol or informed consent.

rhIL-15 administration will be limited to the first 4 cycles of treatment. After completing 4 cycles, patients in the triplet cohort may continue on nivolumab and ipilimumab combination therapy for cycles 5 and onwards; they may not continue receiving rhIL-15. If there are concerns about toxicity during cycles 5 and onwards, patients may discontinue ipilimumab and continue receiving nivolumab monotherapy.

5.1.2.2 Expansion Cohort

An expansion cohort of 15 patients will be treated at the MTD or the maximum administered dose. With 15 patients and a biopsy QA failure rate of 50% with respect to paired biopsies, there is an 85% likelihood of having at least 6 usable samples and a 95% likelihood of having at least 5 usable samples.

Dose levels cohorts	**Expansion cohort**
rhIL-15 (mcg/kg/day)	MTD
Nivolumab (mg)	240
Ipilimumab (mg/kg)	1
Number of patients	15

5.2 Definition of Dose-Limiting Toxicity

Dose escalation will be based on DLTs observed during the first cycle of treatment.

5.2.1 Grade ≥3 non-hematologic toxicity will be considered dose limiting, with the following exceptions:

5.2.1.1 Grade 3 fatigue lasting ≤ 7 days.

5.2.1.2 Grade 3 diarrhea will only be considered dose limiting if it is caused by colitis or, if after 72 hours, it is refractory to treatment. Grade 4 diarrhea will be dose limiting.

5.2.1.3 Grade 3 nausea and vomiting will only be considered dose limiting if after 72 hours it is refractory to maximal anti-emetic therapy and unable to be corrected to Grade ≤2 or baseline.

5.2.1.4 Grade 3 rise in creatinine, not corrected to Grade 1 or baseline after intravenous fluids within 24 hours, will be considered dose limiting. All Grade 4 rises in creatinine will be dose limiting.

5.2.1.5 Grade 3 electrolyte toxicities unable to be corrected to Grade 2 or baseline within 24 hours will be considered dose limiting.

5.2.1.6 Grade 3 liver function test (ALT, AST, alkaline phosphatase, total bilirubin) abnormalities in the absence of clinical signs of hepatic dysfunction (lethargy, confusion, anorexia, pruritus, tremor) that persist ≤3 days will not be considered dose-limiting.

5.2.2 Grade 4 hematological toxicity

5.2.2.1 Neutropenia: Grade 4 neutropenia of any duration accompanied by fever or infection will be considered dose limiting. Grade 4 neutropenia for >5 days without fever or infection will be considered dose limiting. Transient neutropenia (≤5 days) without fever or infection will not be considered dose-limiting. Twice weekly blood draws will be needed (after onset of grade 4 neutropenia) to monitor duration of neutropenia for the first 2 cycles. On subsequent cycles (cycle 3 and beyond), weekly blood draws will be monitored after onset of grade 4 neutropenia.

5.2.2.2 Thrombocytopenia: Grade 4 thrombocytopenia will be considered dose limiting. Grade 3 thrombocytopenia associated with bleeding will be considered dose limiting.

5.2.2.3 Anemia: Grade 4 anemia will be considered dose limiting.

5.2.3 Any neurotoxicity Grade ≥2 that is not reversible to a Grade ≤1 within 2 weeks will be considered dose limiting.

5.2.3.1 Any adverse event requiring steroid treatment, with the exception of short-term use (≤2 weeks) for skin rash or mucositis or use for endocrine replacement, will be considered dose limiting. Any adverse event requiring permanent discontinuation of study drugs will be considered dose limiting.

Any unexpected grade 4 or grade 5 adverse event considered to be at least possibly related to study drug will cause the protocol to be halted and the study design and informed consent reevaluated with the sponsor.

Management and dose modifications associated with the above adverse events are outlined in Section 6.

5.3 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of the study agents 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 Principal Investigator 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 use of. A Patient Drug Information Handout/Wallet Card is provided (Appendix B).

Drugs to be avoided:

- Traditional herbal or homeopathic or natural medicines. Ingredients for such medicines have not been fully studied, and their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity.
- Immunostimulatory agents, including but not limited to interferon (IFN)-α, IFN-γ, anti-TNF-α, or IL-2 (aldesleukin) (prohibited during the study and for 10 weeks after the last dose of study drugs). These agents, in combination with the study drugs, could potentially increase the risk for autoimmune conditions.
- Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide. These agents could potentially alter the activity and the safety of study drugs. However, systemic corticosteroids and other immunosuppressants may be indicated after starting the study drugs to treat immune-related adverse reactions.
- Live vaccines and live, attenuated vaccines (prohibited for 30 days prior to study agents, during the study, and for 100 days after the last dose of study drug). Inactivated vaccines are permitted.
- Initiation of granulocyte colony-stimulating factors (e.g., innovator and biosimilar forms of filgrastim, sargramostim, and/or pegfilgrastim) should be discussed with the Medical Monitor.

5.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression with the caveat that patients that are clinically well may continue

on therapy following RECIST progression with new lesions or increase in target lesions if the increase in disease burden does not meet the definition of PD by immune response criteria [79] per Section 11.2. (In this situation, patients do not have unequivocal progression until immune response criteria are met.)

- Intercurrent illness that prevents further administration of treatment
- Significant toxicity even after two reductions to lower dose levels, or no lower dose level exists (as described in Section 5.1)
- 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

5.5 Duration of Follow Up

Patients will be followed for toxicity for 120 days, until all toxicity resolves, or until they start another treatment, whichever is shortest. Patients removed from study for unacceptable adverse event(s) will be followed at least until resolution or stabilization of the adverse event.

5.6 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS

There are no dose reductions permitted for the ipilimumab and nivolumab study agents; dose delay and management tables are included below. Dose modifications that can be considered for rhIL-15 are described in Section 6.1.

Any unexpected grade 4 or grade 5 adverse event considered to be at least possibly related to study drug will cause the protocol to be halted and the study design and informed consent reevaluated with the sponsor.

6.1 Dose Delay Criteria

For toxicities that are not defined as DLT, next drug doses can be delayed for up to +3 days to allow for toxicities to resolve. Patients who meet criteria to resume treatment, the dosing days of nivolumab and ipilimumab may be adjusted within a +3 day window, as long as consecutive nivolumab doses are given at least 12 days apart. Patients who do not meet the criteria to resume treatment will be managed as specified in the dose delay and adverse event management tables below.

If study treatment is held for >42 days, the patient will go off study.

While doses are being held, the patient will continue to progress through the treatment cycle. When the patient is able to resume treatment, restart drug administration as soon as possible based on the cycle schedule. Omit any missed doses.

rhIL-15 Dose Delays

Patients should be monitored specifically for rhIL-15-associated toxicities that overlap with nivolumab and ipilimumab toxicity. These events include hypotension, hypoxia, rapid changes in peripheral blood lymphocytes, LFT elevation, and skin and organ infiltrates.

If a patient requires steroid treatment to manage toxicities, rhIL-15 should be held until the patient is tapered off steroids. IL-15 will be held for neutropenia grade 2 or higher (continuing other study drugs) if the patient is receiving benefit at the discretion of the PI in consultation with the medical monitor.

Neutropenia	Management/Next Dose for rhIL-15
≤ Grade 1	No change in dose
Grade 2 *	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3 *	Hold* until < Grade 2.
Grade 4	Off protocol therapy
* For neutropenia that does not improve to grade 1 within a 2-week time frame to resume re-treatment patients may be considered for dose-reduction of IL-15 or discontinuation at the discretion of the PI and in consultation with the medical monitor.	

Nivolumab and Ipilimumab Dose Delays

Below are dose delay and management tables for nivolumab and ipilimumab, indicating when study drug should be held or discontinued due to nivolumab or ipilimumab –specific adverse events.

ALL OTHER EVENTS	Management/Next Dose for Nivolumab and Combination Nivolumab/ipilimumab
≤ Grade 1	No change in dose. Continue treatment.
Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below)
Grade 3	Off nivolumab/ipilimumab therapy. For immune-related adverse events, hold nivolumab and ipilimumab until ≤ Grade 1 OR baseline; resume at the same dose level (exceptions as noted below).
Grade 4	Off nivolumab and ipilimumab therapy (exceptions as noted below)
Recommended management: As clinically indicated	

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued study drug dosing should discontinue nivolumab/ipilimumab treatment.
- Any grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires

systemic treatment should discontinue nivolumab/ipilimumab treatment.

- Any grade 3 or 4 drug-related laboratory abnormality or electrolyte abnormality, that can be managed indecently from underlying organ pathology with electrolyte replacement, hormone replacement, insulin or that does not require treatment does not require discontinuation.
- Patients requiring > two dose delays for the same event should go off protocol therapy. Patients may be dose-delayed for evaluation and restarted depending on results.
- Please note that grading and for hypophysitis with symptoms of headache, visual or neurologic changes or radiologic evidence of pituitary enlargement and other CNS events such as aseptic meningitis or encephalitis should be considered grade 3 events.

Skin Rash and Oral Lesions	**Management/Next Dose for Nivolumab and Combination Nivolumab/ipilimumab**
≤ Grade 1	Continue therapy. No change in dose.*
Grade 2	Monitor weekly until 1≤ Grade. May initiate intermediate potency topical steroids (and treatment for pruritis if needed). Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at same level at investigator discretion.
Grade 4	Off nivolumab and ipilimumab treatment.
*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/pemphigoid. 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 algorithm (Appendix C)	

Diarrhea/ Colitis	**Management/Next Dose for Nivolumab and Combination Nivolumab/ipilimumab**
≤ Grade 1	Continue therapy. No change in dose.
Grade 2	Hold until baseline. Treat symptomatically, and restart if improved to baseline or grade 1 at investigators discretion. No change in dose. If worsening or no improvement at 4 weeks or documented colitis by colonoscopy permanently discontinue and initiate steroid treatment.
Grade 3	Discontinue nivolumab/ipilimumab therapy. Obtain colonoscopy, and treat symptomatically
Grade 4	Discontinue nivolumab/ipilimumab therapy.
• Patients with grade 2 symptoms but normal colonoscopy and biopsies may be retreated after resolution. • Patients who require steroids should be taken off nivolumab/ipilimumab treatment. • Please evaluate pituitary function prior to starting steroids if possible without compromising acute care. • Evaluation for all patients for additional causes includes *C. diff*, acute and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD.	
Recommended management: see GI AE management Algorithm (Appendix C)	

GI: Nausea/Vomiting	Management/Next Dose for Nivolumab and Combination Nivolumab/ipilimumab
≤ Grade 1	Continue therapy. No change in dose.
Grade 2	Hold pending evaluation for gastritis duodenitis and other immune adverse events 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, patients should discontinue nivolumab/ipilimumab treatment.
Grade 4	Off nivolumab/ipilimumab treatment.
Patients with grade 2 or 3 N-V should be evaluated for upper GI inflammation and other immune related events.	

Liver Function: AST, ALT, Bilirubin	Management/Next Dose for Nivolumab and Combination Nivolumab/ipilimumab
≤ Grade 1	Continue therapy. No change in dose.
Grade 2	Hold until grade 1 or baseline. Resume at same dose level.
Grade 3	Discontinue nivolumab or nivolumab/ipilimumab treatment and monitor with twice weekly LFTs until Grade ≤ 2. Initiate steroid therapy.
Grade 4	Off nivolumab and nivolumab/ipilimumab therapy.
• Continued treatment of active immune mediated hepatitis may exacerbate ongoing inflammation. Holding drug to evaluate LFT changes and early treatment are recommended.	
Recommended management: see Hepatic AE management algorithm (Appendix C)	

Pancreatitis Amylase/Lipase	Management/Next Dose for Nivolumab and Combination Nivolumab/ipilimumab
≤ Grade 1	Continue treatment. No change in dose.
Grade 2	Continue at current dose level. More frequent monitoring of lipase and amylase. Patients who develop symptomatic pancreatitis should have nivolumab/ipilimumab held if applicable and steroid treatment initiated if clinically indicated.
Grade 3	Hold until ≤ Grade 2. Resume at same dose level if asymptomatic. Patients who develop symptomatic pancreatitis should be taken off nivolumab/ipilimumab treatment. • Monitor lipase and amylase once or twice weekly. • Optional radiographic evaluation if there is new onset of symptomatic pancreatitis. Continue at the current dose level or interrupt per investigator's discretion.
Grade 4	Hold until ≤ Grade 2. Resume at same dose level if asymptomatic. Patients who develop symptomatic pancreatitis should be taken off

Pancreatitis Amylase/Lipase	**Management/Next Dose for Nivolumab and Combination Nivolumab/ipilimumab**
	nivolumab and ipilimumab treatment. • Monitor lipase and amylase once or twice weekly. • Optional radiographic evaluation if there is new onset of symptomatic pancreatitis or new onset of DM Patients who develop symptomatic pancreatitis should be taken off treatment.
For treatment management of symptomatic pancreatitis, please follow the Hepatic Adverse Event Management Algorithm (Appendix C)	

Renal	**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 dose level.
Grade 4	Off treatment

Endocrine: Hypophysitis Adrenal Insufficiency	**Management/Next Dose for Nivolumab and Combination Nivolumab/Ipilimumab**
≤ Grade 1	Asymptomatic TSH elevation*. Patients must be evaluated, endocrine consult. May continue treatment at same dose level at investigator discretion.
Grade 2	Hold until patients are on a stable replacement hormone regimen and symptoms resolve. If treated with steroids, patients must be stable off steroids for two weeks. Resume at same dose level.
Grade 3	Hold until patients are on a stable replacement hormone regimen and symptoms resolve. If treated with steroids, patients must be stable off steroids for two weeks. Resume at same dose level.
Grade 4	Off nivolumab/ipilimumab treatment.
*Patients with thyroiditis may be retreated on replacement therapy. Patients must be evaluated to rule out pituitary disease prior to initiating thyroid replacement. Please evaluate pituitary function before beginning steroid therapy or replacement therapy of any kind. 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.	
Recommended management: See Endocrine Management Algorithm (Appendix C)	

