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Protocol Official Title	Phase II Study of Nivolumab and Ipilimumab in Mucinous Colorectal and Appendiceal Tumors
Documents Included	study protocol and statistical analysis plan embedded within protocol section 9.0
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Phase II Study of Nivolumab and Ipilimumab in Mucinous Colorectal and Appendiceal Tumors

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0.0 Study Summary

Title	Phase II Study of Nivolumab and Ipilimumab in Mucinous Colorectal and Appendiceal Tumors
Short Title	Nivo/Ipi In Mucinous CRC
IRB Number	831705
Protocol Number	UPCC 28218
Phase	Phase II
Methodology	Single Arm Phase II
Study Duration	18-24 months accrual plus 6 months follow-up
Study Center(s)	Abramson Cancer Center at University of Pennsylvania
Objectives	**Primary Objective** 1. To estimate six-month progression-free survival by iRECIST **Secondary Objectives** 1. To determine overall response rate, duration of response, and progression-free survival by iRECIST and RECIST 1.1. To determine overall survival. 2. To estimate the toxicity rates by CTCAE v 5.0. **Exploratory Objectives** 1. To measure T-cell subsets and markers of T-cell function in peripheral blood as a potential biomarker of response 2. To define the immune effects in pre- and post-treatment biopsy specimens with analysis of tumor-infiltrating lymphocytes, including immune subsets, mutational load, and TCR sequencing 3. To correlate imaging response with quantitative changes in cell-free tumor DNA, extracellular vesicles, and/or other circulating tumor materials

Number of Subjects	21
Diagnosis and Main Inclusion/Exclusion Criteria	**Inclusion Criteria**: 1. Colorectal or appendiceal mucinous tumor with peritoneal-only metastatic disease 2. Microsatellite stable by PCR and/or mismatch repair proficient by immunohistochemistry 3. ECOG PS 0-1 4. Standard laboratory parameters 5. Prior therapy with a fluoropyrimidine, oxaliplatin, and irinotecan unless contraindicated or refused. Prior treatment with antiangiogenic and/or anti-EGFR antibody therapy is permitted but not required **Exclusion Criteria:** 1. Significant autoimmune disease 2. Bowel obstruction within the past 60 days 3. Use of systemic steroids other than for adrenal hormone replacement
Study Products, Dose, Route, Regimen	**Product:** Nivolumab **Dose:** 480mg **Route:** IV **Regimen:** Every 4 weeks **Product:** Ipilimumab **Dose:** 1mg/kg **Route:** IV **Regimen:** Every 8 weeks
Duration of administration	Subjects will continue on study therapy until disease progression, unacceptable toxicity, withdrawal of consent, or 24 months of therapy.

Statistical Methodology	For patients with colorectal adenocarcinoma who have progressed on standard chemotherapy, treatment with either TAS-102 or regorafenib in chemotherapy-refractory patients results in median PFS of approximately 2 months and 6-month PFS of approximately 17%. With 21 evaluable subjects, we will have 81% power to reject a 6-month PFS of 17% (H0) versus 40%, assuming exponential survivorship and using a two-sided binomial alpha = 0.10. Toxicity rates will be calculated by category with 95% confidence intervals. We will also utilize a Bayesian toxicity monitoriung plan, and estimate the posterior probability that the rate of treatment discontinuation due to toxicity exceeds 30%. ORR, PFS and DOR will be assessed by both RECIST v. 1.1 and iRECIST and calculated with 90% confidence intervals. Kaplan Meier methods will be used to estimate the survival curves for PFS and OS. Median PFS, OS, and DOR will be calculated with 90% confidence intervals. If progression is confirmed by imaging (iCPD) or clinically (iUPD without follow-up imaging), the date of initial progression on imaging (iUPD) will be used.

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1.0 Objectives

1.1 Primary Objective

To determine six-month progression-free survival by iRECIST

1.2 Secondary Objectives

1. To determine overall response rate, duration of response, and progression-free survival by iRECIST and RECIST 1.1. To determine overall survival.

2. To determine the toxicity rates by CTCAE v 5.0

1.3 Exploratory Objectives

1. To measure T-cell subsets and markers of T-cell function in peripheral blood as a potential biomarker of response

2. To define the immune effects in pre- and post-treatment biopsy specimens with analysis of tumor-infiltrating lymphocytes, including immune subsets, mutational load, and TCR sequencing

3. To correlate imaging response with quantitative changes in cell-free tumor DNA, extracellular vesicles, and/or other circulating tumor materials

2.0 Background

2.1 Mucinous Colorectal and Appendiceal Adenocarcinoma

Mucinous histology is found in about 15% of colorectal adenocarcinoma, and a higher proportion of appendiceal adenocarcinomas, and connotes a poor prognosis in the metastatic setting, with shorter progression-free and overall survival and decreased responsiveness to chemotherapy [1,2]. Despite this unfavorable phenotype, a highly select subset of patients with peritoneal-only disease can achieve long-term disease control with aggressive surgical management using cytoreductive surgery (CRS) in combination with heated intraperitoneal chemotherapy (HIPEC) [3]. ***We hypothesize that the mechanism through which HIPEC results in long-term disease control is not direct cytotoxicity but rather immune activation against mucinous tumor antigens.*** This immune activation has been demonstrated in a "HIPEC-vaccine" murine model, with subsequent immune rejection of distant tumor injections after HIPEC [4].

The mutational landscape of mucinous adenocarcinomas is poorly-described, as samples are frequently paucicellular, but increasing data shows that they are genetically distinct from non-mucinous colorectal cancers [5, 6]. More importantly, mucinous tumors have increased expression of extracellular proteins such as modified mucins that can be highly immunogenic [7]. Only recently have sequencing tools been developed to characterize the immunogenicity of these carbohydrate antigens [8], although a variety of vaccine and engineered T-cell studies have shown these mucins to be targetable by the immune system [9, 10]. In ovarian tumors, immunopeptidomic profiling found that MUC16 was by far the most immunogenic of more than 1,100 tumor-specific antigens, eliciting a T-cell response in 80% of healthy blood donors [11]. Recently, PD-1 has also been shown to play a major role in

suppressing immunity against Tn and other tumor-associated carbohydrate antigens [12]. No study has yet been conducted to evaluate checkpoint blockade in this specific subset of colorectal cancer. This will be a phase II study to determine the efficacy of combination checkpoint blockade nivolumab and ipilimumab in peritoneal-only mucinous colorectal and appendiceal adenocarcinoma.

2.2 Nivolumab Mechanism of Action

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA 4, ICOS, and BTLA. PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression also been noted to inhibit T cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes. These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 $\pm$ 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02). Clinical efficacy has been demonstrated in a variety of tumor types, and it is currently FDA approved for the treatment of melanoma, non-small cell lung cancer, Hodgkin's lymphoma, renal cell carcinoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, microsatellite instability-high tumors, and hepatocellular carcinoma.

2.3 Ipilimumab Mechanism of Action

CTLA-4, an activation-induced T-cell surface molecule, is a member of the CD28:B7 immunoglobulin superfamily that competes with CD28 for B7. CTLA-4 mediated signals are inhibitory and turn off T cell-dependent immune responses. Ipilimumab is a fully human monoclonal IgG1κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4 with B7 molecules on APCs, with subsequent blockade of the inhibitory modulation of T-cell activation promoted by the CTLA 4/B7 interaction. It is currently FDA approved for the treatment of melanoma.

2.4 Rationale for Adding Ipilimumab to Nivolumab

Preclinical and clinical evidence suggests synergy between nivolumab and ipilimumab, which target distinct mechanisms to limit T cell activation, PD-1 and CTLA-4 respectively. In vitro combinations of nivolumab plus ipilimumab increase IFN-γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone. The combination of nivolumab and ipilimumab has been shown to be more effective than either agent in monotherapy

in the treatment of a variety of tumors including melanoma, lung, renal cell carcinoma, and MSI-high colorectal cancer.

2.5 Safety of Nivolumab and Ipilimumab

The combination of nivolumab and ipilimumab has the potential for increased frequencies of AEs compared to ipilimumab monotherapy or nivolumab monotherapy. The toxicity profile of the nivolumab + ipilimumab combination has been shown to correlate with the ipilimumab dose: with increasing doses of ipilimumab, there has been an increase in frequency of AEs and, potentially, the severity of these events; however, no novel toxicities have been demonstrated versus either agent alone. In the current regimen for this protocol, the dose of ipilimumab will be cumulatively lower than the approved dose level for the combination for the treatment of advanced and metastatic melanoma. The toxicity profile with lower doses of ipilimumab has been established to be very similar to that of nivolumab monotherapy as detailed below in section 2.6.

The most common (reported at > 10% incidence) treatment related AEs with the combination are fatigue, rash, pruritus, diarrhea, lipase increased, pyrexia, ALT increase, AST increased, amylase increased and vitiligo. These classes of AEs are expected for the combination of nivolumab and ipilimumab based on the known AE profile of each drug alone. In addition, many of the Grade 3-4 AEs are laboratory in nature (ie, LFTs, lipase, amylase), occur without clinical sequelae, and are been manageable and reversible following intervention dose delays or with systemic steroid treatment. However, immune AEs have the potential to be fatal if not detected early and managed per the established algorithm, and fatal AEs have been reported for both ipilimumab and nivolumab monotherapy. Adverse drug reactions with fatal outcome in clinical trial participants treated with nivolumab monotherapy and nivolumab and ipilimumab combination therapy are listed in the current version of the nivolumab investigator brochure (IB).

A pattern of immune-related AEs has been defined, for which management algorithms have been developed; these are provided in Appendix B. Most high-grade events are manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in these algorithms.