Pneumonitis	Management/Next Dose for Nivolumab and Combination Nivolumab/ipilimumab	Toxicity management
≤ Grade 1	Hold dose pending evaluation and resolution to baseline including baseline pO_2. Resume no change in dose after pulmonary and/or ID consultation excludes lymphocytic pneumonitis.	For Grade 1 (radiographic changes only): - Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated - Consider pulmonary and infectious disease consult
Grade 2	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes ipilimumab and associated lymphocytic pneumonitis. Off nivolumab/ipilimumab if steroids are required.	For Grade 2 (mild to moderate new symptoms) - Monitor symptoms daily and consider hospitalization - Promptly start systemic steroids (e.g. prednisone 1-2 mg/kg/day or IV equivalent) - Reimaging as clinically indicated - If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg/day to be started - If still no improvement within 3-5 days despite IV methylprednisolone at 2-4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5 mg/kg every 2 weeks). *Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab*
Grade 3	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes ipilimumab and associated lymphocytic pneumonitis. Off nivolumab/ipilimumab if steroids are required.	For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening): - Promptly initiate empiric IV methylprednisolone 1-4 mg/kg/day or equivalent - Obtain pulmonary and infectious disease consult - Hospitalize the subject - Supportive care (oxygen etc.) - If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5 mg/kg every 2 weeks) to be started. *Caution: rule out sepsis and refer to infliximab label for general guidance before*

Pneumonitis	Management/Next Dose for Nivolumab and Combination Nivolumab/ipilimumab	Toxicity management
		using infliximab - Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and in particular, anti-PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections)
Grade 4	Off nivolumab/ipilimumab treatment.	See above
All Grades	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. Patients who require steroids should be taken off nivolumab treatment. 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. The investigator is requested to differentiate between non-infectious pneumonitis, and infectious pneumonitis (viral, bacterial, or fungal), aspiration pneumonitis, or other pneumonitis clearly not due to a potential hypersensitivity reaction to the study agent infusions; and provide the basis for his/her assessment that it is infectious or other, as appropriate. The investigator is requested to report with the most specific clinical terms to describe the condition, not simple "pneumonitis".	
Additional guidance can be found in the Pulmonary Adverse Event Management Algorithm (Appendix C). Consider recommending seasonal influenza killed vaccine for all patients.		

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

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 baseline. Off protocol treatment if steroids are required. Resume at same dose level

Neurologic events	Management/Next Dose for Nivolumab and Combination Nivolumab/ipilimumab
	for peripheral isolated n. VII (Bell's palsy).
Grade 3	Off nivolumab/ipilimumab treatment.
Grade 4	Off nivolumab/ipilimumab treatment.
Patients who require steroids should be taken off nivolumab/ipilimumab treatment. Patients with any CNS events including aseptic meningitis, encephalitis, symptomatic hypophysitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, myasthenia gravis should be off study.	
Recommended management: See Neurologic Adverse Event Management Algorithm (Appendix C)	

Infusion reaction	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 dose level with pre-medication at the discretion of the PI.
Grade 4	Off treatment
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever. The following prophylactic premedications for future infusions: diphenhydramine 25-50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab/ipilimumab administrations.	

Fever	Management/Next Dose for Nivolumab and Combination Nivolumab/ipilimumab
≤ Grade 1	Continue therapy. 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 nivolumab/ipilimumab therapy
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever. See table above for *Infusion Reactions.*	

Cardiac Toxicities Nivolumab and combination of nivolumab/ipilimumab

- Drug will be held for any indication suggestion of cardiac dysfunction of any grade pending evaluation.
- For patients with evidence of CHF, MI, cardiomyopathy, or myositis cardiac evaluation including lab tests and cardiology consultations as clinically indicated including EKG,

CPK, troponin, ECHO cardiogram. Drug will be held for grade 2 cardiac dysfunction pending evaluation.

- Drug will be permanently discontinued for grade 3 or 4 cardiac dysfunction and grade 2 events that do not recover to baseline or that reoccur.
- Treatment as clinically indicated for cardiomyopathy.

Cardiac[1]	**Management/Next Dose for Nivolumab and Combination Nivolumab/ipilimumab**
≤ Grade 1	Hold dose pending evaluation and observation.[2] Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis.[3-4] Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize, may resume therapy. If labs worsen or symptoms develop, then treat as below.
Grade >2 with suspected myocarditis	Hold dose.[2] Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone. If no improvement within 24 hours, add either infliximab, ATG or tacrolimus. Resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade >2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone. Add ATG or tacrolimus if no improvement.
[1]Including CHF, LV systolic dysfunction, myocarditis, CPK, and troponin. [2]Patients with evidence of myositis without myocarditis may be treated according to "all other events". [3]Unexplained atrial arrythmias, new onset atrial fibrillation, conduction abnormalities, and focal cardiomyopathy (Takasubo) may be associated with myocarditis even with normal echocardiograms. These events may require evaluation with a cardiac MRI to confirm myocarditis when clinically indicated. [4]Myositis may occur with myocarditis and/or Guillian Barre syndrome. **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.	
Recommended management: See Myocarditis Management Algorithm (Appendix C)	

Neutropenia	**Management/Next Dose for Ipilimumab 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 2.
Grade 4	Off protocol therapy
*Patients requiring a delay resulting in >2 missed doses should go off protocol therapy.	

Thrombocytopenia	Management/Next Dose for Ipilimumab 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 2.
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.	

6.2 Management of Specific AEs

See Appendix C for the management algorithms for gastrointestinal, renal, pulmonary, hepatic, endocrinopathy, skin, neurological, and myocarditis adverse events.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

7.1.1 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.

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Blood and lymphatic system disorders - Other (acquired hemophilia)	
CARDIAC DISORDERS			
	Atrial fibrillation		
		Myocarditis[2]	
		Pericardial effusion	
EAR AND LABYRINTH DISORDERS			
	Hearing impaired		
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Hyperthyroidism[2]		
	Hypophysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
	Testosterone deficiency[2]		
EYE DISORDERS			
	Eye disorders - Other (episcleritis)[2]		
	Uveitis[2]		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		***Colitis[2] (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]		

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%)**	
IMMUNE SYSTEM DISORDERS			
	Autoimmune disorder[2]		
		Immune system disorders - Other (GVHD in the setting of allotransplant)[4]	
INFECTIONS AND INFESTATIONS			
		Infections and infestations - Other (aseptic meningitis)[2]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
		Lymphocyte count decreased	
	Neutrophil count decreased		
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		
	Hyperglycemia		
		Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Arthritis		
		Generalized muscle weakness	
	Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]		
NERVOUS SYSTEM DISORDERS			
		Ataxia	
	Facial nerve disorder[2]		
	Guillain-Barre syndrome[2]		
	Headache		
	Myasthenia gravis[2]		
		Nervous system disorders - Other (immune-mediated encephalitis)[2]	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
	Trigeminal nerve disorder		
PSYCHIATRIC DISORDERS			

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

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

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

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

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

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

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

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (pure red cell aplasia)[2]; Febrile neutropenia
CARDIAC DISORDERS - Conduction disorder; Restrictive cardiomyopathy
EYE DISORDERS - Extraocular muscle paresis[5]; Eye disorders - Other (retinal pigment changes)
GASTROINTESTINAL DISORDERS - Colonic ulcer; Dyspepsia; Dysphagia; Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal hemorrhage[6]; Proctitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure[2]
IMMUNE SYSTEM DISORDERS - Allergic reaction
INFECTIONS AND INFESTATIONS - Infection[7]
INVESTIGATIONS - Creatinine increased; Investigations - Other (rheumatoid factor); Lipase increased; Platelet count decreased; Serum amylase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Joint range of motion decreased; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Dizziness; Dysphasia; Ischemia cerebrovascular; Seizure
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia
RENAL AND URINARY DISORDERS - Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Cough; Dyspnea; Laryngospasm
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Skin hypopigmentation
VASCULAR DISORDERS - Flushing; Hypertension; Vascular disorders - Other (temporal arteritis)

Note: Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived) in combination with other

agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.2 CAEPR for Nivolumab

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Nivolumab (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 Nivolumab.

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

Version 2.6, May 14, 2025[1]

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

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Eye disorders - Other (diplopia)[3]	
		Eye disorders - Other (Graves ophthalmopathy)[3]	
		Eye disorders - Other (optic neuritis retrobulbar)[3]	
		Eye disorders - Other (Vogt-Koyanagi-Harada)[3]	
	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-related hepatitis)	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
		Cytokine release syndrome[5]	
		Immune system disorders - Other (GVHD in the setting of allotransplant)[3,6]	
		Immune system disorders - Other (sarcoid granuloma, sarcoidosis)[3]	
		Immune system disorders - Other (solid organ transplant rejection)	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[7]		
INVESTIGATIONS			
	Alanine aminotransferase increased[3]		***Alanine aminotransferase increased[3] (Gr 3)***
	Aspartate aminotransferase increased[3]		***Aspartate aminotransferase increased[3] (Gr 3)***
	Blood bilirubin increased[3]		***Blood bilirubin increased[3] (Gr 2)***
	CD4 lymphocytes decreased		***CD4 lymphocytes decreased (Gr 4)***

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%)**	
	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)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)	
		Myositis	
		Rhabdomyolysis	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (eruptive keratoacanthoma)	
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-related nephritis)	
		Renal and urinary disorders - Other (renal dysfunction)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleural effusion[3]		
	Pneumonitis[3]		
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia (BOOP))[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 and 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)
GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Malaise; Pain
HEPATOBILIARY DISORDERS - Bile duct stenosis
IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic microangiopathy); Immune system disorders - Other (complications of allogeneic HSCT); Immune system disorders - Other (limbic encephalitis)
INFECTIONS AND INFESTATIONS - Bronchial infection; Lung infection; Sepsis; Upper respiratory infection
INVESTIGATIONS - Blood lactate dehydrogenase increased; GGT increased; Lymphocyte count increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia
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; Skin and subcutaneous tissue disorders - Other (rosacea)
VASCULAR DISORDERS - 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.

7.1.3 CAEPR for rhIL-15

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Recombinant Human IL-15 (NSC 745101)

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. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for Recombinant Human IL-15.

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 1.3, January 2, 2019[1]

Adverse Events with Possible Relationship to Recombinant Human IL-15 (CTCAE 5.0 Term)	Specific Protocol Exceptions to Expedited Reporting (SPEER)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Anemia	***Anemia (Gr 2)***
Bone marrow hypocellular	
CARDIAC DISORDERS	
Sinus tachycardia	***Sinus tachycardia (Gr 2)***
GASTROINTESTINAL DISORDERS	
Abdominal pain	
Diarrhea	
Nausea	***Nausea (Gr 2)***
Vomiting	***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Chills	***Chills (Gr 2)***
Edema limbs	
Fatigue	***Fatigue (Gr 2)***
Fever	***Fever (Gr 2)***
Injection site reaction	
INFECTIONS AND INFESTATIONS	
Sepsis	
INVESTIGATIONS	
Alanine aminotransferase increased	
Aspartate aminotransferase increased	
Blood bilirubin increased	
Creatinine increased	

Adverse Events with Possible Relationship to Recombinant Human IL-15 (CTCAE 5.0 Term)	Specific Protocol Exceptions to Expedited Reporting (SPEER)
Lymphocyte count decreased	***Lymphocyte count decreased (Gr 2)***
Lymphocyte count increased	
Neutrophil count decreased	
Platelet count decreased	
White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS	
Hypoalbuminemia	
Hypophosphatemia	***Hypophosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Generalized muscle weakness	
NERVOUS SYSTEM DISORDERS	
Dizziness	
Headache	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Dyspnea	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Dry skin	
Erythema multiforme	***Erythema multiforme (Gr 2)***
Skin and subcutaneous tissue disorders - Other (rash)	
VASCULAR DISORDERS	
Capillary leak syndrome	
Hypertension	***Hypertension (Gr 2)***
Hypotension	***Hypotension (Gr 2)***

[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

Adverse events reported on Recombinant Human IL-15 trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Recombinant Human IL-15 caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Chest pain - cardiac; Palpitations; Pericardial effusion; Pericardial tamponade; Sinus bradycardia; Ventricular tachycardia
GASTROINTESTINAL DISORDERS - Ascites; Constipation; Duodenal hemorrhage; Gastritis; Gastrointestinal disorders - Other (increased appetite); Ileus; Mucositis oral; Pancreatitis; Visceral arterial ischemia
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Infusion site extravasation; Multi-organ failure; Pain
IMMUNE SYSTEM DISORDERS - Autoimmune disorder
INFECTIONS AND INFESTATIONS - Tooth infection; Upper respiratory infection; Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Infusion

related reaction
INVESTIGATIONS - Alkaline phosphatase increased; Cardiac troponin I increased; Electrocardiogram QT corrected interval prolonged; GGT increased; INR increased; Lipase increased; Serum amylase increased; Weight gain; Weight loss
METABOLISM AND NUTRITION DISORDERS - Anorexia; Dehydration; Hyperkalemia; Hypocalcemia; Hypokalemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Bone pain; Muscle weakness upper limb; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Dysgeusia; Peripheral sensory neuropathy; Presyncope; Vasovagal reaction
PSYCHIATRIC DISORDERS - Anxiety; Psychosis
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Genital edema
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Bronchopulmonary hemorrhage; Cough; Hypoxia; Laryngeal inflammation; Pleural effusion; Pneumonitis; Pulmonary edema; Wheezing
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythroderma; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Rash acneiform; Skin and subcutaneous tissue disorders - Other (skin plaques)
VASCULAR DISORDERS - Hot flashes

Note: Recombinant Human IL-15 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 CTEP Reporting Requirements

7.2.1 Adverse Event Characteristics

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

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in Section 7.3.