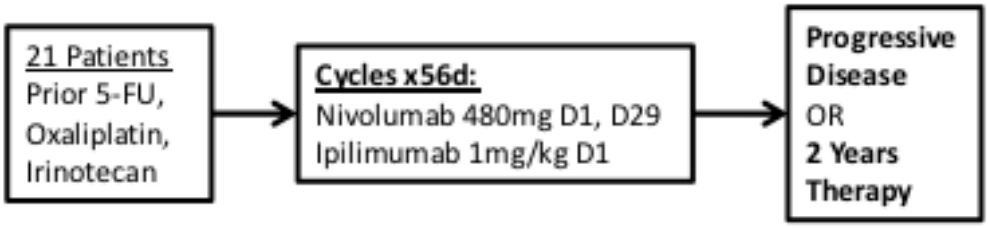
2.6 Rationale for Dose Selections

The nivolumab doses of 480 mg Q4W was selected for this study based on clinical pharmacokinetic data and modeling showing similar drug exposure and no change in safety compared to dosing every 2 weeks using either weight-based (3mg/kg) or flat dose (240mg) regimens [13]. In the CA209012 study in non-small cell lung cancer, ipilimumab 1 mg/kg using Q6W and Q12W schedules were assessed and were found to be safe in combination with nivolumab 3 mg/kg Q2W. Both the Q6W and Q12W arms were associated with improved and manageable tolerability compared to the arms with more frequent ipilimumab dosing (Q3W). Both arms also had encouraging efficacy in all participants and enhanced benefit in participants with PD-L1 expression, with Q6W arm having numerically higher median PFS compared to the Q12W arm. There were some imbalances observed between the Q6W and Q12W arms, as follows. With both schedules showing a similar safety and efficacy profile, a Q8W schedule was chosen to align with nivolumab dosing and maintain expected safety and efficacy.

3.0 Study Design

This is a single-arm phase II study of twenty-one subjects with mucinous adenocarcinoma of the colon, rectum, or appendix with prior systemic therapy with a fluoropyrimidine, oxaliplatin, and irinotecan. Treatment will consist

of nivolumab 480mg every 4 weeks and ipilimumab 1mg/kg every 8 weeks until disease progression, unacceptable toxicity, or 2 years of therapy. Imaging assessments will be conducted every 8 weeks (+/-2 weeks). If progression is noted on imaging in the setting of clinical stability, subjects may remain on study and have confirmatory imaging in 4-8 weeks per iRECIST criteria.



4.0 Study Population

4.1 Inclusion Criteria

1. Subjects must have signed and dated an IRB-approved written informed consent form prior to the performance of any protocol-related procedures that are not part of standard care.
2. Colorectal or appendiceal mucinous adenocarcinoma with peritoneal-only metastatic disease. It is recognized that in some patients, peritoneal disease will predominate without distinction of the site of origin, and such patients will be eligible.
3. Microsatellite stable by PCR and/or mismatch repair proficient by immunohistochemistry
4. ECOG performance status of 0 or 1
5. Prior therapy with a fluoropyrimidine, oxaliplatin, and irinotecan unless contraindicated or refused. Prior treatment with antiangiogenic and/or anti-EGFR antibody therapy is permitted but not required
6. Measurable disease by RECIST v. 1.1
7. Laboratory parameters (within 14 days prior to the start of treatment):
    a. Absolute neutrophil count $\geq$ 1500/μL
    b. Platelets $\geq$ 100,000/μL
    c. Hemoglobin $\geq$ 9.0 g/dL
    d. PT/INR or PTT $\leq$ 1.5xULN
    e. Creatinine $\leq$ 1.5xULN OR creatinine clearance $\geq$ 50 mL/min by Cockcroft-Gault formula
    f. Total bilirubin $\leq$ 1.5xULN
        i. Subjects with Gilbert's Syndrome must have a total bilirubin level of $\leq$ 3.0xULN
    g. Albumin $\geq$ 3.0 g/dL
    h. AST and/or ALT: $\leq$ 3.0×ULN
8. Subjects with HIV are permitted provided they meet the following criteria:
    a. CD4+ cell count $\geq$ 250 cells/mm^3
    b. No history of AIDS-defining conditions other than low CD4+ count
    c. If subject is on antiretroviral therapy, there must not be expected significant drug-drug interactions with study treatment

4.2 Exclusion Criteria

1. Bowel obstruction within the past 60 days

2. Subjects who are currently pregnant, planning to become pregnant, or breast-feeding.
    a. *Females participants of child-bearing potential are required to use an effective contraception method (see Appendix A) or abstain from intercourse during treatment and for at least 5 months following the last dose*
    b. *Males participants with partners of child-bearing potential are required to use an effective contraception method (see Appendix A) or abstain from intercourse during treatment and for at least 7 months following the last dose*
3. Subjects who, in the opinion of the physician, would not be clinically appropriate for receipt of the therapy regimen associated with participation
4. Subjects with contraindications to immune checkpoint therapy, as follows:
    a. Interstitial lung disease that is symptomatic or may interfere with the detection and management of suspected drug-related pulmonary toxicity
    b. Prior organ allograft or allogeneic bone marrow transplantation
    c. Pre-existing thyroid abnormality with thyroid function that cannot be maintained in the normal range with medication
    d. Active autoimmune disease, except for vitiligo, type 1 diabetes mellitus, asthma, atopic dermatitis, or endocrinopathies manageable by hormone replacement; other autoimmune conditions may be allowable at the discretion of the principal investigator
    e. Condition requiring systemic treatment with corticosteroids
        - Systemic steroids at physiologic doses (equivalent to dose of oral prednisone 10 mg) are permitted.
        - Intranasal, inhaled, topical, intra-articular, and ocular corticosteroids with minimal systemic absorption are permitted.
5. Established non-peritoneal metastatic disease, including but not limited to metastases to the liver, lung, brain, extra-abdominal lymph nodes, and bone
6. A second primary malignancy that, in the judgment of the investigator, may affect interpretation of results
7. Prior treatment with an anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibody
8. Toxicities attributed to prior anti-cancer therapy other than alopecia, fatigue, and peripheral neuropathy must have resolved to Grade 1 or baseline before administration of study drug. In addition, a washout period will be required for prior therapies as specified:
    a. No chemotherapy within 14 days prior to first dose
    b. No investigational product(s) (IPs) and/or biologic therapy within 28 days or 5 half-lives, whichever is longer, prior to first dose
    c. No major surgery within 28 days prior to first dose. Any surgery-related AE(s) must have resolved at least 14 days prior to first dose.
    d. No radiation therapy with curative intent within 28 days prior to first dose. Prior focal palliative radiotherapy must have been completed at least 14 days prior to first dose.
9. Active hepatitis B or hepatitis C, defined as the following:
    a. Hepatitis B surface antigen positive or HBV DNA PCR >100 IU/mL
    b. Hepatitis C antibody positive unless HCV RNA PCR is negative (i.e. undetectable viral load)
10. Prisoners or participants who are involuntarily incarcerated. (Note: under specific circumstances a person who has been imprisoned may be included as a participant. Strict conditions apply and BMS approval is required.)
11. Participants who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

4.3 Withdrawal, Removal, Evaluability and Replacement of Subjects

Subjects may withdraw from the study at any time at their own request in which case investigators will seek permission from such subjects for investigators to continue to contact them every 6 months for follow-up; however, subjects may choose to withdraw completely from all procedures and follow-up. Subjects may also be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document the subject outcome, if possible. The Investigator should inquire about the reason for withdrawal, and request the subject to return for a final visit and follow-up regarding any unresolved AEs. If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

An individual subject will not receive any further study drug if any of the following occur in the subject in question:

- Progressive Disease by iRECIST (See Appendix C)
- Complete Withdrawal of consent from the study (no further data collection permitted)
- Withdrawal of consent from further treatment with study drug (data collection as per study schedule permitted)
- Lost to Follow up
- An AE that, in the opinion of the Investigator or the Sponsor, contraindicates further dosing including but not limited to hypersensitivity to any of the therapeutic agents
- Pregnancy or intent to become pregnant
- Subject Non-Compliance that, in the opinion of the investigator warrants withdrawal (e.g., refusal to adhere to the scheduled visits)
- Initiation of another anti-cancer therapy (excluding surgery or palliative radiotherapy), including another investigational agent

4.3.1 Evaluability and Replacement of subjects

Subjects will be evaluable for toxicity if they receive at least one dose of either nivolumab or ipilimumab. Subjects will be evaluable for efficacy if they receive at least one dose of nivolumab and one dose of ipilimumab and undergo repeat imaging at least 4 weeks and no more than 12 weeks after initiating therapy on study. Subjects who do not meet the criteria for evaluability for efficacy will be replaced.

5.0 Treatment Plan

Treatment will consist of nivolumab 480mg every 4 weeks and ipilimumab 1mg/kg every 8 weeks. Imaging assessments will be conducted every 8 weeks (+/-2 weeks) for the first 24 weeks then every 8-12 weeks (+/-2 weeks). If progression is noted on imaging in the setting of clinical stability, subjects may remain on study and have confirmatory imaging in 4-8 weeks per iRECIST criteria (see Appendix C)

Table 1: Treatment Plan

Agent	Dose	Route	Frequency (within a 56-day cycle)
Nivolumab	480mg	IV infusion per institutional guidelines and the Package Insert	Days 1, 29
Ipilimumab	1mg/kg	IV infusion per institutional guidelines and the Package Insert	Day 1

5.1 Duration of Treatment

Subjects will continue on therapy until disease progression, unacceptable toxicity, withdrawal of consent, or two years of therapy. Subjects may remain on either ipilimumab or nivolumab monotherapy if the other agent is discontinued such as for toxicity.