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

7.2.2 Expedited Adverse Event Reporting

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

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

Distribution of Adverse Event Reports

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

Expedited Reporting Guidelines

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

Note: A death on study requires both routine and expedited reporting, regardless of causality. 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 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

An AE is considered serious if it results in **ANY** of the following outcomes:

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

ALL SAEs that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-2 Timeframes	Grade 3-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timeframes are defined as:

- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-Hour notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 3-5 SAEs
- Within 10 calendar days for Grade 1-2 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE 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: August 30, 2024

Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 7.4): These are any grade lymphopenia, any grade alopecia, Grade 2 electrolyte (sodium, potassium, phosphorous, magnesium) abnormalities, Grade 2 anemia, Grade 2 hypoalbuminemia, Grade 2 hyperglycemia, Grade 2 INR, Grade 2 PTT, and Grade 2 hyperuricemia.

Adverse Events of Special Interest

The following AEs are considered of special interest in patients receiving rhIL-15, nivolumab, and/or ipilimumab and must be reported expeditiously through CTEP-AERS during all treatment cycles, irrespective of grade and regulatory seriousness criteria:

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, hyperthyroidism, or adrenal insufficiency
- Hepatitis
- Transaminitis: Grade ≥2 (AST or ALT >3 × ULN and bilirubin >2 × ULN) or AST/ALT >10 × ULN
- Systemic lupus erythematosus
- Guillain-Barré syndrome
- Myasthenia gravis
- Meningoencephalitis
- Nephritis
- Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response syndrome, systemic immune activation, or infusion-reaction syndromes

7.2.2.1 Secondary Malignancy

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

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

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

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

7.2.2.2 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.

7.3 NIH Reporting Requirements

7.3.1 Definitions

Please refer to definitions provided in Policy 801: Reporting Research Events (https://irbo.nih.gov/confluence/display/IRBO/Policies+and+SOPs).

7.3.2 OHSRP Office of Compliance and Training/IRB Reporting Requirements

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at https://irbo.nih.gov/confluence/display/IRBO/Policies+and+SOPs

Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.3.2.1 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at https://irbo.nih.gov/confluence/display/IRBO/Policies+and+SOPs

7.3.2.1 NCI Clinical Director Reporting

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to the Clinical Director/designee at NCICCRQA@mail.nih.gov within one business day of learning of the death.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the agents administered in this

study can be found in Section 7.1-7.3.

8.1 rhIL-15 (NSC 745101)

Other Names: Recombinant Human IL-15

Amino Acid Sequence: The 115 amino acid coding sequence of the pET28b/IL-15 cistron is as follows:

MNWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASI
HDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS

Pharmacologic Class: IL-15 is a cytokine of the 4-α helix bundle family of cytokines whose mature form consists of 115 amino acids. It has two cystine disulfide crosslinkages at positions Cys 42-Cys 88 and Cys 35-Cys 85.

How Supplied: rhIL-15 is supplied by the DCTD and distributed by the Pharmaceutical Management Branch (PMB)/CTEP/DCTD/NCI.

rhIL-15 is supplied as a sterile, frozen liquid product in single use vials containing no preservatives. Currently, rhIL-15 is supplied as 147 mcg/0.3 mL in a 3 mL glass vial. The concentration is 490 mcg/mL. The IL-15 is formulated in 25 mM sodium phosphate containing 0.5 M sodium chloride at a pH of 7.4.

Preparation: Vials of frozen product should be thawed at ambient room temperature and used within 5 hours of thawing. Upon thawing, the solution is clear and colorless with no evidence of particulates or foreign matter.

Instructions for Patient Administration:

- The needles used for study treatment administration should be suitable for subcutaneous (SC) injection.
- Some SC doses of rhIL-15 require dilution prior to administration (see below). IL-15 will be prepared in D5W/0.1% HSA or normal saline at no less than 100 mcg/mL in sterile borosilicate vials prior to being loaded in the syringes.
- Doses should be rounded to the nearest 0.01 mL.
  Patient weight = ____kg X ____mcg/kg = Subjects' dose = _____mcg

For DL 1 (0.5 mcg/kg) and DL 2 (1 mcg/kg):

- Doses will require dilution. Transfer 0.25 mL of rhIL-15 stock into a sterile vial. Add 0.75 mL diluent to the vial and swirl gently for approximately 1 minute. Diluted rhIL15 concentration = 122.5 mcg/mL.
- Draw dose into a 1 mL syringe. Syringe-loaded rhIL-15 must be administered within 8 hours.

Patient	1 mcg/kg dose	0.5 mcg/kg dose

Weight	(Amount of diluted 122.5 mcg/ml)	(Amount of diluted 122.5 mcg/ml)
60 kg	0.49 mL	0.24 mL
75 kg	0.61 mL	0.31 mL
90 kg	0.73 mL	0.37 mL
105 kg	0.85 mL	0.43 mL

For DL 3 (2 mcg/kg):

- Doses will be administered ***undiluted***. Undiluted rhIL15 concentration = 490 mcg/mL.
- Draw dose into a 1 mL syringe. Syringe-loaded rhIL-15 must be administered within 8 hours.

Patient Weight	2 mcg/kg dose (Amount of undiluted 490 mcg/mL)
60 kg	0.24 mL
75 kg	0.31 mL
90 kg	0.37 mL
105 kg	0.43 mL

Storage: IL-15 vials should be stored at or below -70°C.

Stability: Stability studies are ongoing.

Route of Administration: SC injection

8.2 Nivolumab (NSC 748726)

Other Names: BMS-936558, MDX1106

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

Classification: Anti-PD-1MAb **M.W.:** 146,221 Daltons

M.W.: 146,221 Daltons

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

antigens as well as self-antigens.

Description: Nivolumab Injection is a clear to opalescent, colorless to pale yellow liquid; light (few) particulates may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated in sodium citrate dihydrate, 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, CTEP/DCTD/NCI as 100 mg vials (10 mg/mL) with a 0.7mL 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, USP to concentrations no less than 0.35 mg/mL. Nivolumab injection should not exceed a total infusion volume of 160 mL. For patients weighing less than 40 kilograms (kg), the total volume of infusion must not exceed 4 mL per kg of patient weight. During drug product preparation and handling, vigorous mixing or shaking is to be avoided.

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°C-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 in a refrigerator at 2°-8°C (36°-46°F) and a maximum of 8 hours of the total 24 hours can be at room temperature (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 micron to 1.2 micron pore size, low-protein binding (polyethersulfone membrane) in-line filter. When nivolumab and ipilimumab are administered on the same day, administer nivolumab first followed by ipilimumab.

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.

8.3 Ipilimumab (NSC 732442)

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

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.

Classification: Human monoclonal antibody **M.W**.: 147,991 Daltons

M.W.: 147,991 Daltons

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

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

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

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

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

[a]Includes 2.6 mL overfill.

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

In 2023, PMB will transition to a 50 mg/10 mL (5 mg/mL) vial, which will replace the 200 mg vial. The 50 mg vial is packaged in a 10-cc Type I flint tubing glass vial, stoppered with a 20-mm gray butyl rubber stopper, and sealed with a 20-mm aluminum flip-off seal. Each vial includes a 0.7-mL overfill for vial, needle, and syringe (VNS) holdup.

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° to 8° C (35.6°–46.4°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 (35.6°–46.4°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 (35.6°–46.4°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 90 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(s) and rate(s) via a PVC IV infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (0.2 micron to 1.2 micron). When nivolumab and ipilimumab are administered on the same day, administer nivolumab first followed by ipilimumab.

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

Post-marketing surveillance identified a fatal toxic epidermal necrolysis (TEN) event in a patient who received ipilimumab after experiencing a severe or life-threatening skin adverse reaction on a prior cancer immune stimulating therapy. Caution should be used when considering the use of ipilimumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on a prior cancer immune stimulating therapy.

8.4 Agent Ordering and Agent Accountability

8.4.1 Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), 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 investigator at that institution.

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

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an “active” account status and a “current” password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB’s website for specific policies and guidelines related to agent management.

8.4.2 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.

8.4.3 Investigator Brochure Availability

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

8.5 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://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
- 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)
- IB Coordinator: IBCoordinator@mail.nih.gov

9. CORRELATIVE STUDIES

We plan to evaluate the effects of the combination of rhIL-15 and immune checkpoint inhibitors on the anti-tumor immune response. Paired biopsies will be collected pretreatment and at the end of treatment cycle 1 (optional during the doublets and triplet dose escalation phase, mandatory during the expansion phase) and will be analyzed for immune cell populations, including percentages and absolute numbers of Tregs, myeloid-derived suppressor cells (MDSCs), and effector T cell subsets, as well as for endothelial cell phenotype (CAM expression) and intrinsic apoptosis signaling. Phosphorylation of the TCR and ZAP70, expression of T-cell activation markers, and evaluation of JAK/STAT signaling will all be used to better understand the level of TIL activation. Expression of immune checkpoint inhibitor targets, such as PD-L1 on tumor cells and phosphorylated PD-1 on activated T cells, will be measured as well (see Section 2.3).

Patients that respond to treatment may also be asked to undergo an additional optional biopsy for the assessment of genomic alterations and gene expression changes associated with response. These biopsy samples will be compared to baseline and analyzed using WES and RNASeq (see

Section 2.3.1: Exploratory Laboratory Analyses).

Blood samples will also be collected throughout the study and evaluated for the activation status of peripheral T cell subsets. Based on the availability of samples, additional markers of oxidative stress and inflammation will be evaluated in the peripheral blood, for correlation to both treatment response and immune-related toxicities (see Section 2.3).

Laboratory Contact at the NCI
At least 24 hours prior to tumor biopsy or blood sample collection, the research nurse will contact the NCI Phase I/II PK/PD Support Group in NIH Building 10:
E-mail (preferred): NCIPK-PDsupportgroup@mail.nih.gov; Pager (preferred): 102-12798; Phone: 240-858-3963; Fax: 301-480-5871. For biopsies, tubes pre-labeled with the information specified in Section 9.4, biopsy date, and site of tissue biopsy will be provided. Initial processing and shipping of the samples will be completed as described below.

9.1 Correlative Studies in Tumor Tissue

9.1.1 PD Analysis

Targets of PD assays performed by immunofluorescence on biopsy tissue sections will include: PD-L1 levels in cells present in the biopsy, T cell phenotypic markers CD8 and FOXP3, and markers of T-cell activation and inhibition, specifically Zap70 pY493 and pY580 SHP2. Measurements on the Nikon A1/Definiens platform employed by PADIS will include cell enumeration and proximity of tumor cells to T cells (see Section 2.3). Monoclonal antibodies to all markers have been validated by the standard PADIS approach, and PADIS has previously validated and reported on the tumor cell marker set. IFA methodology is currently in development for the T-cell activation markers.

Priority will be given to assays analyzing the status of PD1/PD-L1 checkpoint signaling and TCR activation (specifically Zap70-pY493). The other proposed assays will be performed if sufficient tissue is available.

Biopsies are optional on the doublets and triplet dose escalation cohort and will be collected whenever feasible; they are **mandatory** on the triplet expansion cohort. Biopsies will be collected at the following time points:

- At baseline
- Cycle 1 day 42 (up to 3 days prior)

Samples from patients who will be undergoing a procedure due to medical necessity during which the tissue may be collected, or tumor biopsy tissue from a previous research study or medical care that is available for submission at registration may also be acceptable as a baseline sample (see Section 9.2.2).

9.1.2 Genomic Analysis

At the PI's discretion, patients on the triplet escalation/expansion phases **that have baseline biopsy samples available** (archival or collected on study) may be asked to undergo an additional optional biopsy at the time of confirmed response. If the biopsy is successful, exploratory WES and RNASeq will be performed on both the baseline biopsy sample and the time-of-response biopsy sample, enabling the assessment of genomic alterations that 1) occur with treatment over time and 2) possibly correlate with response (see Section 2.3: Exploratory Laboratory Analyses). Genes of interest would include those involved in the immune response and antigen presentation (JAK/STAT pathway, TGFβ pathway, HLA genes). Data from germline sequencing will be used to determine which tumor mutations are somatic variants (see Section 9.3.2).

Patients that have already given two biopsies on study (at the protocol-specified timepoints, baseline and C1D42) **would not be eligible** for this optional time-of-response biopsy, as the maximum number of biopsies per patient on this study is two.

Additional genomic assays may be performed on leftover tissue/genomic material from the baseline biopsy sample and the time-of-response biopsy sample at the PI's discretion.

9.2 Biopsy Procedure

Serial tumor biopsies will be obtained by the biopsy team by a cutaneous approach, a dermatologist for skin lesions, or an ENT for lesions that are easily biopsiable through ENT exam. The investigators will meet regularly with the Interventional Radiology team to review patient scans and discuss patients' medical history. If a site is deemed appropriate for biopsy with minimal risk to the participant by agreement between the investigators and the biopsy team, an attempt for biopsy will be made. Because approximately 20% of tumor biopsies collected on research trials are not usable due to the presence of stroma or normal and/or necrotic tissue and paired biopsies are necessary for analysis, up to 5 core biopsies ≥18-gauge in diameter and ≥1 cm in length, or equivalent, will be obtained during each procedure to try and ensure adequate tumor content and quality. If possible, the lesion from which each biopsy is taken, and whether the specimen came from the center or periphery of the lesion, will be documented.

Acceptable biopsy procedures are:

- Percutaneous biopsy with local anesthetic.
- Excisional cutaneous biopsy with local anesthetic
- Other biopsy with local anesthetic and/or sedation that has been shown to have a risk of severe complications < 2%
- Removal of additional tumor tissue during a medically necessary surgical procedure
- Biopsy with removal of additional tumor tissue during a medically necessary mediastinoscopy, laparoscopy, gastrointestinal endoscopy, bronchoscopy, or craniotomy

No open surgical, laparoscopic endoscopic procedure will be performed solely to obtain a biopsy for this protocol.
The use of imaging to facilitate biopsies will be decided by members of the biopsy team and may include ultrasound, CT scan, or MRI. Should a CT scan be needed for biopsy, the number of scans for each procedure will be limited to the minimum number needed to safely obtain a biopsy. Tumor biopsies and local anesthesia will be administered only if they are considered to

be of low risk to the participant, as determined by the investigators and the biopsy team. Cores from different areas of the tumor are preferred when feasible. The clinical, radiologic, dermatologic ENT and pharmacodynamic members of the research team will meet monthly to review the adequacy of the biopsy specimens for analysis.