6.0 Dosing Delays/Dose Modifications

The potential immune toxicities of nivolumab and ipilimumab are numerous, and no set of guidelines can account for all possible scenarios. Ultimately, subjects who experience toxicity related to nivolumab and/or ipilimumab will be managed according to standard clinical practice at the discretion of the treatment clinician, including the administration of corticosteroids. The toxicities for nivolumab and ipilimumab overlap considerably and it is uncommon that a toxicity be clearly attributed to only one of the agents.

Treatment algorithms for immune-related adverse events are provided in Appendix B for guidance. No dose modifications for nivolumab or ipilimumab are allowed. ***Specific dose delays and the use of corticosteroids for toxicity is ultimately at the discretion of the treating physician***.

At the end of the study period, Bristol-Myers Squibb Company will not continue to supply study drug to subjects/investigators unless the Sponsor chooses to extend their study. The investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the investigator to treat the condition under study.

7.0 Study Procedures

Study procedures are further detailed in section 17.0 (Schedule of Events).

7.1 Tumor Analysis and Correlative Studies

7.1.1 Tumor Biopsy

Pre-treatment tissue biopsy is mandatory. Archival material cannot be substituted for the pre-treatment biopsy. Subjects in whom pre-treatment biopsy cannot be safely performed require approval of the Principal Investigator to enroll. On-treatment biopsies will be performed on cycle 1 between days 10-14 where safe and feasible, and we expect that this will be in the majority of patients. Testing of these samples may include studies of infiltrating T-

cells such as subtyping, functional assays and receptor sequencing, whole exome or other genomic sequencing of the tumor, immunohistochemistry, and/or other assays that may be developed over the course of this study. Optional biopsies will be requested if a patient undergoes surgery that would permit tumor sampling such as laparoscopy and at disease progression. Procedures for tumor biopsy processing is described in detail in the laboratory manual.

7.1.2 Research Blood Sampling

Sixty mL total of blood in EDTA tubes for circulating tumor materials (circulating tumor cells, extracellular vesicles, and/or cell-free DNA) and peripheral blood mononuclear cells (PBMCs) will be collected at baseline prior to cycle 1 day 1 treatment on the same day as baseline biopsy (or within 3 days if not possible to perform same day), on cycle 1 between days 10-14 (same day as research biopsy if repeat biopsy performed), cycle 1 day 29, on day 1 of each subsequent cycle prior to treatment, and at the end of treatment visit.

A one-time 5mL sample in an EDTA tube will be drawn during screening, or, if not previously obtained, at a later treatment visit for storage of PBMCs for future germline sequencing with the Nathanson lab.

Procedures for research laboratory samples and processing is described in detail in the laboratory manual.

7.2 Assessment of Laboratory Measures and Disease Progression

7.2.1 Laboratory Safety Monitoring

CBC with differential will be assessed at screening, on days 1 and 29 of each treatment cycle, and at the end of treatment visit. Serum pregnancy will be assessed for women of childbearing potential at screening and every 4 weeks. Non-childbearing potential is defined in Appendix A. Serum chemistry labs will be assessed at screening, on days 1 and 29 of each treatment, and at the end of treatment visit. Serum TSH will be assessed at screening, on day 1 of cycle 2 and all subsequent cycles, and at the end of treatment visit.

For all laboratory measures, a window of +/- 3 days is acceptable.

7.2.2 Imaging Assessments

CT/MRI will be performed for disease assessment at screening (within 21 days of first doses of study drugs) and every 8 weeks (+/- 2 weeks). If progression is noted on imaging in the setting of clinical stability, subjects may remain on study and have confirmatory imaging in 4-8 weeks per iRECIST criteria. PET-CT is an acceptable substitute for CT/MRI if determined to be the standard of care by the treating physician.

7.3 Duration of Follow-Up

For this protocol, all subjects, including those who discontinue protocol therapy early, will be followed through review of the medical record for recurrence and survival for up to 3 years from their end of study visit (every 6 months for the first year, then annually for the second two years).

8.0 Study Treatment Details

8.1 Nivolumab

8.1.1 Other Names

Opdivo

8.1.2 Classification

Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that targets programmed cell death-1 (PD-1).

8.1.3 Mechanism of Action

Nivolumab selectively inhibits PD-1 activity by binding to the PD-1 receptor to block the ligands PD-L1 and PD-L2 from binding. The negative PD-1 receptor signaling that regulates T-cell activation and proliferation is therefore disrupted. This releases PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response.

8.1.4 Storage and Stability

The product does not contain a preservative. After preparation, store the nivolumab infusion either at room temperature for no more than 8 hours from the time of preparation (this includes room temperature storage of the infusion in the IV container and time for administration of the infusion) or under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation. Do not freeze.

8.1.5 Dose Specifics

480 mg IV over 30 minutes every 4 weeks

8.1.6 Preparation

Visually inspect drug product solution for particulate matter and discoloration prior to administration. Nivolumab [Opdivo] is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

Withdraw the required volume of nivolumab [Opdivo] and transfer into an intravenous container. Dilute nivolumab [Opdivo] with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. Mix diluted solution by gentle inversion. Do not shake. Discard partially used vials or empty vials of OPDIVO.

8.1.7 Administration

Administer the infusion over 30 minutes or per institutional guidelines through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). Do not coadminister other drugs through the same intravenous line. Flush the intravenous line at end of infusion.

8.1.8 Availability

Nivolumab [Opdivo] is commercially available as a 40 mg/4 mL (10 mg/mL) and 100 mg/10 mL (10 mg/mL) solution in a single-dose vial. Only 100mg vials will be provided for this study.

8.1.9 Side Effects

- Cardiovascular: Edema, peripheral edema, ventricular arrhythmia, pulmonary embolism, vasculitis
- Central nervous system: Fatigue, headache, peripheral neuropathy, peripheral sensory neuropathy, dizziness, peroneal nerve palsy, motor dysfunction, migraine, myasthenia, encephalitis, facial paralysis, Guillain-Barré syndrome, neuropathy
- Dermatologic: Skin rash, pruritis, vitiligo, exfoliative dermatitis, erythema, erythema multiforme, psoriasis, urticarial, palmar-plantar erythrodysesthesia
- Endocrine and metabolic: Hyponatremia, increased serum triglycerides, hyperkalemia, increased thyroid stimulating hormone level, hypocalcemia, increased serum cholesterol, hypercalcemia, hypothyroidism, hypomagnesemia, hypokalemia, hyperglycemia, hyperthyroidism, adrenocortical insufficiency, diabetes mellitus, diabetic ketoacidosis, weight loss, hypophysitis, pituitary insufficiency
- Gastrointestinal: Diarrhea, colitis, decreased appetite, increased serum lipase, nausea, constipation, vomiting, increased serum amylase, abdominal pain, duodenitis, gastritis, pancreatitis
- Hematologic: Lymphocytopenia, anemia, neutropenia, thrombocytopenia
- Hepatic: Increased serum AST, increased serum ALT, increased serum alkaline phosphatase, increased serum bilirubin, hepatitis, hepatic failure
- Immunologic: Antibody development
- Neuromuscular and skeletal: Weakness, musculoskeletal pain, back pain, arthralgia, spondyloarthropathy, limb pain, polymyalgia rheumatica
- Renal: Increased serum creatinine, renal disease, nephritis, renal insufficiency
- Respiratory: Upper respiratory tract infection, productive cough, cough, dyspnea, dyspnea on exertion, bronchopneumonia, pneumonia, pleural effusion, pneumonitis, respiratory failure, pneumonia due to Pneumocystis jiroveci
- Ophthalmic: Iridocyclitis, iritis
- Miscellaneous: Fever, infusion related reactions, hypersensitivity reaction, sarcoidosis

8.2 Ipilimumab

8.2.1 Other Names

Yervoy

8.2.2 Classification

Ipilimumab is a recombinant human IgG1 immunoglobulin monoclonal antibody that binds to the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4)

8.2.3 Mechanism of Action

CTLA-4 is a down-regulator of T-cell activation pathways. Blocking CTLA-4 allows for enhanced T-cell activation and proliferation. In melanoma, ipilimumab may indirectly mediate T-cell immune responses against tumors. Combining ipilimumab (anti-CTLA-4) with nivolumab (anti-PD-1) results in enhanced T-cell function that is greater than that of either antibody alone, resulting in improved antitumor responses in metastatic melanoma.

8.2.4 Storage and Stability

The product does not contain a preservative. Store ipilimumab under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect vials from light.

8.2.5 Dose Specifics

1mg/kg IV every 8 weeks

8.2.6 Preparation

Visually inspect drug product solution for particulate matter and discoloration prior to administration. Solution may have a pale yellow color. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

Allow the vials to stand at room temperature for approximately 5 minutes prior to preparation of infusion. Withdraw the required volume of ipilimumab [Yervoy] and transfer into an intravenous bag. Dilute ipilimimab [Yervoy] with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion. Store the diluted solution for no more than 24 hours under refrigeration (2°C to 8°C, 36°F to 46°F) or at room temperature. Do not shake. Discard partially used vials or empty vials of ipilimumab [Yervpy].

8.2.7 Administration

Administer the infusion over 30 minutes or per institutional guidelines through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter. Do not coadminister other drugs through the same intravenous line. Flush the intravenous line at end of infusion.