Baseline biopsies will be performed following patient enrolling on study. If an initial attempt at biopsy is unsuccessful, the patient will be given an option to proceed with a repeated attempt. A separate consent form must be signed for each biopsy procedure, so patients may choose not to undergo subsequent biopsies. If the baseline biopsy is unsuccessful or the patient refuses to undergo subsequent biopsies, no further biopsies will be performed but the patient will remain on study, receive study medication, and other correlative studies will be performed.

9.2.1 Solid Tumor Biopsy Processing

Five tissue cores, or equivalent, will be obtained at each time point. Each biopsy sample will be transferred into a 1.5-mL pre-chilled cryovial and then flash frozen in liquid nitrogen per DCTD SOP340507 (http://dctd.cancer.gov/ResearchResources/biomarkers/docs/par/SOP340507_Biopsy_Frozen.pdf). Biopsies should be placed in cryogenic vials and frozen within 2 minutes of collection. Three biopsy samples will be used for pharmacodynamic assays to measure immune checkpoint targets and the anti-tumor immune response as described above, and the other two will be used for genomic analysis if appropriate. Remaining samples will be kept in the Frederick National Laboratories CR Biorepository in liquid nitrogen freezers to be used for validation of these assays as necessary.

Shipment should be by CSP Courier and may be arranged by contacting Mike Johnston, FNLCR, Tel.: 301-846-5893. The Clinical Center should notify NCI_PD_Support@mail.nih.gov with sample information.

Flash-frozen biopsy cores for PD analysis will be shipped on dry ice to:

Attn: PADIS IQC Lab
Frederick National Laboratory for Cancer Research
Leidos Biomedical Research, Inc.
1050 Boyles Street
Building 425, Room 105
Frederick, MD 21702
Phone: 301-846-7292
NCI_PD_Support@mail.nih.gov

Please contact Amy Pantella (office: 301.846.6747, cell: 301.401.8070) or Rachel Andrews (office: 301.846.1951, cell: 240.344.5697) (email: NCI_PD_Support@mail.nih.gov) to ask any questions regarding storage or shipment of these specimens.

9.2.2 Archival Tissue Submission

Archival tumor tissue submitted as a baseline specimen for PD studies must have been collected within 3 months prior to patient registration, and the patient must not have received any intervening cancer therapy since collection of the specimen. Archival tissue must have been collected and processed according to NCI DCTD SOP340507 (https://dctd.cancer.gov/ResearchResources/biomarkers/docs/par/SOP340507_Biopsy_Frozen.pdf), including flash-freezing in liquid nitrogen, minimal cold ischemia time (< 5 minutes), and shipment on dry ice. Formalin-fixed biopsy tissue is not compatible with the immunoPD assay.

These restrictions do not apply for the use of archival tissue for genomic studies. Use of archival tissue as a baseline genomic sample will be at the discretion of the PI and the Molecular Characterization Laboratory (MoCha) at Frederick National Laboratory for Cancer Research (FNLCR).

Please send an email to FNLCR PD Specimen Central Receiving (NCI_PD_Support@mail.nih.gov) to advise that archival tissue is being prepared for shipment. State "Protocol Name PD Specimens Ready for Shipment" in the subject line. If needed, FNLCR PD Central Receiving can be contacted directly at 301-846-1951 or 301-846-6747.

9.3 Blood Collection for Correlative Studies

9.3.1 PD Studies

Collection of blood samples for PD studies will be optional during the doublets and mandatory during the triplet escalation/expansion phases.

Blood samples will be used for evaluation of immune signaling and activation using the TCAP1 and TCAP1-NK assays (PADIS) based on the following biomarkers:

- CD3, CD4, CD8 and CD33 as T cell phenotype markers
- PD-1 and PD-L1 as immune checkpoint molecules
- Phosphorylated Lck (pTyr505), Zap70 (pTyr493), SHP-2 (pTyr542) and CD3ζ (pTyr142) to investigate T cell activation
- CD56, CD16, TCR γδ1, and TCR γδ2 to investigate changes in total NK cells and total Gamma Delta (γδ)-T cells

Blood samples will be collected at baseline (pretreatment) and prior to drug administration on the following days shown below. Please note that the additional collection timepoints of day 8 and day 15 will be selected as similarly reported in the Thomas Waldmann IL-15 phase 1 trial that showed NK cell proliferation after rhIL-15 cessation [80]:
During cycles 1 through 4:

- day 1
- day 2
- day 3
- day 8
- day 15 ± 2 days
- day 22 ± 2 days

- day 36 ± 2 days

During cycles 5 and onwards:

- day 1
- day 15
- day 29

Samples will be collected into NaHep tubes (8 mL of blood into one 10 mL tube at each timepoint) and then added to 1x Lyse/Fix buffer per DCTD SOP LHTP003.08.15. Blood must be mixed with Lyse/Fix buffer within 5 minutes of collection. Once samples are processed, they should be stored in 60% methanol at -20˚C for at least one hour (no longer than 6 hours) and then transferred to -80˚C. **Please see DCTD SOP LHTP003.08.15 for detailed guidance.** DCTD SOP LHTP003.08.15 will be made available at: https://dctd.cancer.gov/ResearchResources/ResearchResources-biomarkers.htm. It can also be obtained by emailing NCI_PD_Support @mail.nih.gov.

At NCI, arrangements will be made for pickup with the CSP courier service. At least 24 hours prior to blood sample collection, the research nurse will contact the NCI Phase I/II PK/PD Support Group in NIH Building 10: E-mail (preferred): NCIPK-PDsupportgroup@mail.nih.gov; Pager (preferred): 102-12798; Phone: 240-858-3963; Fax: 301-480-5871. The NCI Phase I/II PK/PD Support Group will arrange for same day processing or immediate shipment to FNLCR; specimens should be held at controlled room temperature (15˚C to 30˚C) prior to processing. Testing and data analysis will be performed by PADIS/FNLCR.

9.3.2 Genomic Studies

For patients who respond to treatment and agree to undergo an additional biopsy for genomic analysis, whole blood samples will be collected at the time of additional biopsy for germline sequencing. Mononuclear cells will be isolated for nucleic acid extraction and **WES/RNAseq**, the results of which will not be returned to patients.

Two 10-mL cell-free DNA BCT (Streck) tubes should be collected and couriered at ambient temperature to Dr. Mickey Williams' laboratory (MoCha) at FNLCR.

Blood samples for genetic analysis should be labeled with only the unique patient ID. **Do NOT include patient identifiers (e.g., medical record number, patient name, or initials) with the samples.**

Ship blood specimens at ambient temperature to:
Molecular Characterization Lab
Frederick National Lab for Cancer Research
1050 Boyles Street, 459/108
c/o Alyssa Chapman or Bishu Das
MoChaSampleReceiving@nih.gov

Email the MoCha Histology group at MoChaSampleReceiving@nih.gov prior to shipping with expected arrival date, protocol number, specimen IDs, histologic classification of the

primary tumor, tracking information, and site information. MoCha should be notified as soon as possible of all protocol deviations or issues, prior to shipment of specimens(s).

Samples should arrive at MoCha within 3 days of collection. Note that FNLCR receiving is closed and unable to receive samples on weekends and on all Federal holidays. Contact MoChaSampleReceiving@nih.gov with any questions regarding sample collection or shipment.

Shipment should be by CSP Courier and may be arranged by contacting Mike Johnston, FNLCR, Tel.: 301-846-5893

9.4 Sample Collection and Processing

Biospecimens will be collected and processed using validated SOPs that will ensure both specimen quality and patient confidentiality pursuant to informed consent provisions. Information about each specimen (e.g., blood, tumor biopsy, per specific protocol) will be recorded on a PK/PD collection worksheet.

Using a computerized inventory system and a backup hardcopy process, all specimen collection and processing steps will be documented and the specific location of each specimen will be tracked. Each new specimen collected will be assigned a unique barcode identifier that can be linked to the original specimen collected and other relevant information within the inventory system. To ensure patient confidentiality, only containers used for the initial specimen collections will be labeled with patient identifiers.

Only the barcode identifier will be applied to all subsequent specimen containers. When specimens are processed and aliquoted, no patient information will be included on the new containers. Original specimen containers will be discarded. Only barcode-labeled specimens without patient identifiers will be shipped for analysis and/or storage. Specimen labels will indicate: CTEP protocol number, unique patient accession number, 3-digit sample number (see list below), collection time, and total volume collected, as appropriate. Samples from sets of at least three patients will be grouped for scientific analysis.

Standardized 3-digit sample collection numbers:
000 series: blood for germline WES (i.e., 099).
500 series: tumor biopsies
800 series: blood for pharmacogenomic or other analysis
900 series: blood for immunoPD

The inventory process contains other security provisions sufficient to safeguard patient privacy and confidentiality. Access to the inventory system and associated documents will be restricted to appropriate individuals. Requests to use specimens stored in the repository must be approved. The only patient information available in the inventory system will be the patient sex, diagnosis, and level of informed consent given. SOPs ensure that any changes in informed consent made by a patient and relayed to the PI will be reflected in the inventory system to ensure that specimens are destroyed as appropriate. All laboratory personnel will be trained to adhere to

SOPs and will be monitored for high-quality performance.

Any new use of these samples will require prospective IRB review and approval. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e., broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

9.5 Management of Genetic Sequencing Results

Whole-exome sequencing (WES) of tumor and blood performed for research purposes can detect non-ambiguous germline variants, which may raise health and privacy implications for the patient and his or her family. WES will not be validated for clinical use, and no clinical decisions can be made based on its results. Subjects will be contacted if a clinically actionable gene variant is discovered in germline WES. Clinically actionable findings for the purpose of this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis (currently ACMG SF v2.0 [81]). A list of current guidelines is maintained on the CCR intranet:
https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists.

Patients who still remain on the study when a clinically actionable gene variant is discovered and confirmed by CLIA testing at MoCha will be contacted, and the subject will be offered the opportunity to come to NIH (at our expense) to have genetic education and counseling to explain this result. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense).

This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

10. STUDY CALENDARS

Eligibility screening evaluations (see Section 3.3) are to be performed within 8 days prior to patient enrollment, with the exception of informed consent, echocardiogram (ECHO), and tumor imaging scans, which must be performed within 28 days prior to patient enrollment. Baseline history, physical examination, laboratory evaluations, and urinalysis are to be conducted within 8 days prior to start of protocol therapy. If protocol therapy is started within 8 days of the screening evaluations, values from the screening evaluations may be used as baseline measurements; if >8 days have passed since the screening evaluations, the medical history, physical examination, laboratory evaluations, and urinalysis must be repeated prior to starting protocol therapy. Baseline imaging scans must be done within 28 days prior to the start of protocol therapy.

In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Each treatment cycle is 42 days long; cycle can start up to 7 days late due to scheduling conflicts. Throughout the course of treatment, treatment administration can be +3 days for toxicities or +/- 3 days for patient scheduling purposes. There must be a minimum of 12 days between nivolumab doses.

10.1 Doublet schedule

	Pre-Study	C1 Wk1	C1 Wk2	C1 Wk3	C1 Wk4	C1 Wk5	C1 Wk6	C2 Wk1	C2 Wk2	C2 Wk3	C2 Wk4	C2 Wk5	C2 Wk6	Off Treatment
Study drug		**rhIL-15 + nivolumab OR rhIL-15 + ipilimumab**[a]												
Informed consent	X													
Demographics	X													
Medical history	X													
HIV/ hepatitis screening[b]	X													
Concurrent meds	X	X----------											----------X	
Physical exam[c]	X	X[l]	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[c]	X	X[l]	X	X	X	X	X	X	X	X	X	X	X	X
Height	X													
Weight	X	X[l]			X	X	X	X		X	X	X		X
Performance status[c]	X	X[l]	X	X	X	X	X	X	X	X	X	X	X	X
CBC w/diff, plts[c]	X	X[l]	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[c, d]	X	X[l]	X	X	X	X	X	X	X	X	X	X	X	X
Fasting lipid profile[f]	X	X[l]						X						X
Urinalysis[c,e]	X	X[l]	X	X	X	X	X	X	X	X	X	X	X	X
CPK/troponin I[f]	X	X[l]						X						
EKG, ECHO[g]	X													
Adverse event evaluation		X----------											----------X	X
Tumor measurements	X	Tumor measurements are repeated every cycle (every 6 weeks) ± 1 week during cycles 1-4 and every 2 cycles (every 12 weeks) ± 1 week thereafter. Documentation must be provided for patients removed from study for progressive disease.[k]												X
B-HCG[h]	X													

Biopsy[i]	X						X							
Blood for PD[j]	X	X			X		X	X		X			X	

a. Each treatment cycle is 42 days long (cycle start +7 days/ drug administration + 3 days due to toxicities or +/- 3 days for scheduling conflicts; minimum of 12 days between nivolumab doses). rhIL-15 given SC days 1-8 and 22-29 (first 4 cycles only) combined with nivolumab given IV on days 8, 22, and 36 OR ipilimumab given IV on day 8. Cycles 5 and onwards will not include rhIL-15; patients will receive nivolumab on days 1, 15, and 29 OR ipilimumab on day 1. A 1-week Transition Period will be required between Cycle 4 and Cycle 5. See Doublet Schema.
b. Hepatitis B Surface Antigen, Hepatitis B Surface Antibody, Hepatitis B Core Antibody, Hepatitis C Core Antibody, and HIV 1/2 serologies as part of screening evaluation.
c. Performed pre-study, weekly during cycles 1 and 2, and within 7 days prior to the start of every subsequent cycle.
d. ACTH, Albumin, alkaline phosphatase, amylase, total bilirubin, bicarbonate, BUN, calcium, chloride, cortisol (a.m.), creatinine, glucose, LDH, lipase, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, TSH. (For patients on replacement hydrocortisone for adrenal insufficiency, ACTH and cortisol can be omitted from the laboratory evaluation.)
e. Protein/creatinine ratio.
f. Baseline and within 7 days of the start of every cycle.
g. Baseline and as clinically indicated.
h. Serum or urine pregnancy test (women of childbearing potential) as part of screening evaluation.
i. Research biopsies (optional). At baseline and C1D42 (up to 3 days prior), as described in Section 9.1.
j. Blood for PD (optional). At baseline; on days 1-3, day 22 ± 2 days, and day 36 ± 2 days during Cycles 1-4: on days 1, 15, and 29 during Cycle 5 and onwards, as described in Section 9.3.
k. Patients positive for tumor markers (PSA, CEA, CA125) will have their serum levels remeasured at the time of radiographic restaging, as described in Section 5.
l. Values from eligibility screening evaluations may be used as baseline values if test was performed within 8 days of start of protocol therapy.