8.2.8 Availability

Ipilimumab [Yervoy] is commercially available as a 50 mg/10 mL (5 mg/mL) and 200 mg/40 mL (5 mg/mL) solution in a single-dose vial. Only 200mg vials will be provided for this study

8.2.9 Side Effects

- Cardiovascular: Edema, peripheral edema, ventricular arrhythmia, pulmonary embolism, vasculitis
- Central nervous system: Fatigue, headache, peripheral neuropathy, peripheral sensory neuropathy, dizziness, peroneal nerve palsy, motor dysfunction, migraine, myasthenia, encephalitis, facial paralysis, Guillain-Barré syndrome, neuropathy
- Dermatologic: Skin rash, pruritis, vitiligo, exfoliative dermatitis, erythema, erythema multiforme, psoriasis, urticarial, palmar-plantar erythrodysesthesia
- Endocrine and metabolic: Hyponatremia, increased serum triglycerides, hyperkalemia, increased thyroid stimulating hormone level, hypocalcemia, increased serum cholesterol, hypercalcemia, hypothyroidism, hypomagnesemia, hypokalemia, hyperglycemia, hyperthyroidism, adrenocortical insufficiency, diabetes mellitus, diabetic ketoacidosis, weight loss, hypophysitis, pituitary insufficiency
- Gastrointestinal: Diarrhea, colitis, decreased appetite, increased serum lipase, nausea, constipation, vomiting, increased serum amylase, abdominal pain, duodenitis, gastritis, pancreatitis

- Hematologic: Lymphocytopenia, anemia, neutropenia, thrombocytopenia
- Hepatic: Increased serum AST, increased serum ALT, increased serum alkaline phosphatase, increased serum bilirubin, hepatitis, hepatic failure
- Immunologic: Antibody development
- Neuromuscular and skeletal: Weakness, musculoskeletal pain, back pain, arthralgia, spondyloarthropathy, limb pain, polymyalgia rheumatica
- Renal: Increased serum creatinine, renal disease, nephritis, renal insufficiency
- Respiratory: Upper respiratory tract infection, productive cough, cough, dyspnea, dyspnea on exertion, bronchopneumonia, pneumonia, pleural effusion, pneumonitis, respiratory failure, pneumonia due to Pneumocystis jiroveci
- Ophthalmic: Iridocyclitis, iritis
- Miscellaneous: Fever, infusion related reactions, hypersensitivity reaction, sarcoidosis

9.0 Statistical Plan

9.1 Endpoints

9.1.1 Primary Endpoint: Progression-Free Survival at 6 Months

Progression-free survival at 6 months (PFS6) is defined as the proportion of patients free from disease progression by iRECIST crieteria (see Appendix D) or death at the time of week 24 restaging imaging (within acceptable 2 week window). Subjects who withdraw from the study prior to week 24 imaging will be considered to have progressed unless imaging is obtained at or after 24 weeks (within acceptable 2-week window), no progression is observed, and the subject has not initiated any other anti-cancer therapy prior to 6-month imaging. The final efficacy analysis will not be performed until all subjects have experienced progression or death, initiated additional anti-cancer therapy prior to 6 months from the start of study therapy (which will be considered progression), been lost to follow-up, or undergone at least six months of follow-up.

9.1.2 Secondary Endpoints

9.1.2.1 Progression-Free Survival

Progression-free survival is defined as the duration of time from start of treatment to time of progression, death, or last patient contact when progression-free. PFS will be calculated using both RECIST v. 1.1 (Appendix C) and iRECIST (Appendix D). For patients who are progression-free, PFS will be censored at the most recent date which documents progression-free status (i.e., scan date or clinical visit date).

9.1.2.2 Overall Survival

Overall survival (OS) is defined as the duration of time from start of treatment to death due to any cause or last patient contact alive. Public records (e.g. obituaries) may be used to ascertain dates of death for subjects where such data is not available in the medical record unless the subject withdraws consent for follow-up. For subjects who enroll in hospice care in whom the specific date of death cannot be determined, date of death will be recorded as the date the patient entered hospice. In subjects who are alive or lost to follow-up, OS will be censored at last date of contact alive.

9.1.2.3 Overall Response Rate

The overall response rate is determined by iRECIST (Appendix D) and RECIST v1.1 (Appendix C). Criteria definitions of CR and PR and is defined as the percentage of individuals on study attaining a CR or PR.

9.1.2.4 Duration of Response

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

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

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

9.1.2.5 Safety Analysis

Safety analysis will be performed on the safety – evaluable population, defined as all enrolled subjects who received at least one dose of study treatment. Summaries of AEs, SAEs, deaths, changes in laboratory test results, vital signs and exposure to study drug will be presented. Drug exposure will be summarized to include treatment duration, number of doses and dose intensity. Laboratory data with values outside reference ranges will be summarized by NCI-CTCAE v 5.0 grades.

We will conduct a Bayesian toxicity monitoring plan every 3 patients with a target discontinuation rate due to toxicity of 30%. We assume a *Beta(1,2)* prior, equivalent to one discontinutation of treatment (both ipilimumab and nivolumab) due to toxicity in 3 treated patients. Early study termination for toxicity will be considered based on a posterior probability that the rate of treatment discontinuation due to toxicity exceeds 30%. Early termination will be considered if treatment discontinuation due to toxicity occurs in 2 of 3 patients (0.84 posterior probability), 3 of 6 patients (0.81), 4 of 9 patients (0.79), 5 of 12 patients (0.78), or 6 of 15 patients (0.78).

9.2 Sample Size Determination and Methods

For patients with colorectal adenocarcinoma who have progressed on standard chemotherapy, treatment with either TAS-102 or regorafenib in chemotherapy-refractory patients results in median PFS of approximately 2 months and 6-month PFS of approximately 17%. In phase III trials of nivolumab in chemotherapy-refractory solid tumors (e.g. non-small cell lung cancer [15], urothelial carcinoma [16]) six-month PFS of 30-40% have correlated with an overall survival benefit, as many patients without progression by 6 months will have durable benefit. We therefore would find a 6-month progression-free-survival of 40% to be highly promising in this study population. With 21 evaluable subjects, we will have 81% power to reject a 6-month PFS of 17% (H0) versus 40%, assuming exponential survivorship and using a two sided binomial test with alpha = 0.10.

The primary endpoint of 6-month PFS will be assessed using iRECIST criteria to account for potential pseudoprogression (See Appendix D). If progression is confirmed by imaging (iCPD) or clinically (iUPD without

follow-up imaging), the date of initial progression on imaging (iUPD) will be used. ORR, PFS and DOR will be assessed by both RECIST v. 1.1 and iRECIST and calculated with 90% confidence intervals. PFS at 6 months will be estimated as a crude rate with a 90% CI. Kaplan Meier methods will be used to estimate the survival curves for PFS and OS. ORR will be summarized as a binomial proportion. Median PFS, OS, and DOR will be calculated with 90% confidence intervals.

Analysis of T-cell function, TCR sequencing, and circulating tumor materials will be an exploratory and hypothesis-generating analysis of potential biomarkers. Immune assays in tissue and blood will seek to demonstrate immune activation, generate potential biomarkers to predict response and identify responding T-cell populations and their respective target(s). Circulating tumor measurements will seek to improve upon measurability of response and generate potential genomic biomarkers of response. Logistic regression will be used to evaluate any association of response status and PFS6 with marker, and markers will be summarized by response status and PFS6. Cox regression will be used to test any association between a time-to-event outcome (PFS, OS) and marker expression. Other analyses will be descriptive.

10.0 Safety and Adverse Events

10.1 Definitions

10.1.1 Unanticipated Problems Involving Risk to Subjects or others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

10.1.2 Adverse Event

An **adverse event** (AE) is any unfavorable symptom, sign, illness or experience that occurs at any dose and develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

10.1.3 Adverse Events of Special Interest

AESIs (serious or non-serious) are defined as AEs of scientific and medical concern specific to the investigational product or program, for which ongoing monitoring and rapid communication by the Principal Investigator to drug manufacturer can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the Principal Investigator to other parties (eg, regulators) might also be warranted.

Details on currently agreed list of AESIs for investigational agents can be found in the current IB. These AESIs are to be reported to drug manufacturer expeditiously within 1 business day of knowledge of the event, during the study through 100 days after receiving the last dose of study treatment, according to the procedures below

10.1.4 Serious Adverse Event

Adverse events are classified as serious or non-serious. A serious adverse event is any AE, that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event
- suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE
- all occurrences of potential drug-induced liver injury (DILI), meeting the defined criteria below, must be reported as SAEs

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

All Serious Adverse Events or pregnancies that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug, within 1 business day of becoming aware of the event. A Medwatch form will be used to report SAEs to BMS.

All SAEs should be faxed or e-mailed to BMS at:
Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
SAE Email Address: Worldwide.Safety@BMS.com

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events.**

Events or Outcomes Not Qualifying as Serious Adverse Events
The following are not considered SAEs and therefore do not need to be reported as such:

- Pre-planned or elective hospitalization including social and/ or convenience situations (eg, respite care)
- Hospital visits of less than 24 hours duration (eg, patient presents to the emergency room, but is not admitted to a ward)
- Overdose of study drugs or concomitant medication unless the event meets SAE criteria (eg, hospitalization). However, the event should still be captured as a nonserious AE
- Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. If the event has a fatal outcome within the safety reporting period, then the event of Progression of Disease must be recorded as an AE and as a SAE with CTC Grade 5 (fatal outcome) indicated.

10.2 Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 100 days following the last administration of study treatment.

10.3 Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an AE if the frequency, intensity, or the character of the condition worsens during the study period

10.4 General Physical Examination Finding
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an AE must also be recorded and documented as an AE.

10.5 Post-Study Adverse Event
All unresolved AEs should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the Principal Investigator of any death or AE occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The Principal Investigator should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

10.6 Abnormal Laboratory Values

An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- an action on the study drug is made as a result of the abnormality
- intervention for management of the abnormality is required
- at the discretion of the investigator should the abnormality be deemed clinically significant

10.7 Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an AE if the condition meets the criteria for an AE.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an AE in the following circumstances:
Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an AE if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

10.8 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis. All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

10.9 Stopping Rule for Adverse Events

Bayesian toxicity monitoring with a target treatment discontinuation rate (both ipilimumab and nivolumab discontinued) of 30% will be implemented as outlined in the statistical plan. If the posterior probability that the treatment discontinuation rate due to toxicity exceeds 30%, the Abramson Cancer Center Data Safety Monitoring Committee will be notified and may decide to terminate the study for toxicity.

10.10 Reporting of Adverse Events

Investigators must conform to the AE reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- Related to study participation,
- Unexpected, and
- Serious or involve risks to subjects or others

If the AE meets institutional reporting citeria, the event will be reported to their IRB. An event may qualify for expedited reporting to regulatory authorities if it is a suspected unexpected serious adverse reaction (SUSAR) in line with relevant regulations.

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study center
- Subject number
- Investigational study product
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment.

10.10.1 Investigator Reporting: Notifying Drug Manufacturer

All SAEs, AESIs, and pregnancies, regardless of relationship to study drug, must be reported to the drug manufacturer during the study through 100 days after receiving the last dose of study treatment, according to the procedures below. After the specified window, only SAEs considered to be treatment related and all AESIs, regardless of treatment relationship, should be reported. It is important that the investigator provide an assessment of relationship of the SAE or AESI to study treatment at the time of the initial report.

10.10.2 Investigator Reporting: Notifying the Penn IRB

This section describes the requirements for safety reporting by investigators who are Penn faculty, affiliated with a Penn research site, or otherwise responsible for safety reporting to the Penn IRB. The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Penn IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

Unexpected (An event is “unexpected” when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

AND

Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Reporting Process
Unanticipated problems posing risks to subjects or others as noted above will be reported to the Penn IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Other Reportable Events:

For clinical drug trials, the following events are also reportable to the Penn IRB:
Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
Breach of confidentiality
Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

10.10.3 Abramson Cancer Center Data Safety Monitoring Committee (DSMC):

Every effort should be made to report an event as a diagnosis, not as a list of symptoms. Symptoms that led to the diagnosis should be included in the event description, but should not be the actual event.

On-Site subjects (this includes any subjects enrolled at other sites on an ACC multi-site study). Only events on studies categorized as HIGH risk based on the ACC Risk table must be submitted to the DSMC as follows:
All grade 3 or higher events regardless of attribution or expectedness within 10 business days of knowledge.
All unexpected deaths within two business day of knowledge.
All others deaths within 30 days of knowledge. Deaths of subjects greater than 90 days from the last study treatment/intervention are not reportable unless a longer time frame is specified in the protocol.

Study PIs have the option to request DSMC review of AEs that do not meet the high risk definition if they would like an independent opinion of the event. The DSMC review will be limited to the scope specifically requested by the PI.

All events must be entered into the ACC Clinical Trials Management System (CTMS using the centralized reporting form.SAEs will be submitted to the DSMC through the Velos Clinical Trial Management System.Once an event is reported, you must keep the information accurate and current in Velos.

Exception

A one time, intentional action (planned prospectively) or process that departs from the IRB and CTSRMC approved study protocol, intended for one occurrence. Advance documented IRB and DSMC approval is required.

For in-house studies with a Medical Monitor or Safety Monitoring Committee (not DSMB), approval must be obtained from the Medical Monitor or Safety Monitoring Committee prior to submitting your exception request to the DSMC.
The following information must be contained in your exception request:

- When it is needed and why it is needed in that timeframe
- Has the Medical Monitor or Sponsor approved and provide the documentation of approval
- Is this an exception from eligibility, treatment, disease progression, study calendar windows, etc.
- Why the exception is needed (cite the section(s) of the protocol) along with the full clinical details of the subject. This must be determined by the sub-Investigator or PI.
- The reason why the protocol currently doesn't allow the situation for which an exception is being requested. This must be determined by the sub-Investigator or PI.
- If there are plans to amend the protocol and if not, why not.
- If additional follow-up or interventions will be required in order to protect the subject as a result of this exception.

Study Exceptions the DSMC may Reject:

Exceptions to eligibility, treatment/dosing, contraindicated treatment/therapies/interventions or safety tests for the following types of studies may be rejected by the DSMC:

- Any investigator-initiated treatment study.
- Any treatment study involving on-campus manufacturing of any component, regardless of sponsor.

To seek approval, you must provide the DSMC with strong and compelling scientific and clinical information to support your request. You should also include a statement explaining whether or not the protocol will be amended.

If the protocol will not be amended your reasoning must be provided. If this situation is likely to happen again, the DSMC will require a protocol amendment.

Deviation
Any unintentional action or process that departs from IRB approval and is identified retrospectively. The deviation is reportable to the DSMC and the IRB within 10 days from the time the event becomes known to the study team only when: one or more participants were placed at increased risk of harm, or, the event has the potential to occur again, or the event has the potential to qualify as serious or continuing noncompliance.

If the PI determines that a deviation has **any potential** to impact participant safety (harm and/or risk), or the integrity of data produced from the participant, or some other overall impact on the study, the PI must report the deviation to the IRB and DSMC as described above. The IRB will make the final assessment of the impact. The DSMC will assess for additional safety and scientific integrity concerns.

The following information must be contained in your deviation report:

- When it happened? When the study team (any member) became aware
- The full description of the deviation including important dates, test results, actions taken towards the subject, etc. Also, why it happened and how it was identified.
- Was the Medical Monitor or Sponsor notified. If so, their response?
- The PIs assessment of the impact on risk, safety and/or outcome. If no impact, why. If impact, what and what will happen next.
- The corrective actions that have been implemented to date and the impact of those corrective action plans.
- Future corrective action plans (if applicable) and the impact of those plans.
- If there are plans to amend the protocol (if applicable to prevent future deviations) and if not, why not.

If the PI determines that the event had no potential to impact participant safety (harm and/or risk) or the integrity of data produced from the participant, the PI must fully document his/her rationale for each category (risk, harm, and participant data).

11.0 Data Handling and Record Keeping

11.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period

11.2 Data Collection and Management

This study will use Velos as the data management system. The study case report form (CRF) is the primary data collection instrument for the study and will be electronically created and completed in Velos. CRFs will be provided for each patient. Subjects must not be identified by name on any CRFs. Subjects will be identified by their patient identification number (PID). All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A.".)

12.0 Study Monitoring, Auditing, and Inspecting

12.1 Study Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment, at least every 6 months, of the number and type of serious adverse events by an independent clinician, Roger Cohen, MD, Department of Medicine, Division of Hematology-Oncology. Additionally, the Medical Monitor will be consulted for protocol exceptions and deviations and as needed for decision-making regarding dose modifications, study eligibility, and any need to stop enrollment or the study for safety concerns.

This study will be monitored in accordance with the Cancer Center's Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) Plan, approved by NCI during the Core Grant's most recent review. This plan requires that the investigator submit a study-specific plan outlining how data will be reviewed In addition, the CTSRMC plan calls for an internal audit by the Cancer Center's Data Safety Committee twice yearly. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

12.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

13.0 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 parts 50 and 56 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent IRB, in agreement with local legal prescriptions, for formal approval of the study conduct.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB and CTSRMC for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject and the investigator-designated research professional obtaining the consent.

14.0 Study Finances

14.1 Funding Source

This clinical study, including correlative work, will be supported by funds provided by Bristol-Myers Squibb.

14.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

15.0 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

16.0 References

1. Hugen N, Brown G, Glynne-Jones R, et al. Advances in the care of patients with mucinous colorectal cancer. Nat Rev Clin Oncol. 2016 Jun;13(6):361-9.

2. Franko J, Shi Q, Goldman CD, et al. Treatment of Colorectal Peritoneal Carcinomatosis With Systemic Chemotherapy: A Pooled Analysis of North Central Cancer Treatment Group Phase III Trials N9741 and N9841. Journal of Clinical Oncology. 2012;30(3):263-267.

3. Elias D, Gilly F, Boutitie F, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol. 2010 Jan 1;28(1):63-8.

4. Zunino B, Rubio-Patiño C, Villa E, et al. Hyperthermic intraperitoneal chemotherapy leads to an anticancer immune response via exposure of cell surface heat shock protein 90. Oncogene. 2016 Jan 14;35(2):261-8.

5. Yoshioka Y, Togashi Y, Chikugo T, et al. Clinicopathological and genetic differences between low-grade and high-grade colorectal mucinous adenocarcinomas. Cancer. 2015 Dec 15;121(24):4359-68.

6. Alakus H, Babicky ML, Ghosh P, et al. Genome-wide mutational landscape of mucinous carcinomatosis peritonei of appendiceal origin. Genome Med. 2014 May 29;6(5):43.

7. Shibahara H, Higashi M, Yokoyama S, Rousseau K, et al. A comprehensive expression analysis of mucins in appendiceal carcinoma in a multicenter study: MUC3 is a novel prognostic factor. PLoS One. 2014 Dec 31;9(12):e115613.

8. Ferreira JA, Magalhães A, Gomes J, et al. Protein glycosylation in gastric and colorectal cancers: Toward cancer detection and targeted therapeutics. Cancer Lett. 2017 Feb 28;387:32-45.