10.2 Triplet schedule

	Pre-Study	C1 Wk1	C1 Wk2	C1 Wk3	C1 Wk4	C1 Wk5	C1 Wk6	C2 Wk1	C2 Wk2	C2 Wk3	C2 Wk4	C2 Wk5	C2 Wk6	Off Treatment
Study drug		**rhIL-15 + nivolumab + ipilimumab**[a]												
Informed consent	X													
Demographics	X													
Medical history	X													
HIV/ hepatitis screening[b]	X													
Concurrent meds	X	X----------X												
Physical exam[c]	X	X[l]	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[c]	X	X[l]	X	X	X	X	X	X	X	X	X	X	X	X
Height	X													
Weight	X	X[l]			X	X	X	X		X	X	X		X
Performance status[c]	X	X[l]	X	X	X	X	X	X	X	X	X	X	X	X
CBC w/diff, plts[c]	X	X[l]	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[c, d]	X	X[l]	X	X	X	X	X	X	X	X	X	X	X	X
Fasting lipid profile[f]	X	X[l]						X						X
Urinalysis[c, e]	X	X[l]	X	X	X	X	X	X	X	X	X	X	X	X
CPK/troponin I[f]	X	X[l]						X						
EKG, ECHO[g]	X													
Adverse event evaluation		X----------X												X
Tumor measurements	X	Tumor measurements are repeated every cycle (every 6 weeks) ± 1 week during cycles 1-4 and every 2 cycles (every 12 weeks) ± 1 week thereafter. Documentation must be provided for patients removed from study for progressive disease.[k]												X
B-HCG[h]	X													

Biopsy[i]	X						X							
Blood for PD[k]	X	X	X		X		X	X		X			X	
Blood for genomics[m]														

a. Each treatment cycle is 42 days long (cycle start +7 days/ drug administration + 3 days due to toxicities or +/- 3 days for scheduling conflicts; minimum of 12 days between nivolumab doses). rhIL-15 given SC days 1-8 and 22-29 (first 4 cycles only) + nivolumab given IV on days 8, 22, and 36 + ipilimumab given IV on day 8. Cycles 5 and onwards will not include rhIL-15; patients will receive nivolumab on days 1, 15, and 29 and ipilimumab on day 1. A 1-week Transition Period will be required between Cycle 4 and Cycle 5 to ensure a 2-week period between nivolumab doses. See Triplet Schema.

b. Hepatitis B Surface Antigen, Hepatitis B Surface Antibody, Hepatitis B Core Antibody, Hepatitis C Core Antibody, and HIV 1/2 serologies as part of screening evaluation.

c. Performed pre-study, weekly during cycles 1 and 2, and within 7 days prior to the start of every subsequent cycle.

d. ACTH, Albumin, alkaline phosphatase, amylase, total bilirubin, bicarbonate, BUN, calcium, chloride, cortisol (a.m.), creatinine, glucose, LDH, lipase, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, TSH. (For patients on replacement hydrocortisone for adrenal insufficiency, ACTH and cortisol can be omitted from the laboratory evaluation.)

e. Protein/creatinine ratio.

f. Baseline and within 7 days of the start of every cycle.

g. Baseline and as clinically indicated.

h. Serum or urine pregnancy test (women of childbearing potential) as part of screening evaluation, and before the start of each cycle.

i. Research biopsies (optional during escalation phase; mandatory during expansion phase). At baseline and C1D42 (up to 3 days prior) as described in Section 9.1. Patients that respond to treatment and have baseline biopsy samples available may be asked to undergo an additional optional biopsy.

j. Blood for PD (mandatory). At baseline; on days 1-3, day 8 (before ipi + nivo), day 15 ± 2 days day 22 ± 2 days, and day 36 ± 2 days during Cycles 1-4: on days 1, 15, and 29 during Cycle 5 and onwards, as described in Section 9.3.

k. Patients positive for tumor markers (PSA, CEA, CA125) will have their serum levels remeasured at the time of radiographic restaging, as described in Section 5.

l. Values from eligibility screening evaluations may be used as baseline values if test was performed within 8 days of start of protocol therapy.

m. Blood for germline sequencing will be collected as needed from patients who respond to treatment and agree to undergo an additional biopsy for genomic analysis.

11. MEASUREMENT OF EFFECT

ANTITUMOR EFFECT – SOLID TUMORS

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [82]. 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.

Overall response will also be explored using iRECIST (see Section 11.2). Increasing clinical experience indicates that traditional response criteria such as RECIST may not be sufficient to fully characterize activity in the new era of target therapies and/or biologics. In studies with therapeutic antibodies, complete response, partial response, or stable disease has been shown to occur after an increase in tumor burden, characterized by progressive disease by traditional response criteria. Therefore, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Long-term effect on the target disease must also be captured. The immune RECIST (iRECIST) criteria, by incorporating specific response patterns that have been observed with immunotherapeutic agents, have been developed to address these issues and provide standardized response criteria for use with immmunotherapy [79].

11.1 RECIST v1.1 Criteria for Assessment of Response and Progression

Definitions

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

Evaluable for objective response. All patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of response to treatment. These patients will have their response classified according to the definitions stated below.

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

Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately

measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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

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

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

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

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

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

Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Response Criteria

11.1.1 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). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment or where the tumour burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Patients that are clinically well may continue on therapy following RECIST progression with new lesions or increase in target lesions if the increase in disease burden does not meet the definition of PD by immune response criteria [79]. In this situation, patients do not have unequivocal progression until immune response criteria are met (see Section 11.2).

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

11.1.2 Evaluation of Non-Target Lesions

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

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

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

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

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

11.1.3 Evaluation of Best Overall Response

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

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

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

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

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

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

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

11.2 iRECIST Response Assessment

Overall response will also be explored using iRECIST [79]. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, resulting in previously undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumour burden, or the appearance of new lesions, does not reflect true tumour progression.

Key differences between RECIST 1.1 and iRECIST are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately.

Confirming Progression

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

iCPD is confirmed if further progression, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued progression where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions (from uPD):
  - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum;
  - Continued unequivocal progression in non-target disease with an increase in tumor burden;
  - Increase in size of previously identified new lesion(s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions);
- RECIST 1.1 criteria are met where progression was not previously identified, including

the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD is the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). As can be seen in the below table, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented.

New Lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form. These data will enable the development and testing of alternate response criteria, or further modifications of RECIST.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

Time-point (TP) iResponse

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	Prior iUPD**
CR / iCR	CR	No	CR	iCR
CR/iCR	Non-CR/Non-PD Non-iCR/Non-iUPD	No	PR	iPR
PR/iPR	Non-CR/Non-PD Non-iCR/Non-iUPD	No	PR	iPR
SD/iSD	Non-CR/Non-PD Non-iCR/Non-iUPD	No	SD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	The appearance NLs confirms PD if Additional NLs or iUPD in last TP based on NLs and increase in size (≥ 5 mm for NLT or any increase for NLNT) If no change in NLs from last TP, remains iUPD
PD	Non-CR/Non-PD Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in sum of at least 5 mm, otherwise remains iUPD

PD	PD	No	iUPD	iCPD if further increase in previously identified*** T lesion iUPD ≥ 5 mm and / or NT lesion iUPD
PD	PD	Yes	iUPD	iCPD if further increase in previously identified T lesion iUPD ≥ 5 mm and / or NT lesion iUPD and / or size or number of new lesion
Non-iUPD	Non-iUPD	Yes	iUPD	iCPD if increase in size of previously identified new lesions of increased number of new lesion

* Using RECIST 1.1 principles. If no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same.
** In any category.
*** Previously identified in assessment immediately prior to this time-point (TP)
NA = not applicable.

iRECIST Best Overall Response (iBOR)

All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined below.

TPR1	TPR2	TPR3	TPR4	TPR5	iBOR
CR	CR, PR, iUPD, NE	CR/iCR, PR/iPR, iUPD, iCPD, NE	iUPD	iCPD	iCR
iUPD	PR, SD, NE	CR	CR, PR, SD, iUPD, NE	CR, PR, SD, iUPD, iCPD, NE	iCR
iUPD	PR	PR, SD, iUPD, NE	PR, SD, iUPD, NE, cPD	PR, SD, iUPD, NE, iCPD	iPR
iUPD	SD, NE	PR	PR, SD, iUPD, NE	PR, SD, iUPD, iCPD, NE	iPR
iUPD	SD	SD, iUPD, NE	SD, iUPD, iCPD, NE	SD, iUPD, iCPD, NE	iSD
iUPD	iUPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

1. Table assumes a randomized study where confirmation of CR or PR is not required.
2. NE = not evaluable that cycle.
3. Designation “I” for BOR can be used to indicate prior uPD to aid in data interpretation.
4. For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.

Methods of Measurement

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. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, which may be treatment arm dependent. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be

recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

Clinical Lesions
Clinical lesions will only be considered measurable when they are superficial and ≥ 10mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

Chest X-ray.
Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI.
CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When 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). Other specialized imaging or other techniques may also be appropriate for individual case [82]. For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

Bone Scan.
^{99m}Tc-methylene diphosphonate radionuclide bone scintigraphy is the standard for bone imaging.

Ultrasound.
Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

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

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

Cytology, Histology.
These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), 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 advised to differentiate between response or stable disease and progressive disease.

11.3 Response and Stable Disease Duration (RECIST 1.1 and iRECIST)

Response duration will be measured from the time measurement criteria for CR/PR or iCR/iPR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

Stable disease duration will be measured from the time of registration/randomization until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Study Oversight

The clinical research team will meet on a weekly basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose modification if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using PROTECT and to the Sponsor. For adverse events related to either agent that have not been reported previously, voluntary MedWatch reporting will be performed.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

12.2 Data Reporting

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.

Requirements to access Rave via iMedidata:

- A valid account, and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

  Rave role requirements:

  - Rave CRA or Rave CRA (Lab Admin) role, must have a minimum of an Associate Plus (AP) registration type,
  - Rave Investigator role, must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR), and
  - Rave Read Only role, site staff must have at a minimum an Associates (A) registration type.
- Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

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 receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management 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.

Monitoring 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://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) 619-7862 or by email at ctms@theradex.com for additional support with Rave and completion of CRFs.

Responsibility for Data Submission

It is the responsibility of the PI(s) at the site to ensure that all investigators understand the procedures for data submission for the protocol and that protocol-specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave. Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due. Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA 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.

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-informaticsresources/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.

12.3 Collaborative Agreements Language

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

terms of award, apply to the use of the Agent(s) in this study:

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

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

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

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

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

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

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

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

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days 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: 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.

12.4 Human Data Sharing Plan

What data will be shared?
We will share human data generated in this research for future research as follows:
x De-identified data in an NIH-funded or approved public repository
x Identified data in BTRIS (automatic for activities in the NIH Clinical Center)
x De-identified or identified data with approved outside collaborators under appropriate agreements

How and where will the data be shared?
Data will be shared through:
x An NIH-funded or approved public repository: clinicaltrials.gov
x BTRIS (automatic for activities in the NIH Clinical Center)
x Approved outside collaborators under appropriate individual agreements
x Publication and/or public presentations

When will the data be shared?
x At the time of publication or shortly thereafter

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The primary objective of this trial is to determine the safety, toxicity profile, DLTs, and MTD of rhIL-15 administered subcutaneously for 8 consecutive days in combination with anti-CTLA-4 and anti-PD1 monoclonal antibodies, in patients with metastatic or treatment-refractory cancers which are not curable or do not have known measures or treatments that are associated with a

survival advantage.

The exploratory objectives include characterization of the biological effects of this treatment on the percentages and absolute numbers of circulating lymphocyte sets (NK and T-cells) and T-cell subsets. The potential antitumor activity of rhIL-15 will be assessed by the clinical response rate and time to progression, as well as by measurement of T-cell infiltration into the tumor and immunologic gene expression in the tumor and in the periphery. Pre- and post-treatment fine-needle biopsies and blood samples throughout the study will be collected and analyzed.

The first 4-6 patients enrolling in the study will be placed into lead-in doublets (2-3 patients on each) and will receive a combination of rhIL-15 and either nivolumab OR ipilimumab. After completion of the doublet phase, the trial will be halted and a safety analysis will be submitted to the IRB. Once toxicity is cleared in both doublets (i.e., at least 2 patients enrolled on each doublet remain free of DLTs for 6 weeks) and a safety analysis is reviewed and approved by the IRB, new patients will be enrolled directly onto the triple agent dose escalation phase.

As of Amendment C (10/3/18), toxicity has been cleared in both lead-in doublets. 3 patients were enrolled on Doublet A (rhIL-15 + nivolumab) and 2 patients were enrolled on Doublet B (rhIL-15 + ipilimumab); none of the 5 patients experienced a DLT in the 6-week period. The IRB has approved enrollment onto the triplet cohort.

The dose escalation phase, which has 3 planned dose levels, is based on the prior clinical experience with each of the 3 investigational agents with the intent to define the MTD for the combination treatment.

The MTD will be based on the assessment of DLTs, and will be defined as the dose level at which less than one-third of patients (0/3 or 0-1/6 patients) treated at that dose experience a DLT, with the next higher dose level demonstrating a one-third or greater number of patients ($\geq$ 2/3 or $\geq$ 2/6 patients) having DLT. A DLT is defined as an AE that is felt to be related (possibly, probably, or definitely) to administration of study drugs, and meets prespecified criteria. This will include any condition requiring long-term treatment with corticosteroids or permanent discontinuation of one of the agents. If a subject did not experience DLT and did not finish 1 cycle of treatment (42 days), he or she will not be evaluable for determination of the MTD and will be replaced in the dose level.

Using the defined dose escalation scheme, the probability of escalating to the next dose level, based on the true rate of DLT at the current dose, is given by the following table (each group will be considered independently of the other):

True Toxicity at a Given Dose	10%	20%	30%	40%	50%	60%
Probability of Escalating	.91	.71	.49	.31	.17	.08

Thus, if the true underlying proportion of DLTs is 50% at the current dose, there is a 17% chance of escalating to the next dose.

Following the dose escalation cohort and determination of the MTD, another 15 patients will be treated at the MTD on an expansion cohort, which will include mandatory biopsies. With 15

patients and a tumor biopsy QA criteria failure rate of 50% with respect to paired (pre- and post-dose) biopsies, we have an 85% likelihood of having at least 6 usable PD samples, and 95% likelihood of having at least 5 usable samples from the expansion cohort. With 6 PD sample pairs, there is 90% power to detect a treatment effect equivalent to 1.85 SD's (associated with the intra-patient baseline variability of the PD marker) with the paired 2-sample T-test, at the 1-sided .05 significance level, for a given PD variable of interest. PD variables may be log-transformed to achieve more nearly normal distributions.

13.2 Sample Size/Accrual Rate

With an anticipated accrual of 3-4 patients per month, it is expected that accrual can be completed in 16 months. The minimum number of patients enrolled in this trial will be 15 and the maximum number of patients enrolled will be 45, including an expansion cohort of 15 patients that will be treated at the MTD or the maximum administered dose. To allow for unevaluable patients, the accrual ceiling has been set at 50 patients.

13.3 Analysis of Exploratory Endpoints

Exploratory evaluations will be performed, with results reported with appropriate caveats about the exploratory nature of the analysis, and without formal adjustment for multiple comparisons.

13.4 Reporting and Exclusions

Evaluation of Toxicity

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

Evaluation of Response

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

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

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been

identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

14. HUMAN SUBJECTS PROTECTION

14.1 Rationale for Subject Selection

This study will be open to all individuals regardless of gender, ethnicity, or race provided that the aforementioned inclusion and exclusion criteria are met. Participants should realize that there is no guarantee of benefit to them from participation in this trial. The results of this trial may benefit future cancer patients. To date, there is no information that suggests that differences in drug metabolism or effect on tumor would be expected in one ethnic group compared to another. Efforts will be made to extend accrual to each representative population, but a balance must be struck between participant safety considerations and limitations on the number of individuals exposed to potentially ineffective treatments on the one hand and the need to explore racial/ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to ethnic identity are noted, a follow-up study may be written to investigate those differences more fully.

14.1.1 Inclusion of Women and Minorities:

This study will be open to all individuals regardless of gender, ethnicity, or race provided that the aforementioned inclusion and exclusion criteria are met. The table below includes accrual estimates for the duration of the study.

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native					
Asian	3	3			**6**
Native Hawaiian or Other Pacific Islander		1			**1**
Black or African American	5	5	1	1	**12**
White	14	13	1	1	**29**
More Than One Race	1	1			**2**
Total	**23**	**23**	**2**	**2**	**50**

14.1.2 Justification for Exclusions

Pregnant women are excluded from this study because data from animal studies suggest that ipilimumab and nivolumab have potential to cause fetal harm [41, 46]; the effects of rhIL-15 on the developing human fetus are unknown. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with these agents, breastfeeding should be discontinued. Participants with unstable or serious medical conditions or psychiatric illness/social situations that would limit compliance with study requirements are excluded due to the possibility that the underlying condition may obscure the attribution of effect and adverse events and may limit study compliance. Because rhIL-15 treatment acts by stimulating the patient's immune system to attack their tumor, patients with HIV, hepatitis B or C that have defective immune systems or immune responses are much less likely to have benefit from this immune-based therapy and are therefore not eligible for this trial.

14.1.3 Participation of Children

Participants under the age of 18 will be excluded from study because dosing or adverse event data are not currently available for the use of the study agents in participants <18 years of age.

14.1.4 Evaluation of Benefits and Risks/Discomforts

There may or may not be any clinical benefit to a patient from participation in this trial. Their participation will benefit future cancer patients. Potential risks include the possible occurrence of any of a range of side effects that are listed in the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients as described in Section 5. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which participants are entitled under applicable regulations.

14.2 Procedure for Protecting Against or Minimizing Any Potential Risks

All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. This study may involve risks to patients, which are currently unforeseeable. All patients will be monitored for side effects from taking study medication. This research represents a greater than minimal risk to participants, but presents the prospect of direct benefit to individual subjects.

For adult patients enrolled at the Clinical Center, NCI, the research component of this study includes up to 2 CT tumor biopsies, conferring radiation exposure at an effective dose of 1.6 rem. This dose is below NIH RSC guidelines and represents a slightly greater than minimal risk to patients.

14.3 Consent Process and Documentation

An associate or principal investigator on the trial will inform patients of the purpose, alternatives, drug administration plan, research objectives, and follow-up of this trial. The patient will be

provided an IRB-approved consent for review and signature and his/her questions will be answered. After a decision is made to enroll into the study, a signature will be obtained from the patient. The original signed consent goes to each participating site's Medical Records; a copy will be placed in the research record.

The initial consent process, as well as re-consent (when required), may take place in person or remotely (e.g., via telephone or other NIH-approved remote platforms used in compliance with policy, including HRPP Policy 303) per the discretion of the designated study investigator and with the agreement of the participant/consent designee(s). When in-person, the informed consent process will be conducted in a quiet room with a closed door with only relevant parties present, to protect the privacy of the subject.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to the participant) or on the electronic document. When required, the witness signature will be obtained similarly as described for the investigator and participant.

When a hand signature on an electronic document is used for the documentation of consent, this study will use the iMed Consent platform (which is 21 CFR Part 11 compliant) to obtain the required signatures. Both the investigator and the participant will sign the electronic document using a finger, stylus, or mouse. Electronic signatures (i.e., "signatures" that are digitally generated) will not be used.

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary, and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason, and because there is a prospect of direct benefit from research participation, all subjects ≥ age 18 **at the NCI only** will be offered the opportunity to fill in their wishes for research and care, and assign a legally authorized representative on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study.

Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate legally authorized representative when indicated; and/or an assessment of the capacity to appoint a legally authorized representative. For those subjects that become incapacitated and do not have pre-determined legally authorized representative (LAR) , the procedures described in NIH HRPP 403 for appointing a LAR for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

All patients must have a physically or electronically signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on study.

14.3.1 Informed consent of non-English speaking subjects (at the NCI only)

We do not anticipate consistent enrollment of any particular group of non-English speaking research participants into this study. In the event there is consistent enrollment of one non-English speaking group, the applicable IRB approved full consent document will be translated into that language in accordance with the Clinical MAS Policy M77-2 at that time.

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the PI and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OSHRP SOP 12, 45 CFR 46.117 (b) (2), 21 CFR 50.27 (b) (2)). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation (using either the long translated form or the short form). Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process for non-English speaking subjects and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

14.3.2 Patient Advocate

At the NCI only, the patients' rights representative is available to patients receiving treatment on this protocol at the NIH Clinical Center at (301) 496-2626 in Building 10 of the Clinical Research Center, Room 1-3521, on the Bethesda NIH campus. Patients will be informed that they can contact the study PI or RN at any time with questions about their medical care, and that the patients' rights representative is also available to answer non-medical questions about the study.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Description	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: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers, and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental agents ipilimumab, nivolumab, and recombinant human interleukin-15 (rhIL-15), and is being treated with a combination of two or all three of these agents. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Ipilimumab and nivolumab are human monoclonal antibodies. As monoclonal antibodies are not metabolized by cytochrome P450 (CYP) enzymes or other drug metabolizing enzymes, inhibition or induction of these enzymes by co-administered medications is not anticipated to affect the pharmacokinetics of ipilimumab or nivolumab. A drug-interaction study of ipilimumab administered alone and in combination with chemotherapy was conducted in patients with treatment-naive advanced melanoma. No clinically relevant pharmacokinetic drug-drug interactions were observed. No drug interaction studies for nivolumab have been conducted.

For all three study drugs, ipilimumab, nivolumab, and rhIL-15, there are no known interactions with other medicinal products or other forms of interactions. However, ingredients for such medicines have not been fully studied, and their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity. Furthermore, these drugs promote an enhanced immune response, and the administration of other immunostimulatory agents including but not limited to IFN-α, IFN-γ, anti-TNF-α, or IL-2 (aldesleukin) are prohibited during the study and for 10 weeks after the last dose of study drug due to potential for increased risk of autoimmune conditions. The use of systemic corticosteroids and other immunosuppressants, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide, should be avoided before study drug administration because of their potential interference with study drug pharmacodynamic activity and efficacy. However, systemic corticosteroids and other immunosuppressants can be used after starting the study drugs to treat immune-related adverse reactions.

Live vaccines and live, attenuated vaccines are prohibited for 30 days prior to study agents, during the study, and for 100 days after the last dose of study drug. Inactivated vaccines, such as the seasonal influenza vaccine, are permitted. Initiation of granulocyte colony-stimulating factors (e.g., innovator and biosimilar forms of filgrastim, sargramostim , and/or pegfilgrastim) should be discussed with the study's principle investigator. Patients should also be advised to avoid traditional herbal or homeopathic or natural medicines

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Ipilimumab, nivolumab, and rhIL-15 all have the potential to interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal, nutritional products, and dietary supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that might interact with the study drugs.

- Please be very careful! Over-the-counter drugs (including herbal, nutritional products, and dietary supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.

- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD	
You are enrolled on a clinical trial using the experimental agents ipilimumab, nivolumab, and rhIL-15. This clinical trial is sponsored by the NCI. The study drugs may interact with other drugs that you are taking. Because of this, it is very important to: ➢ Tell your doctors if you stop taking any medicines or if you start taking any new medicines. ➢ Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	➢ Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that may interact with the study drugs. ➢ Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and he/she can be contacted at _____.

APPENDIX C: MANAGEMENT ALGORITHMS FOR ADVERSE EVENTS

Management Algorithms for Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathy, Skin, Neurological, and Myocarditis Adverse Events

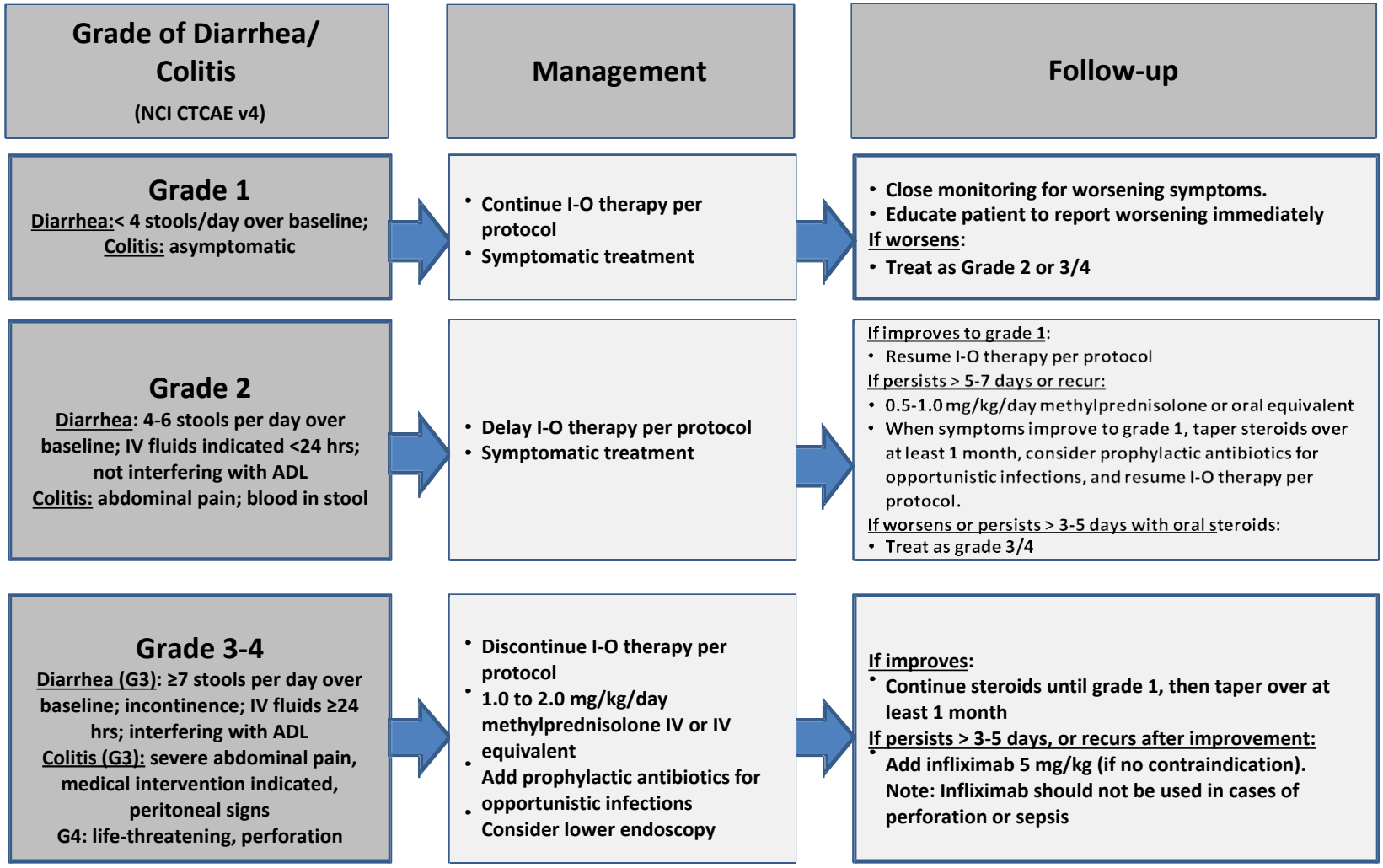
Please note that in some cases the treatment algorithms recommend steroids if symptoms do not resolve in 7 days. However, this recommendation is not meant to delay steroid treatment at any time it is clinically indicated.