9. Morse MA, Niedzwiecki D, Marshall JL, et al. A randomized phase II study of immunization with dendritic cells modified with poxvectors encoding CEA and MUC1 compared with the same poxvectors plus GM-CSF for resected metastatic colorectal cancer. Ann Surg. 2013 Dec;258(6):879-86.

10. Posey AD Jr, Schwab RD, Boesteanu AC, et al. Engineered CAR T Cells Targeting the Cancer-Associated Tn-Glycoform of the Membrane Mucin MUC1 Control Adenocarcinoma. Immunity. 2016 Jun 21;44(6):1444-54.

11. Schuster H, Peper JK, Bösmüller HC, et al. The immunopeptidomic landscape of ovarian carcinomas. Proc Natl Acad Sci U S A. 2017 Nov 14;114(46):E9942-E9951.

12. Haro MA, Littrell CA, Yin Z, et al. PD-1 Suppresses Development of Humoral Responses That Protect against Tn-Bearing Tumors. Cancer Immunol Res. 2016 Dec;4(12):1027-1037.

13. Long GV, Tykodi SS, Schneider JG, et al. Assessment of nivolumab exposure and clinical safety of 480 mg every 4 weeks flat-dosing schedule in patients with cancer. Ann Oncol. 2018 Sep 12.

14. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar;18(3):e143-e152.

15. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015 May 21;372(21):2018-28.

16. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med. 2017 Mar 16;376(11):1015-1026.

17.0 Schedule of Events

Note: study timepoints may be performed within a +/- 3 day window.

	Screening[1]	Cycle 1 (56 days)			Cycles 2+ (56-day cycles)		End of Study Visit	Follow -up
		1	10-14	29	1	29		
Treatments								
Nivolumab		X		X	X	X		
Ipilimumab		X			X			
Tests and Observations								
Informed Consent[2]	X							
Medical History	X							X[6]
Physical Exam and Performance Status	X	X			X	X	X	
AE Assessment		X		X	X	X	X	
CBC w/ differential	X	X		X	X	X	X	
Serum Chemistry[4]	X	X		X	X	X	X	
TSH	X				X	X	X	
CEA[8]	X	X		X	X	X	X	
Pregnancy test[5]	X	X		X	X	X	X	
Disease Assessment (routine CT/MRI)[3]	X				X		X	X[7]
Research Correlates								
Tumor biopsy	X		X					
Research Blood (60mL)	X[9]		X	X	X		X	

[1] Laboratory screening evaluations (section 4.1 #7) are to be conducted within 14 days prior to start of protocol therapy or should be repeated on cycle 1 day 1 prior to treatment to confirm eligibility. Baseline disease assessment with imaging must be conducted within 21 days prior to start of protocol therapy. Screening procedures may also occur on cycle 1 day 1 prior to therapy.

[2] Informed consent will be documented prior to initiation of any other research related activity. If there have been tests/procedures that have been performed as part of subjects work-up or routine practice prior to informed consent and within the screening evaluation window then those tests/procedures do not have to be repeated

[3] CT/MRI, and/or PET/CT in the event that PET/CT is determined to be standard of care.

[4] Sodium, potassium, BUN, serum creatinine, calcium, glucose, AST, ALT, total bilirubin, alkaline phosphatase, albumin

[5] Within 72 hours prior to first dose of cycle 1 immunotherapy. Men and women of childbearing potential must agree to use a medically accepted form of birth control (see Appendix A) OR must agree to completely abstain from intercourse for two weeks before beginning study treatment, during participation in this study, and for 5 months (women) or 7 months (men) after the final study treatment.

[6]Limited to following of survival and disease recurrence through review of the medical record for up to 3 years after the end of study visit (every 6 months for the first year, then annually for the second two years).
[7]MRI/CT scan will be performed at frequency determined by clinical care with data to be collected from the medical record for the purposes of the research.
[8]CEA will be repeated with each cycle if abnormal at screening
[9]Research blood is to be drawn on the same day as the tumor biopsies during screening and cycle 1 days 10-14. It should not be drawn at the initial screening visit. If the biopsy is omitted, research blood draw is still required and can occur during screening window or on cycle 1 day 1 prior to treatment. Research blood can be drawn within 3 days before or after biopsy if required for scheduling.

Appendix A: Definition of Non-Childbearing Potential and Medically Acceptable Methods of Birth Control

Non-childbearing potential is defined as any of the following (by other than medical reasons):

1. ≥45 years of age and has not had menses for >2 years
2. Amenorrheic for <2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon pre-study (screening) evaluation
3. Post hysterectomy, oophorectomy or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by imaging. Tubal ligation must be confirmed with medical records of the actual procedure otherwise the patient must be willing to use 2 other adequate methods.

Females:

Women of child-bearing potential must agree to use 2 of the following forms of contraception OR completely refrain from intercourse during the study and for at least 5 months following the last dose of study drug.

Males:

Men with partners of child-bearing potential must agree along with their partner to use 2 of the following forms of contraception OR completely refrain from intercourse during the study and for at least 7 months following the last dose of study drug.

Acceptable methods include:

- Condoms
- Diaphragm
- Cervical cap
- Intra-uterine device
- Surgical sterilization (tubal ligation or vasectomy)
- Oral contraceptives

Abstinence at certain times of the cycle, such as during ovulation or after ovulation, or withdrawal are not acceptable methods. The list of methods above is not exhaustive and additional contraception methods may also be acceptable. The study doctor must approve the contraceptive methods in subjects with child-bearing potential.

Appendix B: Management Algorithms for Nivolumab and Ipilimumab

These general guidelines constitute guidance to the Investigator and may not be appropriate in all circumstances. Deviation from these guidelines will not be considered a protocol deviation. A general principle of immune adverse events is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

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

GI Adverse Event Management Algorithm

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

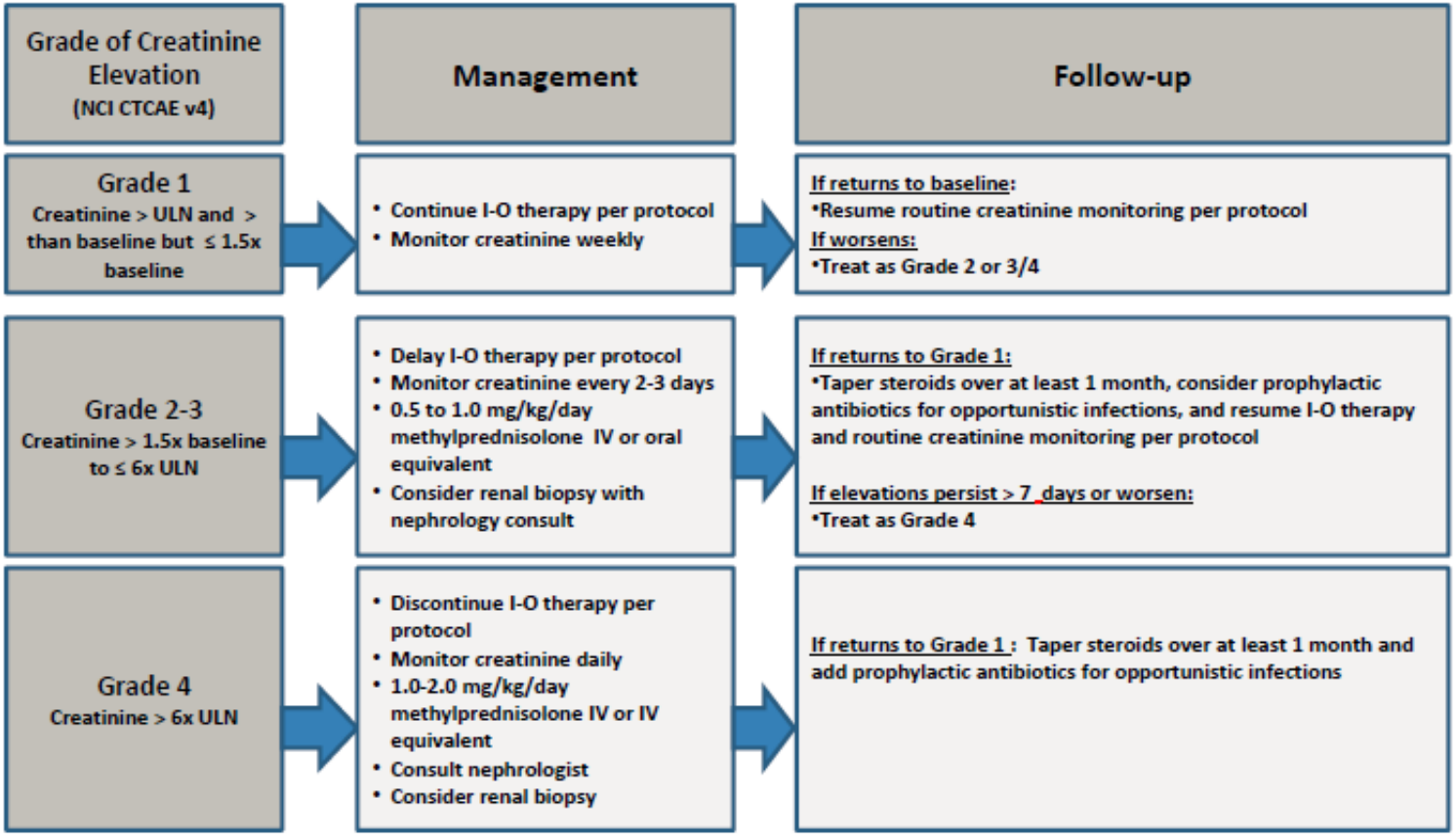
Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat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

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

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

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

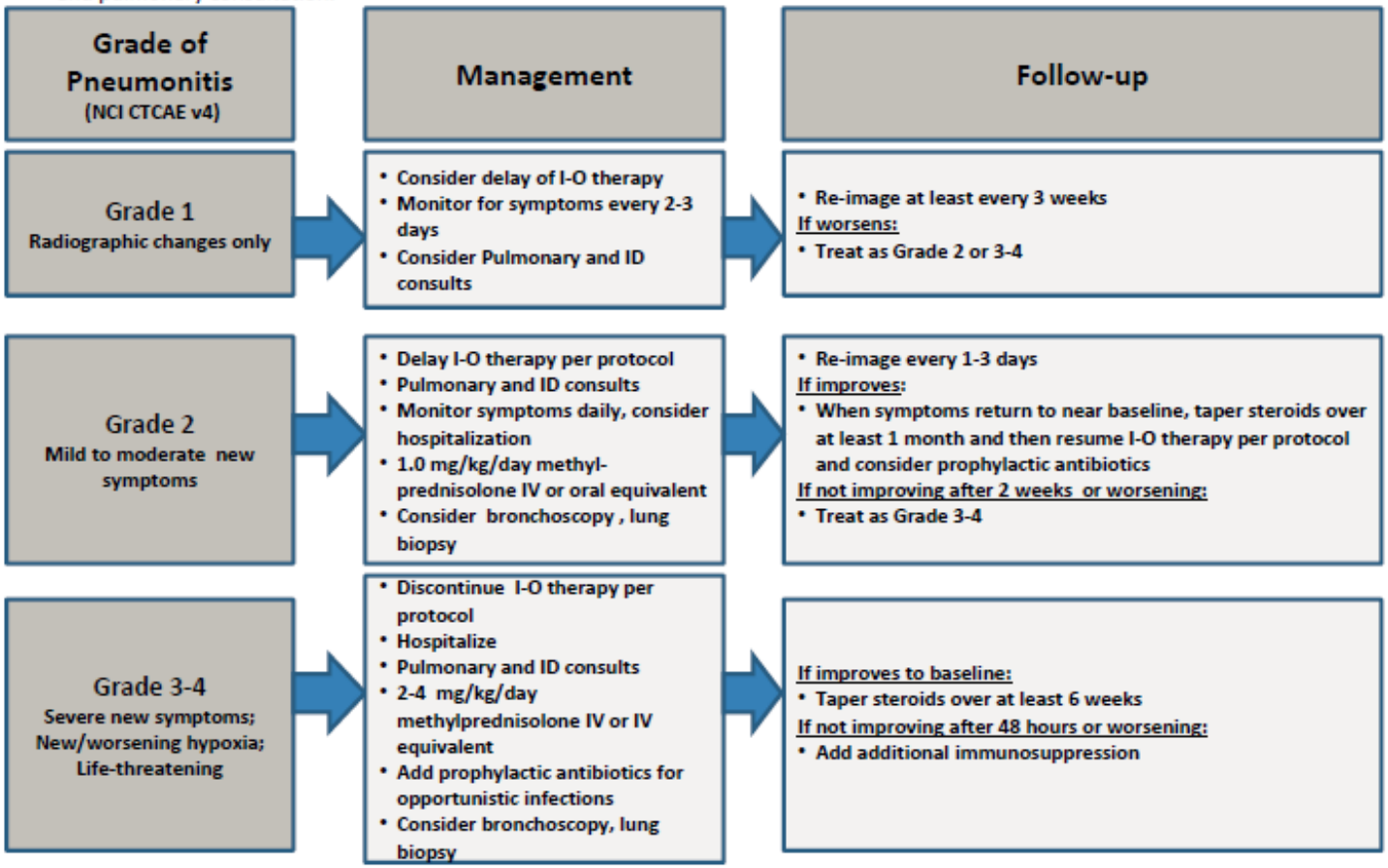


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Pulmonary Adverse Event Management Algorithm

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

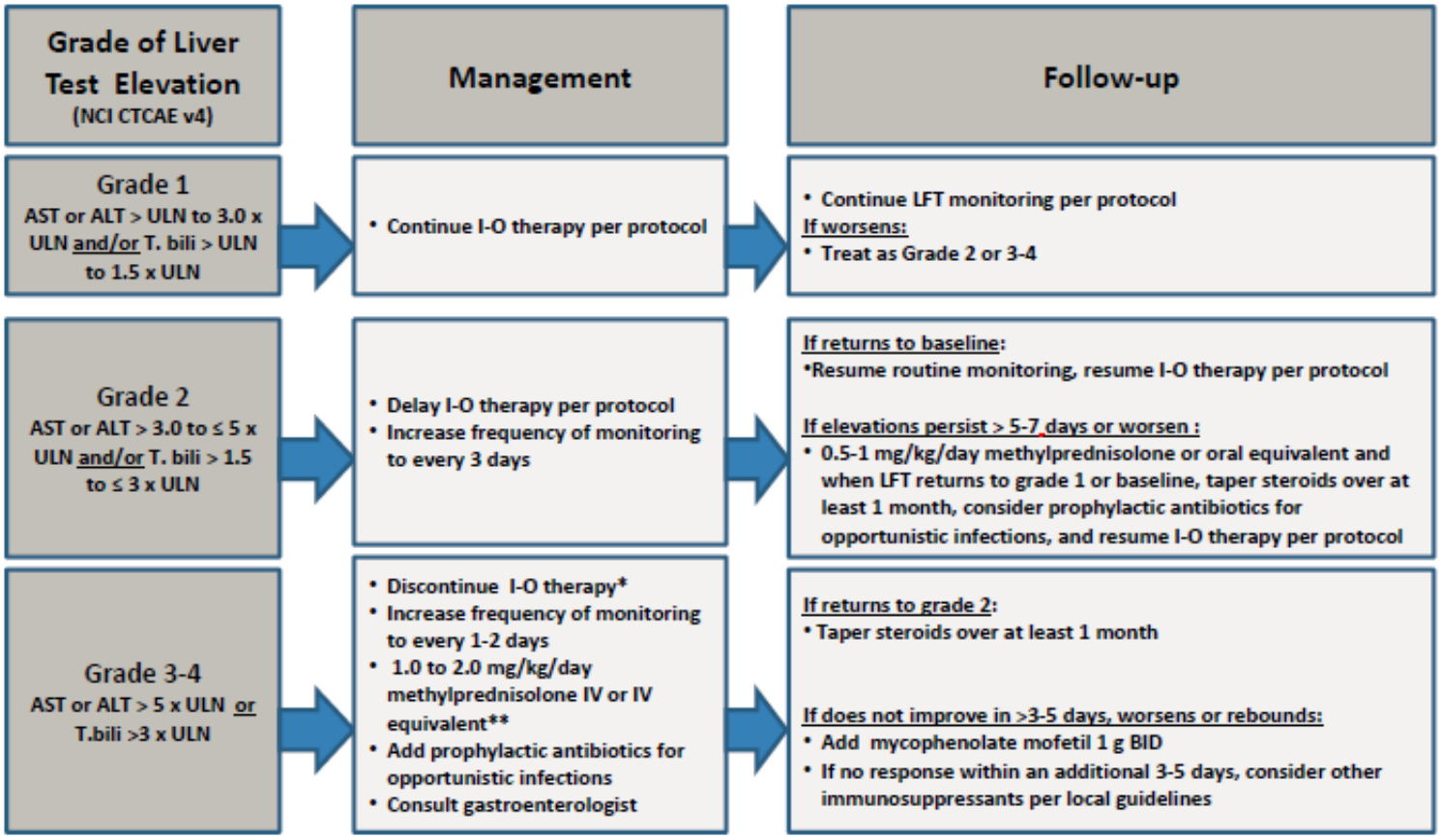


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Hepatic Adverse Event Management Algorithm

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



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

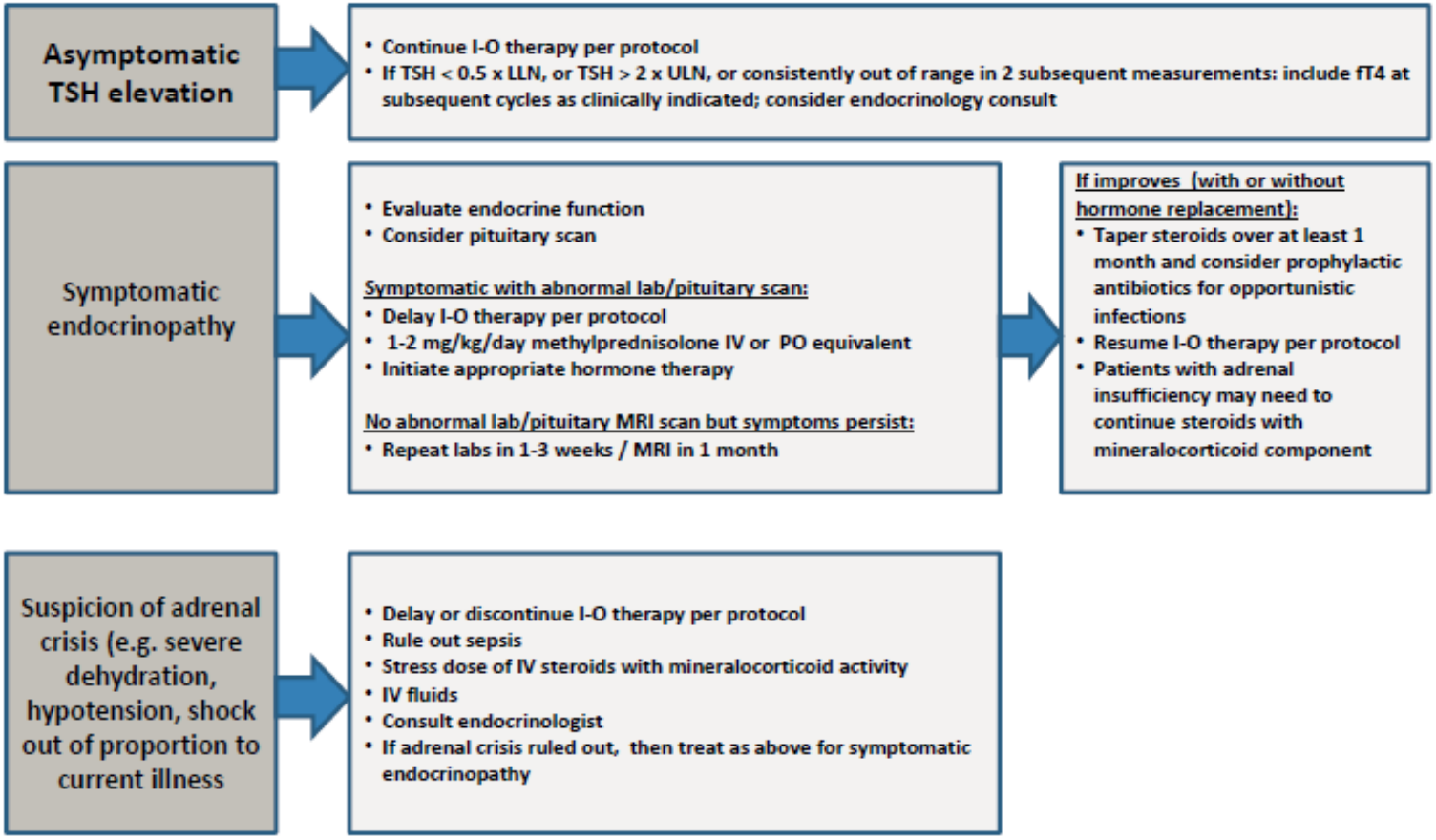
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

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

Updated 05-Jul-2016

Endocrinopathy Management Algorithm

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

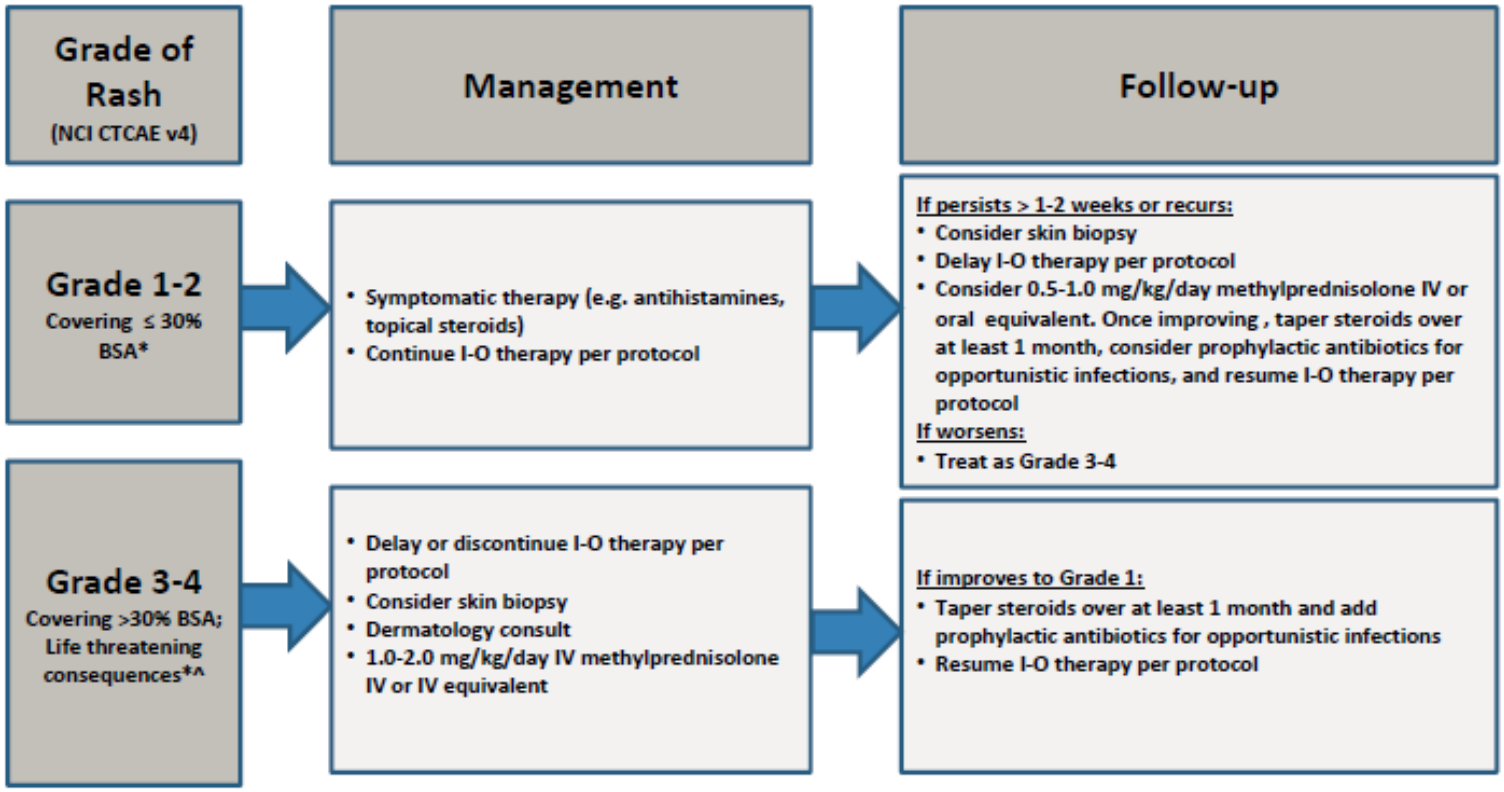


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

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



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Updated 05-Jul-2016

Neurological Adverse Event Management Algorithm

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

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

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

Updated 05-Jul-2016

Appendix C: RECIST 1.1 Criteria

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). 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 or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

Target lesions. All measurable and/or evaluable 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

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

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

Response Criteria

Evaluation of Target Lesions (RECIST 1.1)

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.

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. (Note: the appearance of one or more new lesions is also considered progressions).

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

Evaluation of Non-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.

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. (Note: the appearance of one or more new lesions is also considered progressions).

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

Appendix D: Immune-Related Response in Measurable Lesions (iRECIST)

iRECIST guidelines were established in 2017 to guide response assessments in clinical trials testing immunotherapeutics. Full details of the iRECIST criteria for this study can be found in Seymour L et al, Lancet Oncology 2017 [14].

If initial RECIST 1.1-defined progression (ie, iUPD) is noted on imaging in the setting of clinical stability, subjects may remain on study treatment and have confirmatory imaging in 4-8 weeks (study specified scans every 8 weeks should continue on initial schedule if patient remains on study). An assignment of clinical stability requires that no worsening of performance status has occurred, that no clinically relevant increases in disease-related symptoms such as pain or dyspnea occur that are thought to be associated with disease progression, and that no requirement for intensified management of disease-related symptoms exists, including increased analgesia, radiotherapy, or other palliative care. The imaging findings and the recommendation to continue with treatment despite iUPD should be discussed with the patient before a decision is made about whether or not to continue therapy. Patients who have iUPD and are not clinically stable should be designated as not clinically stable in the case report form. This designation will allow the best overall response to be calculated and the date of iUPD to be used in estimates of progression-free survival.

If radiologic progression is confirmed (iCPD), they will be determined to have progressive disease and discontinued from study therapy, but if repeat imaging shows stable disease or response by RECIST 1.1 they may remain on study therapy with imaging continuing as previously scheduled every 8 weeks (cycle 3 day 1, cycle 5 day 1, etc.).

Table 1: Comparison of RECIST 1.1 and iRECIST

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before CR, PR, or SD
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Consideration of clinical status	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumours. iUPD=unconfirmed progression. iCPD=confirmed progression. iCR=complete response. iPR=partial response. iSD=stable disease.

Table 2: Assignment of timepoint response using iRECIST

	Timepoint response with no previous iUPD in any category	**Timepoint response with previous iUPD in any category**
Target lesions: i CR; non-target lesions: iCR; new lesions: no	iCR	iCR
Target lesions: iCR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iPR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iSD; non-target lesions: non-iCR/non-iUPD; new lesions: no	iSD	iSD
Target lesions: iUPD with no change, or with a decrease from last timepoint; non-target lesions: iUPD with no change, or decrease from last timepoint; new lesions: yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
Target lesions: iUPD; non-target lesions: non-iCR/non-iUPD, or iCR; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥5 mm; otherwise, assignment remains iUPD
Target lesions: iUPD; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures >5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified

Target lesions: non-iUPD or progression; non-target lesions: non-iUPD or progression; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified

Target lesions, non-target lesions, and new lesions defined according to RECIST 1.1 principles; if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same.

*Previously identified in assessment immediately before this timepoint. “i” indicates immune responses assigned using iRECIST. iCR=complete response. iPR=partial response. iSD=stable disease. iUPD=unconfirmed progression. non-iCR/non-iUPD=criteria for neither CR nor PD have been met. iCPD=confirmed progression. RECIST=Response Evaluation Criteria in Solid Tumours.