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

Note: All treatment algorithms should be interpreted in the context of CTCAE v5.

GI Adverse Event Management Algorithm

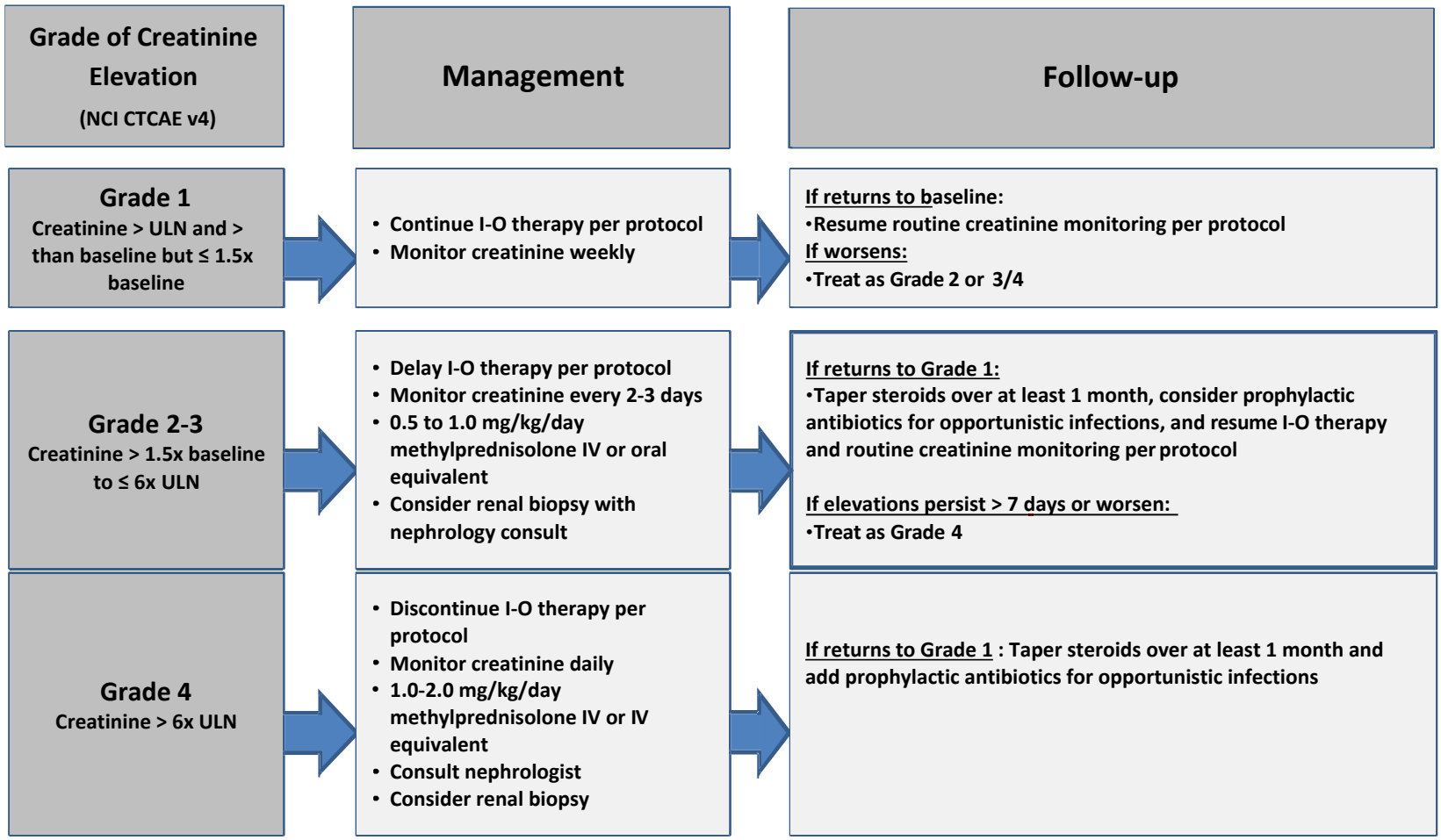
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

Renal Adverse Event Management Algorithm

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

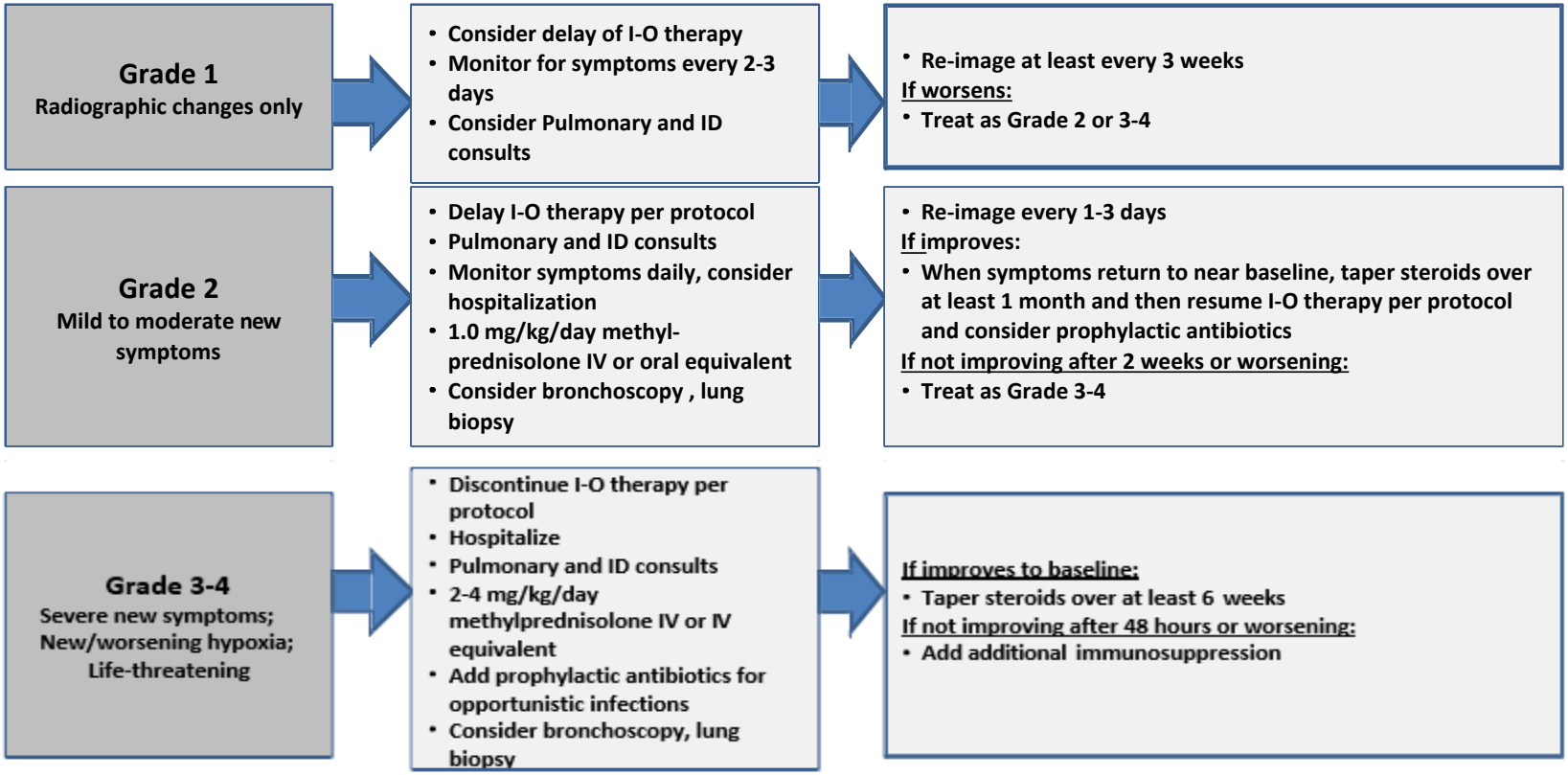


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Pulmonary Adverse Event Management Algorithm

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

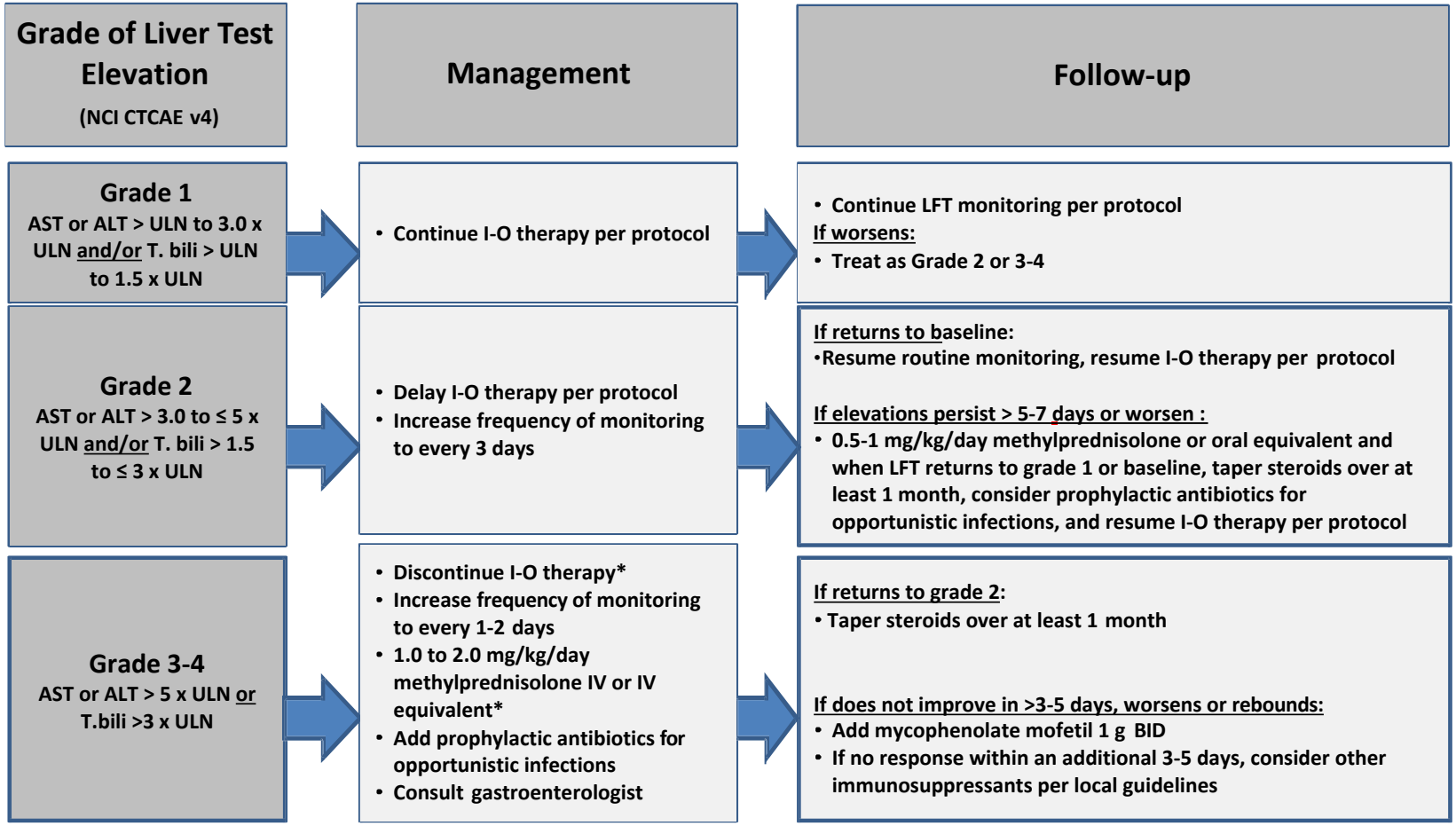
Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up



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.

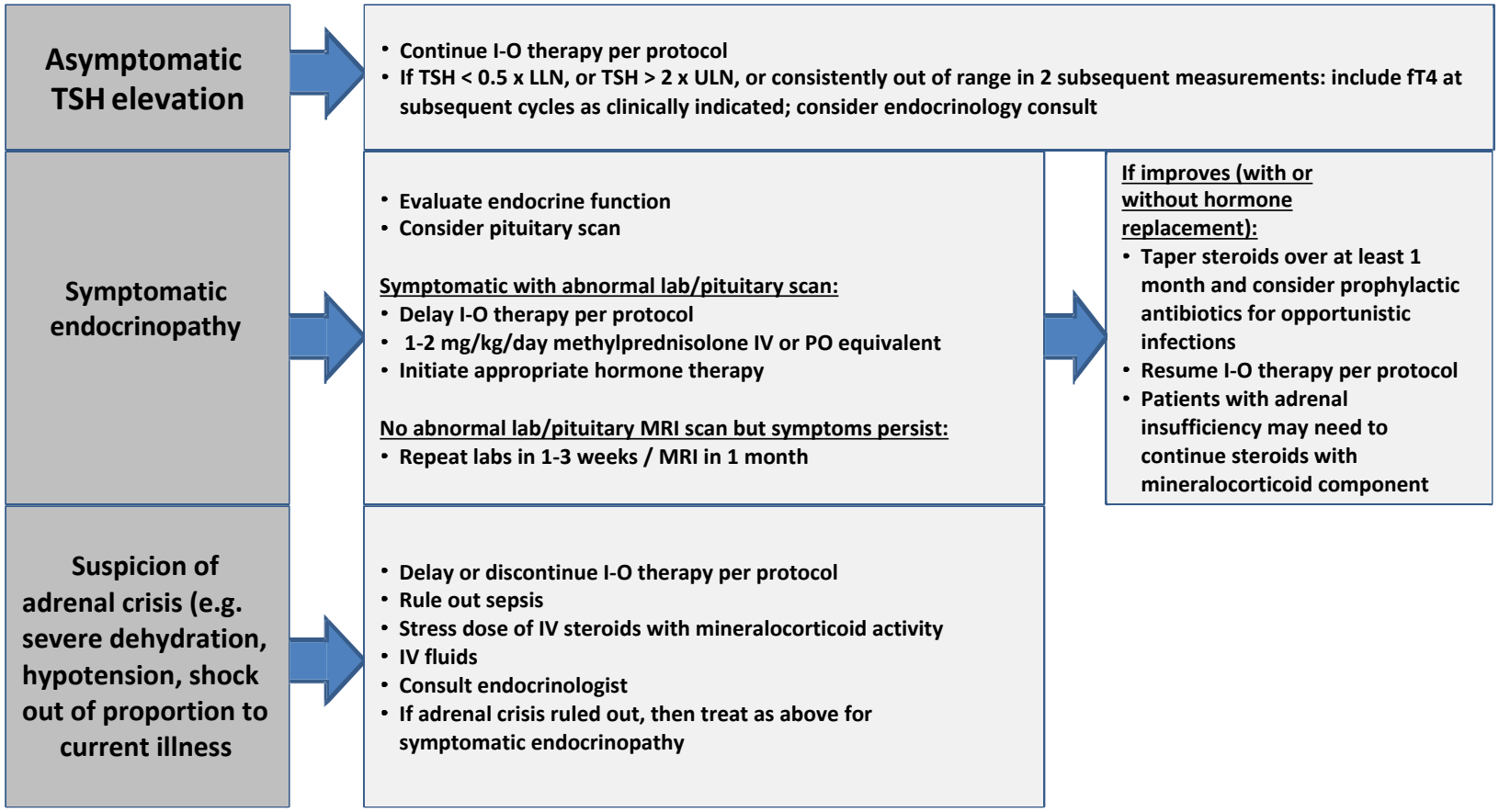


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

Endocrinopathy Adverse Event Management Algorithm

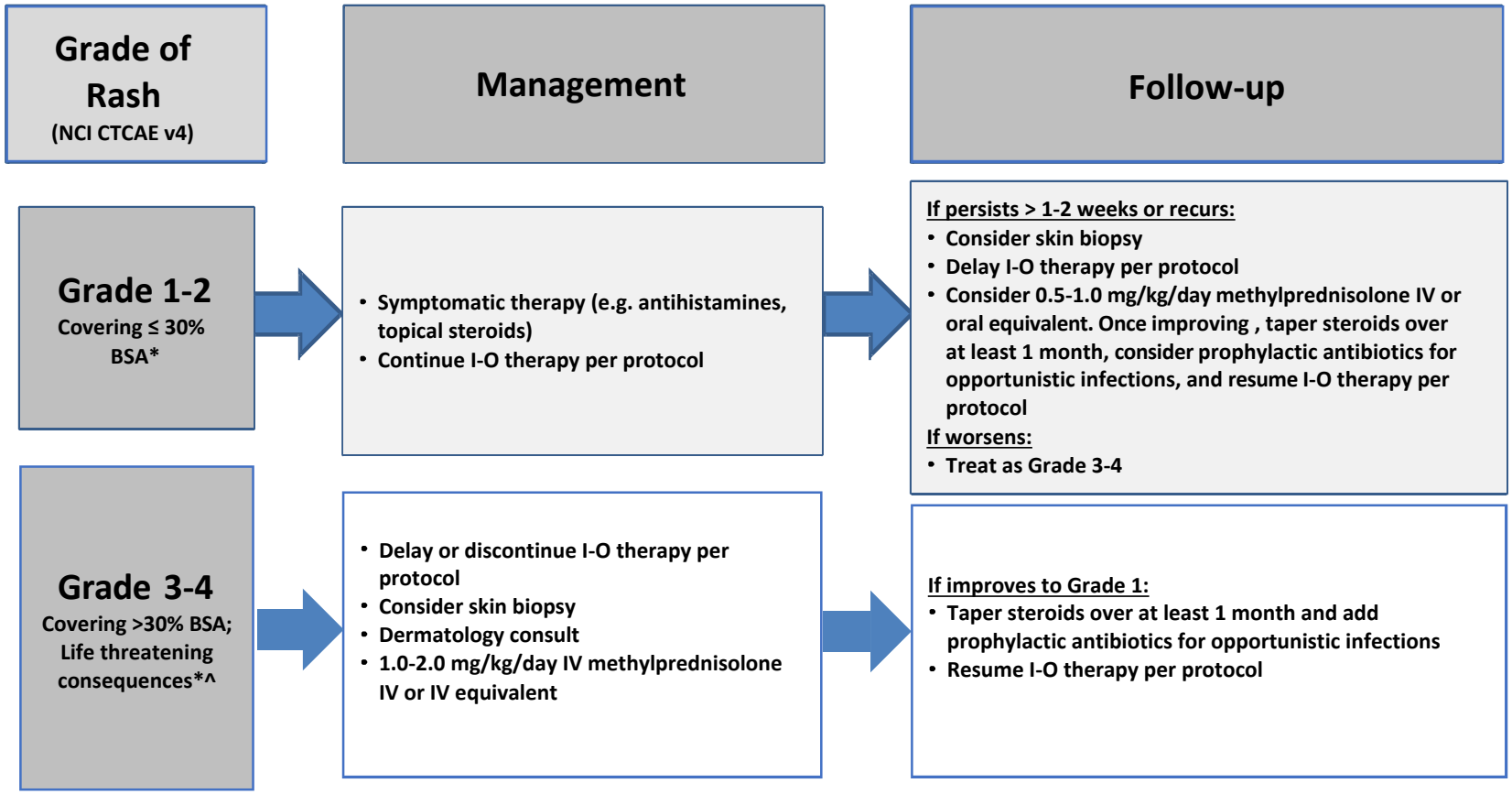
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

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



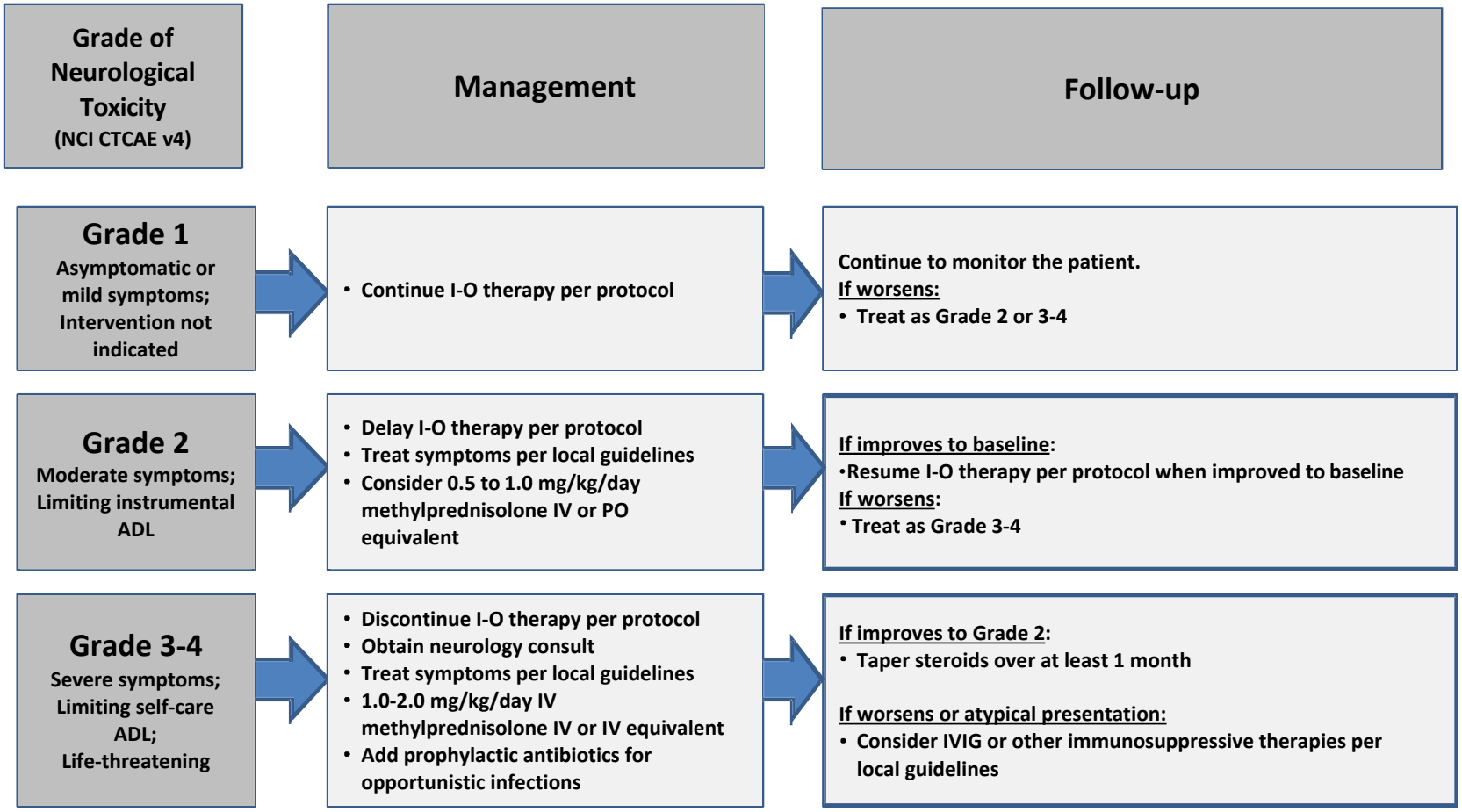
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

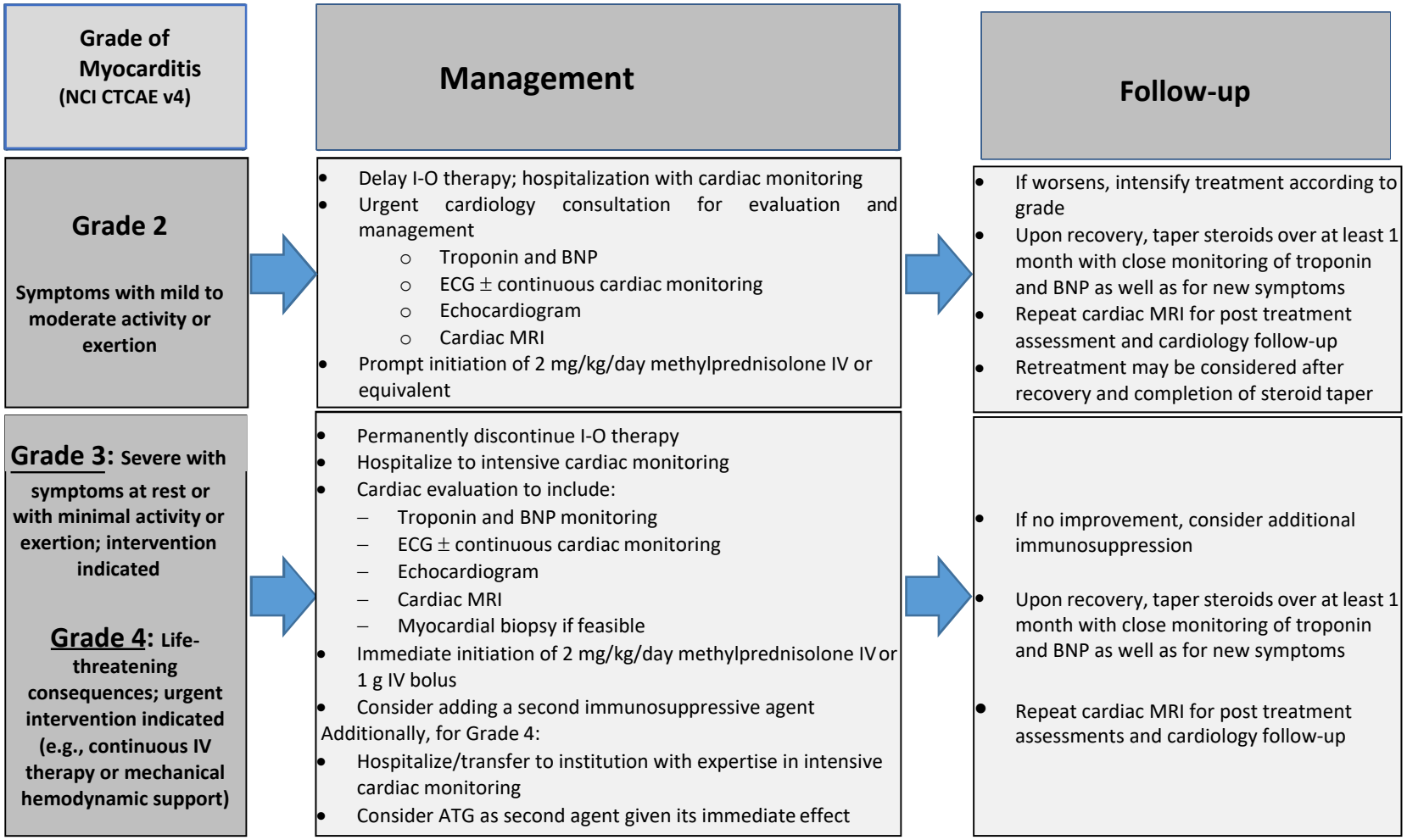
Neurological Adverse Event Management Algorithm

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



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

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging