Update #07

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A082002

A RANDOMIZED PHASE II/III TRIAL OF MODERN IMMUNOTHERAPY BASED SYSTEMIC THERAPY WITH OR WITHOUT RADIATION THERAPY FOR PD-L1-NEGATIVE, ADVANCED NON-SMALL CELL LUNG CANCER

NCI-supplied agents: Nivolumab (NSC #748726), Ipilimumab (NSC #732442)

IND Holder: DCTD, NCI; IND #126146
ClinicalTrials.gov Identifier: NCT04929041

[X] **Update:**	[ ] **Status Change:**
[X] Eligibility changes	[ ] Activation
[ ] Therapy / Dose Modifications / Study Calendar changes	[ ] Closure
[ ] Informed Consent changes	[ ] Suspension / temporary closure
[ ] Scientific / Statistical Considerations changes	[ ] Reactivation
[ ] Data Submission / Forms changes	
[X] Editorial / Administrative changes	
[X] Other: CTSU language changes	

If your site utilizes the CIRB as your IRB of record
No recommended IRB level of review is provided by the Alliance since the CIRB is the IRB of record for this trial.

The site has 30 days after the posting of this amendment to implement it at their site. Please refer to the amendment application and CIRB guidelines for further instructions.

If your site utilizes a local IRB as your IRB of record
IRB approval (or disapproval) is required within 90 days. Please follow your local IRB guidelines.

UPDATES TO PROTOCOL:

Cover Page

- The study title has been updated to replace "SBRT" with "Radiation Therapy."
- Contact information for the Protocol Coordinator has been updated.

Study Resources

- Angelina Raimonde-Taylor has replaced Donna Vattanakul as A082002 Pharmacy Contact; all corresponding contact information has been updated.
- The telephone number for imaging under "IROC" has been updated.
- Under the "Protocol-related questions" table, the "Contact" column has been updated to indicate "cc Protocol Coordinator" for questions regarding patient eligibility, treatment, and dose modification.

CTSU Contact Information

The row regarding Quality of Life booklets has been removed from the table to reflect the new process for downloading booklets from the CTSU website.

Eligibility Criteria

- The study title has been updated to replace "SBRT" with "Radiation Therapy."

Schema, Section 2.1 (Primary objective), Section 4.6.2 (Treatment Assignments), Section 7.1 (Patients will be randomized to one of 2 Arms), Section 11.1 (Target Lesions), Section 12.2 (Criteria for Discontinuation of Protocol Treatment/Intervention), Section 13.0 (Statistical Considerations), Section 13.3 (Provide sample size with power justification), Section 14.1 (Quality of Life (Alliance A082002-HO1)), Section 14.2 (Correlative Science (Alliance A082002-ST1))

"SBRT" has been replaced by "radiation" and/or "radiation therapy" throughout these sections.

Section 1.0 (Background)

- The first sentence of the second paragraph has been updated to clarify that radiation therapy is often delivered via SBRT.
- The third sentence of the third paragraph has been updated to specify consolidative local therapy.
- The term "SBRT" has been replaced by "radiation" and "radiation therapy" as appropriate throughout the third, fourth, and eighth paragraphs.

Section 1.1 (Importance of trial)

- The fourth sentence of this section has been updated to replace "SBRT" with "three 8 Gy doses of radiation" and remove "low dose SBRT."
- The term "SBRT" has been replaced with "radiation" in the last sentence.

Section 3.2 (Eligibility Criteria)

In criterion 3.2.2, the term "SBRT" has been replaced with "three 8 Gy doses of radiation."

Section 4.1 (Investigator and Research Associate Registration with CTEP), Section 4.2 (Cancer Trials Support Unit Registration Procedures), Section 4.4 (Patient registration/randomization procedures), Section 6.1.2 (Medidata Rave), Section 6.4 (Submission of Patient Completed Measures), Section 9.1 (Routine Adverse Event Reporting)

Text throughout these sections have been updated to align with the current CTSU boilerplate language.

Section 4.3.2 (previously Pre-authorization Required)

This section has been removed, as SBRT pre-authorization no longer applies effective with this protocol update.

Section 4.3.2 (Patient-reported outcomes)

This section has been revised in its entirety to reflect the new process for downloading patient questionnaire booklets from the CTSU website and the removal of Appendix III from the protocol document.

Section 5.0 (Study Calendar)

- The column header "Day 1 of SBRT (Arm B Only)" has been edited to "Day 1 of Radiation (Arm B Only)."
- Footnote 2 has been updated to correct the eligibility criterion being referenced.
- Footnote 4 has been edited to reflect the removal of Appendix II from the protocol document.
- Footnote C has been edited to clarify that chest CT scans should be obtained every 12 weeks versus every 3 months.

Section 6.1.1 (Data submission schedule)

This section has been revised in alignment with the Alliance protocol template.

Section 6.3.4 (Imaging Data Submission Methods)

- Under the options for imaging data electronic submission of imaging data, #2 "Web Transfer" has been updated to replace the URLs "http://upload.IROCOhio.org or https://moveit.imres.med.ohio-state.edu" with "http://upload.wci.uc.edu."
- Under the options for imaging data electronic submission of imaging data, #4 "Mail/CD Shipment" has been updated to include the new mailing address for IROC Ohio.
- At the end of the section, the phone number for IROC Ohio has been updated.

Section 6.4 (Submission of Patient Completed Measures)

- The first paragraph has been revised in its entirety to reflect the new process for downloading patient questionnaire booklets from the CTSU website.
- The footnote beneath the table in this section have been removed to reflect the removal of Appendix III from the protocol document.
- The last sentence of this section has been moved to the end of the second paragraph in alignment with the Alliance protocol template.
- The second sentence of Section 6.4.1 has been removed in alignment with the Alliance protocol template.

Section 7.3 (Radiotherapy)

- "SBRT" has been replaced by "radiation therapy," "protocol radiation," or removed as needed throughout this section.
- The second sentence has been updated to reflect the required radiation therapy dosage and specify acceptable techniques.
- A sentence was added above Table 1.1 to clarify radiation techniques and dosages required by this protocol.
- In Table 1.1, the following information has been removed from the last column in the Beam Modality row: "ViewRay & Linac are allowed."
- Under Table 1.1, the erroneous reference to Section 2.2.6 has been removed from the "Note."

- In Table 1.2, the first sentence in the Guideline column of the Immobilization row has been updated to replace "Proper" with "Custom" and remove list of immobilization examples.
- Under Table 1.3, the section referencing the IGTV definition has been corrected to Section 7.3.2.
- In Table 1.4, a new sentence has been added to the second column in the Number of Beams row to reflect the acceptable beam arrangements per protocol, and clarification has been added regarding past SBRT recommendations.

Section 7.4 (Imaging)
Under Baseline scan requirement "CT of the chest," "abdomen" has been replaced by "including upper liver and adrenals" to align with the study calendar text.

Section 8.1.5 (Diarrhea management is per the discretion of the treating physician. Diarrhea could be managed conservatively with medications such as loperamide)
Appendix IV has been renumbered accordingly, reflecting the removal of previous Appendices II and III.

Section 8.3 (Dose Modifications for Immunotherapy)
Appendix IV has been renumbered accordingly in the Fever and Infusion Reaction tables, reflecting the removal of previous Appendices II and III.

Section 9.0 (Adverse Events)
The following sentence has been removed from the second paragraph to reflect the removal of Appendix II: "The specific PRO-CTCAE items for this protocol can be found in Appendix II."

Section 9.3.1 (Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention)
The "Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention" has been updated to align with updated AE/SAE language.

Section 10.2 (Nivolumab (BMS-936558, MDX-1106, ONO-4538 NSC #748726, IND #129803, IND holder: DCTD, NCI))
The reference to the CAEPR under the Adverse Events subsection has been corrected to Section 9.4.

Section 10.3 (Ipilimumab (BMS-734016, MDX-010, NSC#s 732442, IND #129803, IND holder: DCTD, NCI))
The reference to the CAEPR under the Adverse Events subsection has been corrected to Section 9.5.

Section 13.2 (Stratification)
"SBRT" has been replaced by "radiation" in the first sentence of the second paragraph.
The second sentence of the second paragraph has been revised to remove outdated reference to six systemic therapy options.

Appendix II (previously PRO-CTCAE) and Appendix III (previously EORTC QLQ-C30 + LC-13)
The PRO-CTCAE and EORTC QLQ-C30 + LC-13 appendices have been removed and are available on the CTSU website.

UPDATES TO MODEL CONSENT FORM:

Study Title
The study title has been updated to replace "SBRT" with "Radiation Therapy."

Why is this study being done?
The study question has been updated to replace "SBRT" with "radiation therapy" and to add "used to treat lung cancer."

What will happen if I decide to take part in this study?, What are the risks and benefits of taking part in this study?, What is the purpose of this study?, What are the study groups?, What risks can I expect from taking part in this study?
The term "SBRT" has been replaced by "radiation" throughout these sections.

What are the costs of taking part in this study?
The second paragraph of this section has been removed, to align with the replacement of SBRT with radiation.

A replacement protocol document and model consent have been issued.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

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Study Resources:

Expedited Adverse Event Reporting **http://eapps-ctep.nci.nih.gov/ctepaers/**	**Medidata Rave® iMedidata portal** https://login.imedidata.com
OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org	**Biospecimen Management System** http://bioms.allianceforclinicaltrialsinoncology.org

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Protocol-related questions may be directed as follows:

Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, and (where applicable) Data Manager (cc Protocol Coordinator)
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox *regulatory@allianceNCTN.org*
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox *pharmacovigilance@alliancenctn.org*
Questions regarding specimens/specimen submissions:	Alliance Biorepository
Questions regarding drug supply	PMB
Questions regarding drug administration	Pharmacy Contact

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878) at CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.		
For clinical questions (i.e., patient eligibility or treatment-related) see the Protocol Contacts, Page 2.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or email: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		

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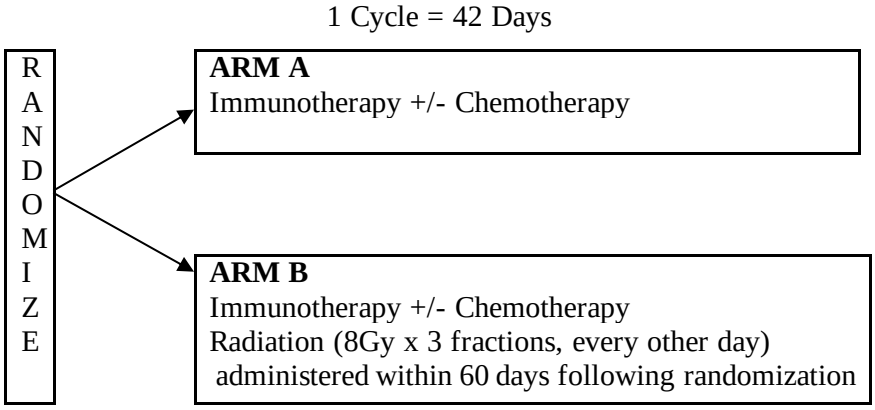
Eligibility Criteria	**Required Initial Laboratory Values**	
Histologic or cytologic documented NSCLC Stage IV or Stage IIIB-C if not a candidate for chemo-RT	ANC	$\geq 1500/mm^3$
PD-L1 TPS <1%	Platelet count	$\geq 100,000/mm^3$
EGFR, ALK and ROS1 negative (non-squam only)	Calc create Clear	≥ 45 ml/min
Measurable disease	Total Bili	≤ 1.5 x ULN
Age $\geq$ 18 years	AST/ALT	≤ 2.5 x ULN
ECOG PS 0-2		
No prior treatment per Section 3.2.5		
No comorbid conditions per Section 3.2.6		
Non-pregnant and non-nursing		
No currently active second malignancy		
No hypersensitivity to immunotherapy		
No live vaccine within 30 days		

Schema



Treatment will continue until disease progression and no longer benefiting clinically, or unacceptable adverse event. Treatment may continue beyond disease progression per iRECIST guidelines. That is, treatment may continue beyond assessment of progressive disease (PD) provided the patient is clinically stable and felt to be continuing to benefit from therapy. A patient may be deemed clinically stable provided that no worsening of performance status has occurred, there have been no clinically relevant increases in disease-related symptoms such as pain or dyspnea that are thought to be associated with disease progression, and there has been no requirement for intensified management of disease-related symptoms, including increased analgesia, radiotherapy, or other palliative care. Repeat imaging should be obtained within 4-8 weeks if feasible, and no later than 3 months. If the subsequent scan shows additional new lesions or increase in new lesion size (sum of measurements $\geq$ 5 mm), treatment should be discontinued.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

Table of Contents

1.0 BACKGROUND

Up until quite recently, stage 4 NSCLC was an invariably fatal disease. Immunotherapy has revolutionized therapy with the real prospect of achieving 5-year survival in 16 to 23% of select patients.[1,2] This study intends to see if we can enhance the outcome of immunotherapy in select patients who historically were felt to benefit less from immunotherapy, specifically patients with low PD-L1 levels, defined as PD-L1 ≤1%.

Radiation Therapy, often delivered in a technique called Stereotactic Body Radiation Therapy (SBRT) (also termed stereotactic ablative body radiotherapy (SABR)), has shown promise in trials of select patients with metastatic disease. For example, the SABR-COMET Trial (phase 2 trial) randomized 99 pts with various oligometastatic (≤5 metastases) tumors (including NSCLC) to conventional systemic therapy with or without SBRT (16-24 Gy/1fraction or 30-60 Gy/3-8 fractions) to all metastases.[3] The median survival was 28 months with conventional systemic therapy vs. 41 months with conventional systemic therapy plus SBRT (p=0.090). This met the primary statistical endpoint of the trial design. The benefit of longer survival came at the cost of adverse events (grade ≥2) that occurred in 29% of those who received SBRT compared to 9% with conventional therapy (p=0.026).

Another example specific to NSCLC patients is the study of Gomez et al,[4] which intended to determine the role of local consolidative therapy for oligometastatic NSCLC. This was a randomized phase 2 trial of patients with oligometastatic NSCLC (≤3 metastases) without progression after systemic therapy. Forty-nine subjects were randomized to maintenance therapy or observation vs. consolidative local therapy (resection or RT) to all active sites of disease. The RT was varied and included both SBRT and conventional RT. There was a significant survival benefit to the local therapy arm (median, 41.2 mo vs. 17.0 mo) (P=0.017). They concluded that patients with oligometastatic NSCLC who did not progress after front-line systemic therapy had better OS with the addition of local therapy. This may be due to greater tumor antigen release, antigen presentation, and T-cell infiltration following RT. These trials demonstrate the safety of radiation in the metastatic setting, and the potential benefit in patients with oligometastatic disease. This is being further evaluated in LU002, a trial specifically for oligometastatic (3 or fewer metastases) NSCLC addressing the value of local consolidative therapy to each lesion.

The synergistic effect of radiation therapy and immunotherapy was further studied in PEMBRO-RT trial,[5] a randomized phase 2 study of 92 stage IV NSCLC patients that assessed whether adding radiation to one lesion prior to pembrolizumab enhanced response. In contrast to the prior trials mentioned above, PEMBRO-RT was not an oligometastatic study and all patients had received prior chemotherapy. Patients were randomly assigned to either pembrolizumab (200mg q 3 weeks) alone or following radiation until progression, unacceptable toxicity, or a maximum of 24 months. In the radiation arm, the first pembrolizumab dose was given <7 days after radiation. Three doses of 8 Gy were delivered on alternate days to a single safe & convenient tumor site but not the biopsy site or a site previously irradiated. The 3-month response rate was 8% in the control arm vs 36% in the radiation arm (P = .07). Improvement in the disease control rate (64% vs 40%; P = .04) at 12 weeks was observed in the radiation arm. A significant benefit of radiation with respect to PFS was seen in the PD-L1–negative subgroup (HR, 0.49; 95% CI, 0.26-0.94;P = .03). For the entire group, the median survival was 7.6 months vs. 15.9 months (HR,0.66; P=.16) for pembrolizumab versus pembrolizumab plus radiation. Subgroup analyses found a benefit for radiation with respect to survival but only in the PD-L1 negative patients (HR, 0.48; P = .046). No increase in toxicity occurred in the radiation arm (probably because of the dose-fractionation utilized). In spite of a doubling of response rate, this outcome did not meet the pre-specified criteria for meaningful clinical benefit. Positive results were largely influenced by the PD-L1 negative patients, who had significantly improved survival. The authors concluded that a larger trial will be needed to determine whether radiation activates the microenvironment, thereby potentiating the outcome of immunotherapy for

stage IV NSCLC patients. This study was important in identifying a patient subgroup (those with PD-L1 negative tumors) that appeared to benefit from the use of radiation to alter the tumor microenvironment in a manner potentiating the effects of pembrolizumab immunotherapy improving survival in the patient subgroup with PD-L1 negative tumors.

Checkmate 227 established the potential value of immunotherapy for PD-L1 (-) NSCLC.[6] All patients were treatment-naïve, with stage IV or recurrent NSCLC, without known EGFR or ALK alterations, and had ECOG of PS 0–1. Patients with PD-L1 < 1% (n = 550) were randomized 1:1:1 to nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W, nivolumab 360 mg Q3W + chemotherapy, or chemotherapy alone. Patients were stratified by histology. They were treated until disease progression, unacceptable toxicity, or 2 years of immunotherapy**.** For patients with a PD-L1 expression of <1%, there was an improvement of median overall survival observed with nivolumab plus ipilimumab versus chemotherapy (17.2 months versus 12.2 months (HR 0.62, 95% CI 0.48 to 0.78), with an improvement in 2-year OS (40.4% versus 23.0%).

The current FDA approved regimens for patients with PDL1 <1% are a combination of immunotherapy plus chemotherapy. The benefit of pembrolizumab in addition to a carboplatin plus pemetrexed was observed in patients with non-squamous histology, PD-L1 0%, with a 12-month overall survival rate of 61.7% vs 52.2% (HR 0.59, 95% CI 0.38 to 0.92). [7] This was similarly observed with the addition of pembrolizumab to carboplatin plus paclitaxel or nab-paclitaxel in patients with squamous histology, with a 12 month OS of 64.2% vs 43.3% (HR 0.61; 95% CI 0.38 to 0.98). [8] Similar efficacy was seen with the combination of ipilimumab, nivolumab, and chemotherapy in the PD-L1 <1% population, with a 12 month OS of 63% versus 45% (HR 0.62; 95% CI 0.45 to 0.85). [9]

The potential synergy of immunotherapy, chemotherapy, and radiation therapy is one of the greatest areas of interest in NSCLC, currently in the setting of Stage III NSCLC. The current standard of care for Stage III NSCLC is chemoradiation followed by a year of durvalumab immunotherapy. This is based on the results of the PACIFIC trial, which demonstrated an improvement of 24 month OS of 66.3% vs 55.6% (p=0.005).[11] The safety of the addition of pembrolizumab to concurrent chemoradiotherapy was shown to be tolerable, with immune-related adverse events of at least grade 3 occurring in 18% (4/21 patients). [12] Similar results were seen with atezolizumab in the DETERRED trial, where 20% (6/30 patients) experienced a grade 3 or higher immune-related toxicity.[13] PACIFIC-2, as well as EA5181, are two currently ongoing large randomized trials which will attempt to determine the role of immunotherapy earlier in the treatment of Stage III NSCLC in combination with radiation.

As summarized above, there is data from randomized trials establishing the role of local consolidative therapy (primarily RT) in oligometastatic NSCLC. [3],[4] For patients with PD-L1 <1% with more widespread stage 4 NSCLC, a benefit was observed when radiation to a single lesion was added to pembrolizumab therapy. [5] Additionally, there is randomized data that shows immunotherapy with nivolumab plus ipilimumab yielded improved OS over chemotherapy alone in this group (PD-L1 negative patients).[6] A similar benefit of OS was seen with the addition of both single agent pembrolizumab as well as ipilimumab/nivolumab to a chemotherapy backbone.[7-10] Therefore, we hypothesize that the addition of radiation to immunotherapy, with or without chemotherapy, will improve overall survival for patients with PD-L1 expression <1%. Pragmatically, we will need to move this concept forward with more FDA approved systemic options in order to accrue an adequate number of patients to test the hypothesis. Mechanistically, the benefit appears due to the ability of radiation to lyse tumor cells releasing antigens, raise PD-L1 levels, and enhance the immunologic response and outcomes of patients treated with PD-1/PD-L1 inhibitors.[14,15]

1.1 Importance of trial

Advanced stage NSCLC carries a poor prognosis, and approximately half of these patients demonstrate PD-L1 levels of <1%. These patients appear to benefit from immunotherapy to a lesser degree than those with higher levels of PD-L1. While immunotherapy has improved the survival of advanced stage NSCLC patients, the majority still succumb to this disease. We hypothesize the addition of three 8 Gy doses of radiation, a relatively safe intervention (to a single lesion), to immunotherapy will improve survival for these patients. If positive, this trial will establish radiation as an important immunomodulatory factor in improving survival in approximately half of all advanced stage NSCLC patients (those with PDL-1 negative tumors).

2.0 OBJECTIVES

2.1 Primary objective

To assess if radiation improves the progression free survival (PFS, phase II portion) and overall survival (OS, phase III portion) of advanced stage NSCLC patients with PD-L1 TPS <1% who receive immunotherapy with or without chemotherapy.

2.2 Secondary objectives

2.2.1 To estimate and compare the rates of ≥ grade 3-4 and all grade adverse events by CTCAEv5.0 between the arms.

2.2.2 To summarize and compare progression-free survival (PFS) per RECIST between the arms.

2.2.3 To determine and compare the objective response rate (ORR) per RECIST between the arms (including at both irradiated and un-irradiated sites).

2.3 Quality of Life (QOL) Objective

2.3.1 To assess the health-related QOL in both treatment arms.

2.4 Correlative Science Objective

2.4.1 To evaluate changes in the peripheral immune microenvironment between the arms.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.

- Patients with a "currently active" second malignancy other than non-melanoma skin cancers, cervical carcinoma in situ, or DCIS or treated localized (T0-N0, M0) prostate cancer. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.
- Patients who would have completed adjuvant chemotherapy within 6 months prior to the start of study treatment.

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study and for 5 months for women and 3 months for men after the last protocol treatment due to the teratogenic potential of the therapy utilized in this trial. Include as applicable: Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

___ **3.2.1 Documentation of Disease**

___ Histologic or cytologic diagnosis of Stage IV NSCLC using version AJCC 8th edition (includes M1a, M1b, and M1c stage disease). Patients with Stage IIIB and IIIC disease are eligible if they are not a candidate for combined chemotherapy and radiation.

___ **PD-L1 IHC:** PD-L1 expression Tumor Proportion Score (TPS) <1% in tumor cells. If PD-L1 expression TPS is unevaluable or the testing could not be completed patients are not eligible. The assay must have been performed locally by a CLIA (or equivalent) certified laboratory. The type of assay will be recorded.

___ **For non-squamous patients only (adenocarcinoma or adenosquamous): EGFR, ALK and ROS1** testing must be done locally. No patients with known actionable EGFR mutations (except exon 20 insertion), ALK or ROS1 mutations that can be treated with oral tyrosine inhibitors.

___ **3.2.2 Measurable disease** based on RECIST 1.1, including at least two cancerous deposits. At least one deposit must be RECIST measurable (and not to be irradiated) while

at least one OTHER deposit (measurable or non-measurable) must meet criteria for three 8 Gy doses of radiation (See Section 7.3)

___ **3.2.3 Age ≥ 18 years**

___ **3.2.4 ECOG Performance Status 0-2**

___ **3.2.5 Prior Treatment**

___ No more than three weeks of treatment with systemic chemotherapy or immunotherapy for advanced NSCLC.

___ No more than three weeks of treatment with checkpoint inhibitors for metastatic lung cancer.

___ No treatment with chemotherapy or immunotherapy for non-metastatic disease (e.g., adjuvant therapy) within 6 months prior to registration.

___ No systemic immunostimulatory or immunosuppressive drugs, including >10mg prednisone equivalent per day, within 2 weeks or 5 half-live of the drug, whichever is shorter. Steroid premedication per local standard is allowed.

___ ≥ 1 week prior to registration since palliative (including CNS) radiotherapy to any tumor site.

___ No prior allogeneic tissue/solid organ transplant.

___ **3.2.6 Comorbid Conditions**

___ No uncontrolled intercurrent illness including, but not limited to, serious ongoing or active infection, symptomatic congestive heart failure, uncontrolled cardiac arrhythmia, unstable angina pectoris, that would limit compliance with study requirements.

___ No current pneumonitis or history of non-infectious pneumonitis that required steroids.

___ HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months of registration.

___ No active auto-immune disease that requires systemic therapy within 2 years prior to registration. Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid release therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

___ No known history of Hepatitis B (defined as HBsAg reactive) or known Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

___ No patients with symptomatic central nervous system metastases and/or carcinomatous meningitis. Patients with small asymptomatic brain metastases are eligible as are patients with treated brain metastases that require no steroids.

___ **3.2.7 Not pregnant and not nursing,** because this study involves radiation as well as potentially chemotherapy which have known genotoxic, mutagenic and teratogenic effects.

Therefore, for women of childbearing potential only, a negative urine or serum pregnancy test done ≤ 7 days prior to registration is required.

___ **3.2.8 No patients with a "currently active" second malignancy that is progressing or has required active treatment within the last 2 years.** Participants with non-

melanoma skin cancers or carcinoma in-situ (e.g., breast carcinoma, urothelial carcinoma or cervical cancer in situ) or localized prostate cancer (T1-3, N0, M0) that have undergone potentially curative therapy are eligible.

___ **3.2.9 No hypersensitivity (≥ Grade 3) to immunotherapy and/or any of its excipients.**

___ **3.2.10 No live vaccine within 30 days prior to registration.** Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed. COVID-19 vaccine is allowed.

___ **3.2.11 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC) ≥ 1,500/mm3

Platelet Count ≥ 100,000/mm3

Calc. Creatinine Clearance ≥ 45 mL/min

Total Bilirubin ≤ 1.5 x upper limit of normal (ULN)

AST / ALT ≤ 2.5 x upper limit of normal (ULN)

4.0 PATIENT REGISTRATION

Sites that have NRG LU002 (Maintenance Systemic Therapy Versus Local Consolidative Therapy (LCT) Plus Maintenance Systemic Therapy For Limited Metastatic Non-Small Cell Lung Cancer (NSCLC): A Randomized Phase II/III Trial) open should prioritize that trial for those patients who have oligometastatic non-small cell lung cancer and otherwise qualify.

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes four person registration types that are applicable to this study.

- **Investigator (IVR)**—MD, DO, or international equivalent;
- **Non-Physician Investigator (NPIVR)**—advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- **Associate Plus (AP)**—clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave; acting as a primary site contact, or with consenting privileges; and
- **Associate (A)—**other clinical site staff involved in the conduct of NCI-sponsored trials.

RCR requires the following registration documents:

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

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites in RCR to allow the following:

- Addition to a site roster;
- Selection as the treating, credit, or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting or treating investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Refer to the **NCI RCR** page on the CTEP website for additional information. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 Cancer Trials Support Unit Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support Unit (CTSU) members' website.

This study is supported by the NCI CTSU.

IRB Approval:

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory

Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email (CTSURegPref@ctsu.coccg.org) or by calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an Active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

4.2.1 Additional site registration requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB signatory Institution; and
- Compliance with all applicable protocol-specific requirements (PSRs).

4.2.2 Protocol Specific Requirements for A082002 Site Registration

IROC credentialing:

This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. Only an individual with a primary role on a treating site roster can update the provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU members' website.

IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC Houston to verify credentialing status or to begin a new modality credentialing process.

To complete protocol-specific credentialing the RTI provider or enrolling site should follow instructions in the protocol to submit documentation or other materials to the designated IROC Quality Assurance (QA) center. Upon the IROC QA center approving

the RTI provider for the study modality, IROC will automatically send the approval to the Regulatory and Roster Maintenance applications to comply with the protocol specific requirement unless otherwise noted at the bottom of the IROC Credentialing Approval notification. IROC will continue to copy the provider and/or enrolling site on modality approvals.

Upon site registration approval in the Regulatory application, the enrolling site may access Oncology Patient Enrollment Network (OPEN) to complete enrollments. If the study is using the IROC integration suite, the enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen and may need to answer additional questions related to treatment in the eligibility checklist.

4.2.3 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org);
- Click on *Protocols* in the upper left of the screen:
    - Enter the protocol number in the search field at the top of the protocol tree; or
    - Click on the By Lead Organization folder to expand, then select *Alliance*, and protocol number *A082002*.
- Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.4 Submitting Regulatory Documents

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

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

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.

4.2.5 Checking Site Registration Status

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

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

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol

requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.2.6 Delegation of Task Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application which is accessible via the Delegation Log link on the CTSU members' website or directly at https://dtl.ctsu.org. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an Approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and to activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and describe DTL task assignments, CI signature, and CTEP registration requirements as well as include a Master Task List.

4.3 Patient Registration Requirements

4.3.1 Informed consent

The patient must be aware of the neoplastic nature of their disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

Patients with impaired decision making capacity may be enrolled on this study, where institutional policy and IRB of record allow.

4.3.2 Patient-reported outcomes

Patient questionnaire booklets

The current versions of the patient questionnaire booklets can be downloaded from the CIRB Approved Documents tab of the A082002 page of the CTSU website at the time of patient registration. Patient questionnaire booklets will only be available in English and Spanish.

4.4 Patient registration/randomization procedures

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

Requirements for OPEN access:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN Corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and

- Have an approved site registration for the protocol prior to patient enrollment.

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

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

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

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

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

4.5 Registration to Substudies and Companion Studies

4.5.1 Registration to Substudies described in Section 14.0

There are two substudies within Alliance A082002. These correlative science studies must be offered to all patients enrolled on Alliance A082002 (although patients may opt to not participate). These substudies do not require separate IRB approval. The substudies included within Alliance A082002 are:

- Blood collection in A082002, Alliance A082002-ST1 (Section 14.2)
- QOL study in A082002, Alliance A082002-HO1 (Section 14.1), available in English and Spanish

If a patient speaks English and Spanish and answers "yes" to "I choose to take part in the Quality of Life study and will fill out these forms," Question #1 in the model consent, they have consented to participate in the substudy described in Section 14.2. The patient should be registered to Alliance A082002-HO1 at the same time they are registered to the treatment trial (A082002). Questionnaires should be submitted per Section 6.4.

If a patient answers "yes" to "I agree that my samples and related health information may be used for the laboratory studies described above," Question #2 in the model consent, they have consented to participate in the substudy described in Section 14.1. The patient should be registered to Alliance A082002-ST1 at the same time they are registered to the treatment trial (A082002). Samples should be submitted per Section 6.2.

4.6 Stratification Factors and Treatment Assignments

The randomization routine is found in Section 13 (Statistical Considerations).

4.6.1 Stratification Factors

1. ECOG PS: 0-1 vs. 2
2. Systemic Therapy: Immunotherapy (IO) alone vs. IO plus Chemotherapy

4.6.2 Treatment Assignments

The factors defined in Section 4.6.1 will be used as stratification factors.

After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the standard block allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups.

Arm A: Immunotherapy based systemic therapy

Arm B: Immunotherapy based systemic therapy plus radiation therapy

5.0 STUDY CALENDAR

Pre-study Testing Intervals

The pre-study testing intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

To be completed ≤ 28 DAYS before registration: All laboratory studies, history and physical.

To be completed ≤ 42 DAYS before registration: CT scan which is utilized for tumor measurement per protocol

	Prior to Registration*	Day 1 of each cycle	Day 1 of Radiation (Arm B only)	Post-treatment follow-up**
Tests & Observations				
History and physical, weight, PS***	X	X	X	X
Height	X			
Pulse, Blood Pressure	X	X	X	
ECG	A			
Adverse Event Assessment	X (4)	X (4)	X	X
Registration Fatigue/Uniscale Assessment	X (1)			
Laboratory Studies				
Complete Blood Count, Differential, Platelets	X	X		
Serum Creatinine	X	X		
Albumin, glucose	X	X		
AST, ALT, Alk. Phos., Bili	X	X		
TSH	B	B		
Serum or Urine HCG	X (2)			
Staging				
CT Chest, including upper liver and adrenals	X (3)	C		C
Brain Imaging (MRI or CT)	X			D
Tumor Measurement	X			
Correlative studies: For patients who consent to participate				
QOL assessment	*See Section 6.4*.			
Tissue and Blood samples	*See Section 6.2*.			

* Labs completed prior to registration may be used for day 1 of cycle 1 tests if obtained ≤ 14 days prior to treatment. For subsequent cycles, labs, scans, tests and observations may be obtained ≤ 48 hours prior to day of treatment.

** For ongoing treatment-related toxicity ≥ Grade 2 (with the exception of fatigue and endocrinopathies being managed with physiologic replacement hormones) patients should be evaluated with post-treatment follow-up assessments every 4 weeks (+/-2 weeks) until all IO (immunotherapy)-related toxicity improves to Grade < 2.

All patients will be followed with history and physical, weight and PS every 3 months for 3 years, and then every 6 months for years 4-5 following randomization until disease progression. Following disease progression patients will be followed for survival every 6 months for up to 5 years following randomization. Follow with CT scans per Footnote C.

*** Drug dosages need not be changed unless the calculated dose changes by ≥ 10%.

1 To be completed after registration and ≤ 21 days prior to treatment.

2 For women of childbearing potential (see Section 3.2). Must be done ≤ 7 days prior to registration.

3 Baseline scans can include either: 1) a CT or MRI, or 2) an FDG-PET scan and diagnostic CT performed with both IV and oral contrast, and the CT acquired with 5 mm or less slice thickness. Supporting documentation is to be submitted, per Section 6.1.1.

4 For those patients who consent, the PRO-CTCAE should be administered prior to treatment and then on day 1 of each cycle.
Patients who develop Grade 3–5 AEs that are at least possibly related to immunotherapy are encouraged to enroll, if eligible, on A151804, "Establishment of a National Biorepository to Advance Studies of Immune-Related Adverse Events."

A. EKG and echocardiograms should be conducted as clinically indicated for any patients with a history of CHF or at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs.

B. Thyroid function tests should be done prior to registration if clinically indicated in all patients. Thyroid function testing includes TSH. Free T3 and free T4 should be performed if TSH is abnormal. Results are not required prior to dosing on a specified cycle. TSH is required < 48 hours prior to all even cycles.

C. For all patients, a CT scan of the chest, including upper liver and adrenals (with or without contrast) will be obtained every 12 weeks (+/- 2 weeks) for 3 years then every 6 months (+/- 4 weeks) for years 4-5 following randomization, until disease progression, death, or early withdrawal. Following disease progression CT scans will no longer be required. Once a patient progresses, follow the patient for survival every 6 months (+/- 4 weeks) for up to 5 years from the date of randomization or death.
If there is progressive disease but the investigator feels it appropriate to treat beyond progression, confirmatory scans should be performed obtained within 4-8 weeks if feasible, and no later than 3 months (in the absence of clinically significant deterioration). If confirmatory progression is not found every attempt should be made to perform the subsequent assessments at their next scheduled radiologic assessment.

D. Required only if patient had CNS metastasis at baseline. For patients without CNS metastasis, follow-up brain MRI required only if signs or symptoms suggestive of metastases develop.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

6.1.1 Data submission schedule

A Data Submission Schedule (DSS) is available on the CTSU study webpage.

6.1.2 Medidata Rave

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

Requirements to access Rave via iMedidata:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only or Rave SLA role must have at a minimum an Associate (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. No action will be required; each study invitation will be automatically accepted and study access in Rave will be automatically granted. Site staff will not be able to access the study in Rave until all required Medidata and study-specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

No action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application. Pending study invitations (previously sent but not accepted or declined by a site user) will be automatically accepted and study access in Rave will be automatically granted for the site user. Account activation instructions are located on the CTSU website in the *Data Management* section under the Data Management Help Topics > Rave resource materials (*Medidata Account Activation and Study Invitation*).

Additional information on iMedidata/Rave is available on the CTSU members' website in the *Data Management* > *Rave* section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

6.1.3 Data Quality Portal

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

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

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

6.1.4 Supporting documentation to be submitted to the Alliance

This study requires supporting documentation for diagnosis, response, and progression. Supporting documentation will include immunohistochemistry, pathology, and radiology reports. The following supporting documentation must be submitted at the required time points:

- Surgical pathology report
- PD-L1 report
- EGFR, ALK and ROS1 report
- Radiology report at study enrollment, each disease assessment and progression

Supporting documentation is to be submitted via Rave.

6.1.5 Rave-CTEP-AERS integration

See Section 9.1.1 for information regarding submission of adverse event information utilizing the Rave-CTEP-AERS integration.

6.1.6 ICAREdata®

Selected sites will be participating in the ICAREdata® project. - The Integrating Clinical Trials and Real-world Endpoints data (ICAREdata®) initiative is a program led by the Alliance Data Innovation Lab which is a component of the Alliance for Clinical Trials in Oncology.

The ICAREdata® project aims to expand the ability to achieve clinical research goals by providing new ways to collect data required for clinical trials. Today, virtually all clinical trials data are collected using special forms and computer applications, such as a software known as Medidata Rave. Instead of using these "add on" data collection systems, the ICAREdata® project will gather study data directly from the Electronic Health Record (EHR). As with all research data collections, data collected by the ICAREdata® project are stored in a secured repository.

Select institutions will be invited to participate and will receive training on the specific ICAREdata® requirements. As with all clinical trials data management, the nature of data collected using the ICAREdata® methods will be specific to a particular research protocol, and might include demographic information, diagnosis, laboratory values, physician assessments, and other results, such as adverse event reports. The Data Innovation Lab will manage data collection, working with the IT department at these sites to configure the EHR to deliver mCODE (minimal common oncology data elements) data and other required outcome data in the form of structured ICAREdata® questions. Clinicians will provide the study required data by answering standardized questions or data fields as part of their encounter visit with the subjects. The IT departments will also work to implement the data transfer capability from the site EHR to the Alliance Data Innovation Lab via a secure/tested extraction method.

Investigators and research staff at limited select sites that utilize the EHR research adverse events data collection tool will be asked to complete a brief voluntary survey. The research staff and investigator's email addresses at these predetermined sites will be submitted at the time of Adverse Events data collection tool training. The survey will take approximately 5 minutes to complete. It will solicit feedback on the investigators and study staff experiences including overall staff acceptance, usability, preferences for using the tool to document any adverse events. The plan survey administration timeline is at baseline and then a select period thereafter. Ultimately, the survey will be used to gather general feedback of the usability of the tool across multiple site level stakeholders.

Data will be encrypted at-rest and in-transit using a secure interface with an established authorization protocol handled by the ICAREdata® infrastructure. Alliance Data Lab staff will issue a client ID and credentials to participating ICAREdata® sites that will be used to authenticate those sites for access to the ICAREdata® infrastructure service/extraction method to submit data. The clinical site will be responsible for securely storing these credentials (e.g., installed on a server that an IT administrator manages) such that those staff responsible for submitting data will have the proper access. Data will be stored and maintained in HIPAA compliant data repositories (such as AWS) and access controlled by an identity server with strict management to ensure confidentiality, integrity, and availability of PHI. Strict access controls will be maintained. Only authorized Alliance Data Lab personnel will have access to the data and scope of access will be further controlled based on role and level of need to know.

Participating institutions may email the Alliance Data Innovation Lab at ICAREdata@alliancefoundationtrials.org with any questions.

6.2 Specimen collection and submission

Correlative Science Manual (CSM): The Alliance A082002 Correlative Science Manual (CSM) contains instructions for specimen collection, processing, and shipping. The manual can be found on the study-specific webpage on the Alliance, BioMS, and CTSU websites. Questions regarding the CSM should be directed to the contact(s) specified in the manual.

For patients registered to substudy A082002-ST1: All participating institutions must ask patients for their consent to participate in the correlative substudies planned for Alliance A082002-ST1, although patient participation is optional. Rationale and methods for the scientific components of these studies are described in Section 14.0. For patients who consent to participate, tissue, and blood will be submitted at the following time points for these studies:

	After consent, prior to treatment	**Prior to treatment on Day 1 of Cycles 3, 5, 7, 9 and end of treatment***
For patients registered to A082002-ST1, submit the following		
Tumor tissue	X	
	Number and volume of tubes to draw	
Whole blood in EDTA tubes for plasma	3 x 10 ml	3 x 10 ml
Whole Blood in EDTA tubes for PBMC	2 x 10 mL	2 x 10 ml

*Once a patient discontinues therapy, obtain an end of treatment sample, if possible.

6.3 Digital radiation therapy data submission using Transfer of Images and Data (TRIAD)

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

6.3.1 TRIAD Access Requirements

- A valid Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) (CTEP-IAM) account.
- Registration and Credential Repository (RCR) registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR) registration type. Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

6.3.2 TRIAD Installations

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

6.3.3 Procedures for Data Submission via TRIAD

The list of data to be submitted for RT QA is detailed in Section 7.3.7.

6.3.4 Imaging Data Submission Methods

Data must be submitted according to the protocol requirements for ALL patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible.

DICOM images uploading is preferred to be submitted using TRIAD, however these methodologies are supported:

a. TRIAD-based (a PC with internet access and TRIAD software installation will be needed)

b. Web transfer-based (a PC with internet access and a web browser will be needed)

c. FTP transfer-based (a PC with internet access and any FTP software will be needed)

d. Mail/CD Shipment-based (only if electronic transfer approaches cannot be achieved)

Questions regarding image submissions can be sent to ALLIANCE082002@irocohio.org.

Detailed Steps of Data Submission

Collection of standard of care images is required. Images will be collected digitally for central archiving and curation. Imaging studies will be collected digitally of the following time points:

1) Baseline – within 42 days before registration

2) Restaging – every 12 weeks (+/-14 days) for 3 years then every 6 months for years 4-5 after randomization

3) Progression

4) Post-progression follow-up, including confirmatory scans at 4-8 weeks and no later than 3 months (in the absence of clinically significant deterioration).

The complete imaging data set in digital DICOM format will be submitted electronically to the Imaging and Radiation Oncology Core at Ohio (IROC Ohio) within no more than 3 business days upon the image acquisition completeness. BMP files, JPG files, or hard copies (films) are not acceptable. The raw data of the entire study should be saved until the imaging data is accepted by IROC Ohio

Sites need to de-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the Alliance patient ID number (e.g., 112136) and protocol number (e.g., A082002), respectively.

DICOM tag dates and times cannot be altered prior to submission as they are used to put submissions into context regarding patient treatment.

Additional changes to DICOM tags prior to submission impede further technical analysis and should be avoided whenever possible.

Imaging data should be submitted electronically to IROC Ohio via TRIAD, Web Transfer or FTP Transfer:

1) TRIAD based data transfer
The standard TRIAD based data transfer approach will be provided separately through IROC efforts via the specific trial e-mail ALLIANCE082002@irocohio.org per the request by participating sites before their first data submission.

2) Web Transfer
(http://upload.wci.uc.edu)
Any PCs with internet access and web browser (e.g., Chrome, Edge, Internet Explorer, Mozilla Firefox) can be used to web transfer DICOM images and other required files to IROC Ohio. The standard Web Transfer information will be provided separately through the specific trial e-mail ALLIANCE082002@irocohio.org per the request by participating sites before their first data submission.

3) FTP Transfer
Any FTP software can be used to initiate access to the secure FTP Server of IROC Ohio. The standard FTP access information will be provided separately through the specific trial e-mail ALLIANCE082002@irocohio.org per the request by participating sites before their first data submission.

4) Mail/CD Shipment
Only if electronic data transfer approaches cannot be achieved, the de-identified images in digital DICOM format can be burned to a CD and mailed to IROC Ohio. Submit only one patient's images per CD, with the patient's Alliance ID number, study type, date of scans, and name of submitting institution.

Submit these data to:
IROC Ohio
Attn: ALLIANCE A082002
Digital Futures Research Building, Suite 310
3080 Exploration Avenue
Cincinnati, OH 45206
Office: (513) 556-7920

Once the imaging data submission is done, send an e-mail to IROC Ohio at the specific trial email ALLIANCE082002@irocohio.org to inform that the study has been submitted from the institution. IROC Ohio will notify site and ALLIANCE A082002 imaging committee within 2 business days of the data receipt, and then, within 3 business days following the data receipt, of the quality check report.

Send any questions or problems about the data submission to IROC Ohio email ALLIANCE082002@irocohio.org or call +1-513-556-7920 for help.

Submission Deadlines

Complete submission of imaging acquisitions in DICOM format within 3 business days of image acquisition at the site.

6.4 Submission of Patient Completed Measures

The current version of the patient questionnaire booklets can be downloaded from the CIRB Approved Documents tab of the A082002 page of the CTSU website Booklets must be given to patients to complete and patients should be instructed to return the booklets/responses to site staff (either in person, by mail, by email, or by phone), and site staff will enter patient responses

into Rave. The method of administration (in person, by mail, etc.) should be documented in the source documents. At visits in which booklets are to be completed, the booklet should be given to the patient before any discussion of the patient's health status or test results. The method of collection should be documented in Rave. Booklet administration schedule is provided below.

Please note that PRO-CTCAE is contained in a separate booklet and is optional for all patients per the study calendar. The schedule below only pertains to patients who consent to participate in the Quality of Life study. Verbal administration of the measures for visually impaired patients is permitted if the measure and verbal administration of the measure is conducted in a language understandable to the patients.

Forms	After consent, prior to first treatment	After Cycles 2 and 8
For patients registered to A082002-HO1, submit patient-completed questionnaires* at the following time points:		
EORTC QLQ-C30 with LC-13	X	X

* Patients must complete the EORTC QLQ-C30 with LC-13 questionnaire in booklet format.

Once a patient discontinues therapy the QOL measure can be discontinued.

6.4.1 Patient Language Considerations

The QOL measures are available in English and Spanish. Ad-hoc translation of patient-completed measures is not permitted.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 14 days of registration.

For questions regarding treatment, please see the study contacts page.

It is acceptable for individual systemic treatment doses to be delivered ≤ a 24-hour (business day) window before and after the protocol-defined date for Day 1 of a new cycle. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Thursday through the following Monday. In addition, patients are permitted to have a new cycle of systemic therapy delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

This is a randomized trial. Protocol therapy will consist of a total of 18 cycles administered every 42 days, for a total of 2 years of therapy. Dosing frequency is dependent upon the investigator's choice of systemic therapy.

Treatment will continue until disease progression and no longer benefiting clinically, or unacceptable adverse events. Treatment may continue beyond assessment of progressive disease (PD) provided the patient is clinically stable and felt to be continuing to benefit from therapy. A patient may be deemed clinically stable provided that no worsening of performance status has occurred, there have been no clinically relevant increases in disease-related symptoms such as pain or dyspnea that are thought to be associated with disease progression, and there has been no requirement for intensified management of disease-related symptoms, including increased analgesia, radiotherapy, or other palliative care. Repeat imaging should be obtained within 4-8 weeks if feasible, and no later than 3 months. If the subsequent scan shows additional new lesions or increase in new lesion size (sum of measurements ≥ 5 mm), treatment should be discontinued.

7.1 Patients will be randomized to one of 2 Arms:

- Patients in Arm A will receive treatment with immunotherapy (+/-chemotherapy).
- Patients in Arm B will receive treatment with immunotherapy (+/- chemotherapy) + radiation.

One Cycle = 6 weeks

7.2 Systemic Therapy (immunotherapy +/- chemotherapy)

Patients can be treated either with nivolumab/ipilimumab as below, or with any systemic therapy that incorporates a PD1/PDL1 antibody with chemotherapy per local standard.

7.2.1 Immunotherapy Alone, either non-squamous or squamous histology

Drug	Dose	Route	Treatment Day
Nivolumab	360 mg	IV over 30 minutes	Days 1 and 22 of each 6 week cycle
Ipilimumab	1 mg/kg	IV infusion over 30 minutes	Day 1 of each 6 week cycle

Patients will receive treatment with nivolumab 360 mg as an approximately 30-minute infusion every 3 weeks (Day 1, Day 22 of each 6-week cycle) and ipilimumab 1 mg/kg as an approximately 30-minute infusion every 6 weeks for a maximum of 24 months of uninterrupted treatment or until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. The drug administration order should follow institutional practice.

7.2.2 Treatment per local standard

Patients may receive any standard of care therapy as appropriate for their histology.

Treatment will continue for a maximum of 24 months of uninterrupted treatment or until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. The drug administration order should follow institutional practice.

7.3 Radiotherapy

Patients in Arm B will start treatment with immunotherapy (+/- chemotherapy) and receive radiation therapy to one site (8Gy x 3 fractions, administered every other day) within 60 days of randomization but not on days where systemic therapy is administered. The technique used to deliver the three fractions of 8 Gy (24 Gy total) is at the discretion of the treating radiation oncologist and can be SBRT, 3DCRT, IMRT, and in some cases electron therapy.

Patients in Arm B will receive three 8 Gy doses of radiation for a total dose of 24 Gy to a single cancer deposit. Each treatment will be delivered every other day but not on days systemic therapy is administered. In cases where the treated tumor is superficial, the use of an electron 3D conformal plan is permitted if it provides superior sparing of the organs-at-risk.

Selection of the Lesion to be Irradiated:

In general, the following guidelines in order should be followed when selecting the metastasis to be irradiated.

1. Do not re-irradiate a previously irradiated malignant lesion that has received > 5Gy.

2. Do not re-irradiate previously irradiated OAR that have reached the following tolerances in conventional fractionation (please contact study chairs if patient has previously received other fractionation for guidance on prior radiation delivery):
    - Spinal cord previously irradiated to > 40 Gy
    - Brachial plexus previously irradiated to > 50 Gy
    - Small intestine, large intestine, or stomach previously irradiated to > 45 Gy
    - Brainstem previously irradiated to > 50 Gy
    - Lung previously irradiated with prior V20Gy > 30%
3. Prioritize irradiating a visceral metastasis or the primary lesion over an osseous metastasis.
4. Of visceral metastases, prioritize treating a lung or nodal metastasis.
5. Prioritize treating a larger metastasis.
6. Limit the treated lesion diameter to 10 cm.

7.3.1 Technical radiotherapy requirements:

To successfully treat using radiation, centers must satisfy technology requirements for immobilization, simulation, planning, and image-guidance (IGRT) for radiotherapy described below in the following tables. Questions regarding appropriate technology for this protocol can be directed to the Radiation Oncology PI. While these techniques are commonly used for SBRT, for the purposes of this protocol, delivery of the protocol dose while adhering to normal tissue tolerances are the goals of protocol treatment and any techniques used to achieve these are acceptable.

Table 1.1 Technology Requirements for Protocol Radiation

Technology	Requirement	Comments
Beam Modality	MV Photons	For superficial tumors, electrons are allowed**. Other charged particles including protons, and heavier ions are not permitted.
Beam Energy	1 to 10 MV For targets in the lung, >50 % of target dose should be delivered by beams with energy ≤10 MV 10-18 MV may be used in selected cases with >10 cm from skin to target	Minimize use of high energy in lung. 6 MV or lower energies should be predominately used in low-density tissue.
Treatment Technique	3DCRT (static, arc) Intensity modulation (IMRT, VMAT)	Tomographic and robotic^ techniques allowed.
Image Guidance	Treatment machine must be equipped to provide daily volumetric 3D image guidance* (kV cone-beam, MV-cone beam, CT on rails, MRI)	Non-ionizing guidance (RF transponders, optical surface imaging) is permitted but does not preclude the volumetric imaging requirement. Use of 2D orthogonal image guidance (kV OBI, ExacTrac) is permitted for targets with implanted fiducials

		or spinal targets but does not preclude the volumetric imaging requirement.

***Note:** Each treatment fraction must be documented with volumetric imaging to enable delivered dose assessment with the exception of a) robotic systems that do not possess this capability and b) treatments delivered with electrons.

****Exception:** Select metastases located within 2cm of the skin may be targeted with a 3D conformal plan developed with *electron beams*. In these cases, the institution must be capable of generating a 3D conformal plan calculated on a CT scan. All calculation algorithms for electrons are permitted (e.g., pencil beam, Monte Carlo). If the skin normal tissue constraints cannot be met with an electron plan, 3D conformal radiation approach with photons should be used instead.

^Note: Robotic techniques without the ability to acquire volumetric image guidance (e.g., CyberKnife) are excluded from the volumetric imaging requirement.

Table 1.2 Simulation Guidelines

Topic/Parameter	Guideline*
Immobilization	Custom immobilization with appropriate clinical devices to ensure reproducibility is required. Patient comfort should be prioritized. Positioning the patient on the treatment couch without any support is discouraged.
Motion Assessment	Ascertain the characteristics of target (and normal tissue) motion with regard to magnitude (amplitude), timing (period), and regularity to determine the need or success of motion control. This is carried out both in simulation and treatment using real time monitoring (e.g., fluoroscopy, 4D CT, beacon tracking, etc.).
Motion Control	Motion control is strongly encouraged when the GTV excursion > 1 cm in any direction. Typical motion control maneuvers include inhibition strategies (e.g., abdominal compression and active breath hold), tracking based on a motion model, and gating to part of the breathing cycle, but others may be applicable. Internal organ management maneuvers must be reliable enough to ensure that the GTV does not deviate beyond the confines of the PTV with any significant probability (i.e., < 5%).
CT Slice Thickness	Within 10cm of the PTV, ≤3 mm is recommended. Do not exceed 3 mm. Slices of 1-2 mm are recommended for tumors that are 1 cm or less in the largest dimension.
Use of Contrast	IV contrast is required for treatment of a metastasis in the liver. For targets in other sites, IV contrast is encouraged for better delineation between tumor, pathologic lymph nodes, atelectasis, and vascular structures as well as better definition of normal tissue contours. Oral contrast can be used for OAR delineation at the clinical discretion of the treating physician. Generally, contrast scans are acceptable for dose calculations, although density overrides may be applied in areas of strong contrast (e.g., oral contrast in esophagus). No overrides should be used in the GTV.

CT Scan Range	The CT scan range should include the entirety of the organ that the metastasis to be treated resides in. Additionally, at minimum it should be 10 cm superior and inferior to the treated tumor.

***Note:** A target amenable to treatment with electron beams should adhere to these guidelines. If motion for such a target > 1cm, please consider instead the use of a 3DCRT technique with photon beams.

Table 1.3. IGRT Motion Assessment/Management Recommendations for Simulation and Treatment

Treatment Technique	Recommended Method for Motion Assessment During Simulation	Minimum Method for Motion Assessment During Simulation	Scan(s) Recommended for Treatment Planning	Imaging Recommended for Treatment
Free-breathing using an internal gross target volume (IGTV) approach including abdominal compression	4D CT or fluoroscopy as long as tumor can be directly visualized	Repeated slow acquisition CT scanning through the target (to sample motion) fused to the planning CT dataset	Average intensity projection (AIP) scan from a full field-of-view 4D CT for dose calculations; Maximum intensity projection (MIP) scan to aid IGTV definition; Free-breathing scans are not recommended.	Free-breathing 3D IGRT to ensure visible tumor aligns to IGTV*
Gating with a gating window	4D CT	Exhale CT plus fluoroscopy (free-breathing + fluoroscopy strongly discouraged due to baseline shift)	Reconstructed average of gating window scans from 4D CT. Maximum intensity projection (MIP) scan limited to gating window to aid IGTV definition.	Gated 3D IGRT or fluoroscopy; if not available, then free-breathing CT to ensure visible tumor aligns to MIP contour from 4D CT limited to the gating window
Breath hold (i.e., ABC)	Reproducibility of breath hold confirmed (examples: multiple low dose scans over tumor, repeat fluoroscopy or scout images)	N/A	Scan in breath hold position (inhale recommended since it maximizes lung volume)	Gated 3D IGRT; if not available use manual beam-hold during CBCT acquisition over multiple breath-holds to ensure tumor aligns to IGTV*

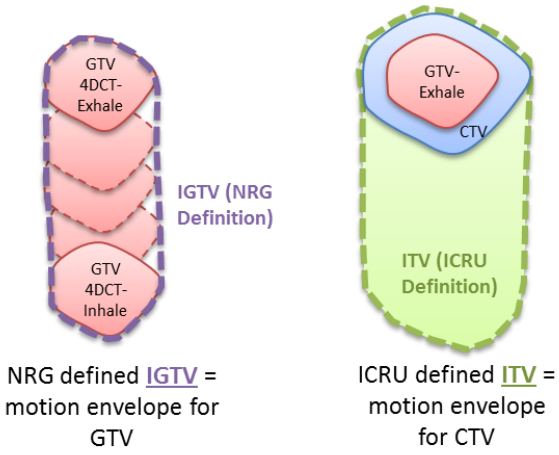
Tracking^	4D CT or breath hold CT	N/A	4D CT or breath hold CT	Volumetric imaging or real-time imaging of tumor surrogate required based on treatment machine capabilities.

***Note:** IGTV is defined in Section 7.3.2. In the case when tumor is not visible, please use an appropriate organ surrogate for alignment (i.e., liver as surrogate for a non-visible liver metastasis).
^**Note**: Tracking methods refer to use of robotic or similar systems that provide real-time imaging (i.e., CyberKnife, ViewRay).

7.3.2 Target Volumes and Margins

Definitions of GTV, CTV, IGTV, PTV:

- GTV: The GTV will consist of all known radiographic, metabolic, and clinical extent of the metastasis to be treated as contoured on the planning CT scan.
- For tumors with respiratory motion, the motion encompassing GTV will be defined at the internal gross tumor volume (IGTV). Note that the term "ITV" is explicitly avoided to prevent confusion between a motion encompassing CTV and GTV:



- The GTV (or IGTV) = CTV
- The PTV = IGTV (or GTV when strict motion control is applied/unnecessary) + 5mm

All PTV structures must be named for digital RT data submission as listed in the table below.

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Standard Name	***Description***
PTV_2400	PTV to be treated to 2400cGy.
GTV_2400	GTV to be treated to 2400cGy.

IGTV_2400	IGTV to be treated to 2400cGy.
PTV20	PTV with 2cm expansion
E-PTV_2400	External minus PTV
E-PTV20	External minus PTV_20 (PTV with a 2 cm expansion)

7.3.3 Organs-At-Risk (OAR) Naming/Delineation

Note: All structures must be named for digital RT data submission as listed in the table below.

Resubmission of data may be required if labeling of structures does not conform to the standard name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Standard Name	***Description***
BileDuct_Common	Common Bile duct
Bladder	Bladder
BrachialPlex_L	Left Brachial Plexus
BrachialPlex_R	Right Brachial Plexus
BrachialPlexs	Left plus Right Brachial Plexus
Bronchus	Carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus, right and left lower lobe bronchi
Bronchus_NAdj	Non Adjacent Bronchus
Bowel_Large	Large Bowel
CaudaEquina	Cauda equina
Duodenum	Duodenum
Esophagus	Esophagus
Esophagus_NAdj	Non Adjacent Esophagus
External	Body surface
Femur_L	Left whole Femur
Femur_R	Right whole Femur
Femurs	Combined Left and Right Femurs
GreatVes	Great Vessels of the heart (aorta, vena cava S&I, pulmonary A&V)
GreatVes_NAdj	Non Adjacent Great Vessels
Heart	Heart
Jejunum_Ileum	Both ileum and jejunum
Larynx	Larynx
Liver	Liver
Liver-GTV	Liver minus GTV
Lung_L	Left Lung
Lung_R	Right Lung
Lungs	Left plus Right Lungs
Lungs-GTV	Lungs minus GTV
Kidney_Cortex	Renal cortex for both Kidneys
PenileBulb	Penile Bulb
Rectum	Rectum
Rib	Ribs within 10cm of the PTV
SacralPlex	Sacral Plexus
Skin	Outer 0.5cm of the body surface (rind)
SpinalCord	Spinal cord
Stomach	Stomach

Trachea	Trachea
Trachea_NAdj	Trachea non-adjacent wall
Ureter	Ureter

Critical structure contours will be drawn in axial planes of the primary planning dataset. In general, critical structures should be contoured if they are found within an axial slice within 10 cm in the craniocaudal direction of the PTV to be treated on protocol. Parallel organs must be contoured in their entirety.

Detailed instructions for the contouring of these organs are as follows:

Spinal Cord
The spinal cord will be contoured based on the bony limits of the spinal canal. The spinal cord should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 below the inferior extent of the PTV.

Cauda Equina
Starting at the conus (end of spinal cord, typically around L1 or L2) include the entire spinal canal into the sacrum to the filum.

Sacral Plexus
Include the nerve roots from L5 to S3 on each side from the neuroforamina to the coalescing of the nerves at the obturator internus muscle.

Esophagus
The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The esophagus should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV.

Brachial Plexus
The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neuroforamine on the involved side from around C5 to T2. However, for the purposes of this protocol, only the major trunks of the brachial plexus will be contoured using the subclavian and axillary vessels as a surrogate for identifying the location of the brachial plexus. This neurovascular complex will be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the second rib. If PTV of all metastases are more than 10 cm away from the brachial plexus, this structure need not be contoured.

Heart
The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the inferior aspect of the aortic arch (aortopulmonary window) and extend inferiorly to the apex of the heart.

Trachea and Proximal Bronchial Tree
The trachea and proximal bronchial tree will be contoured as two separate structures using mediastinal windows on CT to correspond to the mucosal, submucosa and cartilage rings and airway channels associated with these structures. For this purpose, the trachea will be divided into two sections: the proximal trachea and the distal 2 cm of trachea. The proximal trachea will be contoured as one structure, and the distal 2 cm of trachea will be included in the structure identified as proximal bronchial tree.

Proximal Trachea
Contouring of the proximal trachea should begin at least 10 cm superior to the extent of the PTV for lung metastases or 5 cm superior to the carina (whichever is more superior) and continue inferiorly to the superior aspect of the proximal bronchial tree.

Proximal Bronchial Tree
The proximal bronchial tree will include the most inferior 2 cm of distal trachea and the proximal airways on both sides. The following airways will be included according to standard anatomic relationships: the distal 2 cm of trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the lingular bronchus, and the right and left lower lobe bronchi. Contouring of the lobar bronchi will end immediately at the site of a segmental bifurcation. If there are parts of the proximal bronchial tree that are within GTV, they should be contoured separately, as ―proximal bronchial tree GTV‖, not as part of the ―proximal bronchial tree.

Lungs
Both the right and left lungs should be contoured individually (Lung_L, Lung_R) and also combined as one structure (Lungs). Contouring should be carried out using pulmonary windows. All inflated and collapsed lung should be contoured; however, gross tumor (GTV) and trachea/ipsilateral bronchus as defined above should not be included for the structure created and labeled as Lungs - GTV.

Skin
The skin will be defined as the outer 0.5 cm of the body surface. As such it is a rind of uniform thickness (0.5 cm) which envelopes the entire body in the axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations (e.g., the scalp on the top of the head).

Great Vessels
The great vessels (aorta and vena cava, not the pulmonary artery or vein) will be contoured using mediastinal windowing on CT to correspond to the vascular wall and all muscular layers out to the fatty adventitia. The great vessel should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV. For right sided tumors, the vena cava will be contoured, and for left sided tumors, the aorta will be contoured.

Non-adjacent Wall of a Structure
For the esophagus, trachea and proximal bronchial tree, and great vessels, the nonadjacent wall corresponds to the half circumference of the tubular structure not immediately touching the GTV or PTV, these contours would start and stop superiorly and inferiorly just as with the named structure. The half lumen of the structure should be included in this contour.

Stomach
The entire stomach and its contents should be contoured as a single structure as a continuation of the esophagus and ending at the first part of the duodenum.

Duodenum
The wall and contents of the 1st, 2nd, and 3rd parts of the duodenum will be contoured as one structure beginning where the stomach ends and finishing as the superior mesenteric artery crosses over the third part of the duodenum.

Jejunum/Ileum (Small bowel)

As a conglomerate of bowel loops within the abdomen distinguished from stomach, duodenum, and colorectum.

Bowel (Large)
From the ileocecal area to include the ascending, transverse, descending and sigmoid colon as one structure.

Rectum
The entire rectum with contents from the peritoneal reflection of the sigmoid to the anus.

Bladder
This organ will be contoured as bladder wall exclusive of urinary contents

Kidney (renal cortex)
Both the right and left kidney, excluding renal pelvis/collecting system, should be contoured in their entirety (the renal cortex)

Liver
The entire liver minus the GTV targets.

Bile ducts
May use the portal vein from its juncture with the splenic vein to its right and left bifurcation in the liver as a surrogate to identify the bile ducts.

Femoral Heads
The ball of the head and socket joint.

Rib
Ribs within 10 cm of the PTV should be contoured by outlining the bone and marrow. Typically, several portions of adjacent ribs will be contoured as one structure. Adjacent ribs, however, should not be contoured in a contiguous fashion (i.e., do not include the inter-costal space as part of the ribs).

PTV + 2 cm
As part of the QA requirements for ―low dose spillage‖ listed above, a maximum dose to any point 2 cm away in any direction is to be determined (D2cm). To facilitate this QA requirement, an artificial structure 2 cm larger in all directions from the PTV is required. If possible, this structure should be constructed as a single contour that is 2 cm larger than the PTV.

Other Structures
The constraints tables below contain other structures. These are required if the structure is within 10 cm of the PTV.

7.3.4 Treatment Planning Guidelines

Table 1.4 Summary of General Treatment Planning Guidelines

Number of Beams	Given that the protocol doses are unlikely to exceed OAR tolerances, any beam arrangement that achieves protocol dose specifications and meets protocol OAR constraints is acceptable. For SBRT plans, historically 7-13 static radiation beams with equal weighting are generally suitable and it was recommended that at least 10 beams be used when possible. Note that dose should be properly distributed between beams due to skin toxicity considerations. Similarly, arcs should cover an appropriate range ($\geq 340^{o}$) so

	as to deliver a safe dose to the skin. Single arc plans may be suitable for simple geometries while additional arcs are preferred for more complex geometries.
Beam Arrangement	Coplanar or non-coplanar (non-coplanar are encouraged), non-overlapping, non-opposing beams or arc therapy (non-coplanar arcs encouraged to improve conformity and OAR sparing in complex geometries). Combination of static and arc beams allowed. Gantry clearance verification prior to treatment is recommended.
Minimum Field Size	As planning dictates although only the smallest field size accurately commissioned (e.g., small field output factors are within 5% of published standards or values) at the institution should be used. Because of concerns with small field dosimetry, field sizes above 2 cm x 2 cm are preferable.
Dose Calculation Algorithm*	Modern algorithms that accurately handle tissue heterogeneity and scatter should be used. IROC maintains an updated list of approved algorithms (http://irochouston.mdanderson.org/RPC/home.htm). Density corrections must be applied. Density overrides of the GTV are not recommended for photon treatment.
Dose Grid Resolution	3 mm x 3 mm dose grid resolution or smaller is required. Use of 2 mm x 2 mm is recommended, especially for targets less than 2 cm in diameter.

***Note:** For treatment of a superficial metastasis with electrons, the institution must be capable of generating a 3D conformal plan calculated on a CT scan. All calculation algorithms for electrons are permitted (e.g., pencil beam, Monte Carlo).

Table 1.5 Dosimetric Guidelines for Target Coverage

Metric	Guideline
Dose Heterogeneity within PTV	Rather than prioritizing target dose homogeneity, Protocol radiation treatment planning prioritizes adequate minimum target coverage and rapid dose fall-off gradients outside of the target. This is achieved using typical normalization of 60-90% with the hotspot located within GTV*.
R100% (Rx Isodose volume/PTV) See Table 1.6 below.	Every attempt should be made to achieve R100% <1.2, unless the block/MLC margin is larger than PTV to satisfy small field dosimetry criteria. Avoid dose > 105% of the prescription dose outside of the PTV.
R50% (50% Rx Isodose volume/PTV) D2cm[%] (Max dose at 2cm from PTV) See Table 1.6 below.	Effort should be made to reduce the 50% isodose volume and the maximum dose at 2cm.

***Note**: If target overlaps with OAR please use planning priorities in Section 7.3.5 to determine dose coverage.

Table 1.6 Recommendations for Allowable Dose Spillage

PTV Volume (cc)	**R50%** Ratio of 50% Isodose Volume to the PTV Volume		**D2cm**[%] Maximum Dose at 2 cm from PTV in any direction as % of Prescription Dose	
	Per Protocol	Acceptable	Per Protocol	Acceptable

		Variation		Variation
1.8	<5.9	<7.5	<50.0	<57.0
3.8	<5.5	<6.5	<50.0	<57.0
7.4	<5.1	<6.0	<50.0	<58.0
13.2	<4.7	<5.8	<50.0	<58.0
22.0	<4.5	<5.5	<54.0	<63.0
34.0	<4.3	<5.3	<58.0	<68.0
50.0	<4.0	<5.0	<62.0	<77.0
70.0	<3.5	<4.8	<66.0	<86.0
95.0	<3.3	<4.4	<70.0	<89.0
126.0	<3.1	<4.0	<73.0	<91.0
163.0	<2.9	<3.7	<77.0	<94.0

Note: For values of PTV dimension or volume not specified, linear interpolation between table entries is required.

Note: For tumors within 2 cm of the skin, it may be difficult to meet the values for D2cm and R50%. In these cases, these criteria will not be applied.

7.3.5 Treatment Planning Priorities

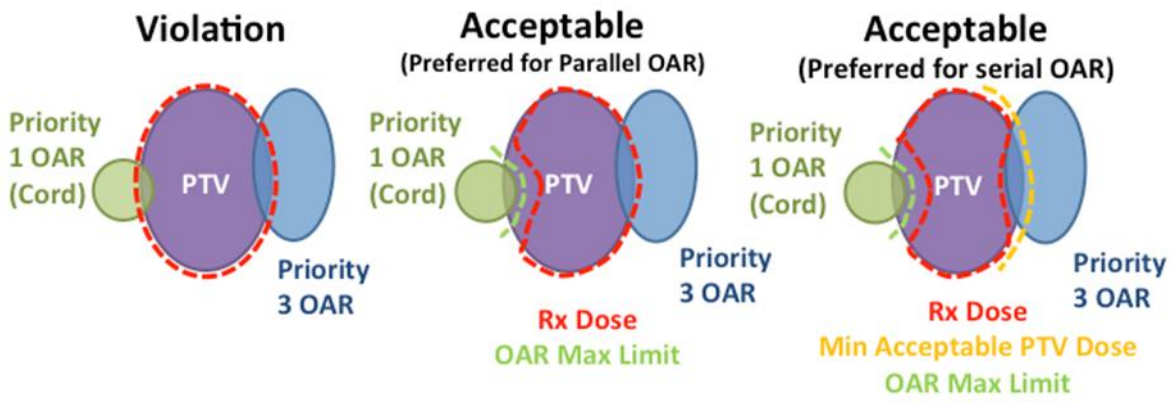
In general, attempts should be made to successfully satisfy all of the treatment planning criteria without deviation. In some circumstances, improvements can be made to the dosimetry plan beyond simply meeting the specified goals. In other circumstances, it may not be possible to meet the per protocol or variation acceptable criteria for all metrics. In cases where tradeoffs are required, the priorities listed in Table 1.7 should be followed. Figure 1 demonstrates these priorities graphically.

Table 1.7 Treatment Planning Priorities

Planning Priority	Instructions
1	Respect constraints for all priority 1 OAR in Table 1.9 regardless of the dose delivered to the PTV*.
2	Meet dose "compactness" constraints by: a) Covering 95% of the PTV with the prescription isodose (or at a minimum the variation acceptable dose in Table 1.8). b) Limiting the hotspot (>100% of the prescribed dose) volumes and limiting their location to within the PTV volume. In cases where the PTV overlaps with OARs, it is recommended to allow variation acceptable levels of target coverage and to minimize hotspots in OAR overlap areas. Intensity modulated planning techniques may be beneficial in this scenario. c) Limiting intermediate dose spillage (D2cm and R50) according to Table 1.6.
3	Meet critical structure constraints other than those listed in 1 (i.e., priority 3 in Table 1.9).

***Note**: PTV coverage that falls below the variation acceptable range in Table 1.8 in order to meet priority 1 OAR constraints will not be scored an unacceptable deviation.

Figure 1 Graphical representation of preferred planning tradeoffs in areas of overlap. See Table 1.7 for more detail.



7.3.6 Dose Constraints

Table 1.8 Dosimetry Compliance for Target

Structure	Dosimetric Parameter	Per Protocol	Variation Acceptable
PTV_2400	**D95%[Gy]**	**24**	**22.5-25.6 (excluding 24)**

Table 1.9 Normal Structure Constraints and Compliance Criteria

Serial Organ	Dosimetric Priority	Volume	Volume Dose (Gy)
Spinal Cord	1	<0.03 cc	22.5
		<1.2 cc	13
Ipsilateral Brachial Plexus	1	< 0.03 cc	26
		<3 cc	22
Cauda Equina	1	<0.03 cc	22.5
		<5 cc	21.9
Sacral Plexus	1	<0.03 cc	24
		<5 cc	22.5
Trachea and Ipsilateral Bronchus (Non-adjacent wall)	3	<0.03 cc	30
		<5cc	25.8
Esophagus (Non-adjacent wall)	1	<0.03 cc	27

		<5cc	17.7
Heart/Pericardium	1	<0.03cc	30
		<15 cc	24
Great vessels (Non-adjacent wall)	3	<0.03cc	45
		<10 cc	39
Skin (non-tumor involved)	1	<0.03cc	33
		<10cc	31
Stomach	1	<0.03cc	30
		<10cc	22.5
Duodenum*	1	<0.03cc	24
		<10cc	15
Jejunum/ileum*	1	<0.03cc	27
		<30cc	17.4
Bowel*	1	<0.03 cc	34.5
		<20cc	24
Rectum*	3	<0.03 cc	49.5
		<3.5 cc	45
		< 20 cc	27.5
Bladder	3	0.03cc	33
		<15 cc	16.8
Ureter	3	<0.03 cc	40
Penile bulb	3	< 3cc	25
Femoral heads	3	<10 cc	24
Bile duct	3	< 0.3 cc	36
Renal hilum/vascular trunk	3	<15 cc	19.5

Rib	3	< 0.03 cc	50
		<5 cc	40
Parallel Organ		**Volume**	**Volume Dose (Gy)**
Lung (total)	3	<15% lung volume	20
		< 37% lung volume	11
		≥1500 cc**	10.5
		≥1000 cc**	11.4
Total Kidney	3	≥200cc**	15
Liver	3	≥700 cc**	17.1

*__NOTE:__ Avoid circumferential irradiation.
**__NOTE:__ These are complementary volumes or "cold volumes" for parallel tissues equal to the minimum volume of tissue receiving the indicated dose or less.
NOTE: For all priority-1 OAR, these are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation.

Table 1.10 OAR Compliance Criteria

Structure	Dosimetric Parameter	Per Protocol	Variation Acceptable
OAR priority 1	Maximum point dose* & Dose volume constraint	See Table 1.9	Must meet constraints in Table 1.9
Serial OAR priority 3	Maximum point dose* & Dose volume constraint	See Table 1.9	< 25.2 Gy** (105% of prescription dose)
Parallel OAR priority 3	Dose volume constraint	See Table 1.9	< 105% of dose in Table 1.9

*__Note:__ Maximum point dose is assessed using dose to a volume of 0.03cc.
**__Note:__ This dose is considered acceptable only when OAR are adjacent to or overlapping with PTV (see Figure 1). Otherwise, every effort should be to meet constraints in Table 1.9.

7.3.7 Submission of Digital Radiation Therapy Data

Submission of treatment plans in digital format as DICOM RT is required. Digital data must include CT scans, structures, plan, and dose files. This study uses TRIAD for RT data submission. Use of TRIAD requires several preliminary steps. See Section 6.3 for details. Additional information is available at:

https://triadinstall.acr.org/triadclient/

Any items on the list below that are not part of the digital submission may be included with the transmission of the digital RT data.

One week prior to the start of radiotherapy, the following data shall be submitted for pre-treatment review for all cases:

Treatment Planning System Output

RT treatment plans including CT, structures, dose and plan files. These items are included in the digital plan.

Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.

Supportive Data

Copies and reports of all imaging studies used to define the target volume.

Prescription sheet for entire treatment.

Forms

RT-1 Dosimetry Summary Form

Motion Management Reporting Form

Within 21 days of the completion of radiotherapy, the following data shall be submitted for all patients:

The RT-2 Radiotherapy Total Dose Record Form

A copy of the patient's radiotherapy record including the prescription, and the daily and cumulative doses to all required areas.

Documentation listed above showing any modifications from the original submission.

Supportive data and forms may be included with the transmission of the digital RT data or submitted separately via e-mail to DataSubmission@qarc.org.

Questions regarding the dose calculations or documentation should be directed to:

Protocol Dosimetrist
IROC Rhode Island QA Center
Phone: (401) 753-7600
Email: physics@qarc.org

7.3.8 Compliance Criteria

Definitions of Deviations in Dose to Target Volumes

Per Protocol: The dose to the target volume meets the "Per Protocol" requirements specified in Tables 1.6 and 1.8.

Variation Acceptable: The dose to the target volume falls within the "Variable Acceptable" range specified in Tables 1.6 and 1.8.

Deviation Unacceptable: The dose to the target volume falls outside the "Variable Acceptable" range specified in Tables 1.6 and 1.8.

Definitions of Deviations in Dose to Normal Structures

Per Protocol: The dose to normal structures meets the constraints in Table 1.9.

Variation Acceptable: The dose to normal structures falls within the "Variable Acceptable" range specified in Table 1.9 & 1.10.

Deviation Unacceptable: The dose to normal structures falls outside the "Variable Acceptable" range specified in Table 1.9 & 1.10.

Definitions of Deviations in Volumes Drawn

Per protocol: All specified contouring volumes are drawn as specified in the protocol.

Variation Acceptable: Delineation of specified contouring volumes deviates from protocol guidelines but the protocol intended volumes are adequately covered by the prescribed doses.

Deviation Unacceptable: Delineation of specified contouring volumes deviates significantly from protocol guidelines and the protocol intended volumes are not adequately covered by the prescribed doses

7.4 Imaging

Alliance A082002 prescribes limited image acquisition requirements, so any imaging acquired is expected to be done per protocol rather than the site's own standard of care. Specifically, CT, PET/CT, and MRI, must be acquired at the following times and subsequently submitted. Supporting documentation must accompany all submissions for this trial.

1. Baseline – either of the following options, plus an MRI (preferred) or CT of the brain:
    a. CT of the chest, including upper liver and adrenals
    b. PET/CT of the whole body or limited whole body
        i. CT must be of diagnostic quality
        ii. CT must have slice thickness 5mm or less
2. Restaging
    a. CT of the chest and abdomen
    b. Brain imaging only if metastases found at baseline or if signs/symptoms develop
3. Progression
    a. Once a patient has documented disease progression, CT scans will no longer be required per protocol.
4. Post-progression follow-up
    a. If there is progressive disease but the investigator feels it appropriate to treat beyond progression, confirmatory scans should be performed 4-8 weeks, and no later than 3 months, after the prior assessment of PD (in the absence of clinically significant deterioration). If confirmatory progression is not found every attempt should be made to perform the subsequent assessments at their next scheduled radiologic assessment.

8.0 DOSE AND TREATMENT MODIFICATIONS

8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

8.1.1 Patients should not receive any other treatment which would be considered treatment for the primary neoplasm or impact the primary endpoint.

This includes any surgical intervention, radiotherapy, cryotherapy, ablation, etc., performed on the primary neoplasm.

8.1.2 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study

treatment administration until 30 days after the final dose will be recorded in the medical records.

8.1.3 Treatment with hormones or other chemotherapeutic agents may not be administered except for steroids given for adrenal failure; hormones administered for non-disease-related conditions (e.g., insulin for diabetes); and intermittent use of dexamethasone as an antiemetic. **Systemic glucocorticoids** for any purpose other than to modulate symptoms from an event of clinical interest, supplement a known deficiency, or for use as a pre-medication for chemotherapeutic agents specified in the protocol are not allowed.

8.1.4 Antiemetics may be used at the discretion of the attending physician, with the exception of steroids above.

8.1.5 Diarrhea management is per the discretion of the treating physician. Diarrhea could be managed conservatively with medications such as loperamide.

Patients with severe diarrhea should be assessed for intravenous hydration and correction of electrolyte imbalances. For patients with clinically significant diarrhea consider immune-related toxicities and refer to Appendix IV.

8.1.6 Palliative radiation therapy may be administered. Prior to registration palliative radiotherapy to any site, including brain, is allowed but it must be completed 7 days prior to registration.

Patients who require palliative radiation therapy during protocol treatment will be removed from protocol therapy due to disease progression. However, patients who received palliative radiation prior to A082002 registration do not need to discontinue protocol therapy.

8.1.7 Alliance Policy Concerning the Use of Growth Factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 33: 3199-3212, 2015 and American Society of Clinical Oncology – American Society of Hematology Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin in Adult Patients with Cancer. J Clin Oncol 28:4996-5010, 2010.

Epoetin (EPO): Use of epoetin in this protocol is prohibited.

Filgrastim (G-CSF) tbo-filgrastim, and sargramostim (GM-CSF) is discouraged but permitted at the discretion of the treating physician. It is not allowed on days that patients receive radiotherapy.

Growth factors are NOT allowed during radiation therapy.

8.1.8 Hypersensitivity/infusion reactions

Treat hypersensitivity and infusion reactions to both chemotherapy and immunotherapy per institutional standards.

8.1.9 Immunotherapy Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Study Chair. The final decision on any supportive therapy or vaccination rests with the

investigator and/or the patient's primary physician; however, the decision to continue the patient on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, Study Chair, and the patient.

Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 30 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded.

Prohibited Concomitant Medications

Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- More than 21 days of antineoplastic systemic chemotherapy or biological therapy.
- More than 21 days of treatment with immunotherapy not specified in this protocol.
- More than 21 days of treatment with chemotherapy not specified in this protocol.
- Investigational agents other than specified in this protocol.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology or for chemotherapy premedication. The use of physiologic doses of corticosteroids may be approved after consultation with the study PI and CTEP.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Patients may receive other medications that the investigator deems to be medically necessary.

8.2 Chemotherapy Dose Modifications

Chemotherapy dose modifications can be administered at the discretion of the treating physician. Dose modifications can be performed per local standards.

8.2.1 Dose Modifications for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by actual weight without any modification unless explicitly described in the protocol. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of

drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with calculating doses based on actual body weight should recognize that doing otherwise would be a protocol violation. Physicians may consult the published guidelines of the American Society of Clinical Oncology Appropriate Chemotherapy Dosing for Obese Adult Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 30(13): 1553-1561, 2012.

8.3 Dose Modifications for Immunotherapy

Nivolumab + Ipilimumab Dose Modifications

- Dose reductions or escalations of nivolumab and ipilimumab are not permitted, only dose delays.
- If nivolumab and ipilimumab are held for > 6 weeks, discontinue protocol therapy.

Skin Rash and Oral Lesions	Management/Next Dose for Nivolumab and Ipilimumab
Grade 1	Continue protocol therapy.*
Grade 2	Hold* until ≤ Grade 1. Resume at same level
Grade 3	Hold* until ≤ Grade 1. Resume at same level at MD discretion
Grade 4	Discontinue protocol therapy.
* Patients with purpuric or bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome, toxic epidermal necrolysis (TEN), and autoimmune bullous disease including oral lesions of bullous pemphigus/pemphigoid. Pruritus may occur with or without skin rash and should be treated symptomatically if there is no associated liver or GI toxicity. Note skin rash typically occurs early and may be followed by additional events particularly during steroids tapering.	
Recommended management: See Skin AE management Algorithm.	

Liver function ALT/AST/Bilirubin	Management/Next Dose for Nivolumab and Ipilimumab
Grade 1	Continue protocol therapy.
Grade 2	Hold therapy until ≤ grade 1 then restart nivolumab/ipilimumab at same dose.
Grade 3	Hold therapy until ≤ grade 1 then restart nivolumab/ipilimumab at same dose at MD discretion if ≤ grade 1 within 7 days without steroids. If persistent or steroids are required, discontinue protocol therapy.
Grade 4	Discontinue protocol therapy.
Continued treatment of active immune mediated hepatitis may exacerbate ongoing inflammation. Holding drug to evaluate liver function test (LFT) changes and early treatment are recommended. LFT changes may occur during steroid tapers from other events and may occur together with other GI events including cholecystitis/pancreatitis. Please note: Grades for liver function follow UNL rather than multiples of baseline.	

Liver function ALT/AST/Bilirubin	Management/Next Dose for Nivolumab and Ipilimumab
Recommended management: See Hepatitis AE management Algorithm.	

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

Pancreatitis Amylase/Lipase	Management/Next Dose for Nivolumab and Ipilimumab
Grade 1	Continue protocol therapy if asymptomatic at MD discretion
Grade 2	Continue protocol therapy if asymptomatic at MD discretion. If symptomatic resume at same doe level when resolved.
Grade 3	Continue at same dose level if asymptomatic at investigator discretion. Patients should have imaging study when clinically indicated (grade 3 symptomatic pancreatitis) before resuming treatment. Patients who develop diabetes mellitus should be taken off treatment.
Grade 4	Hold until grade 2. Resume at same dose level if asymptomatic. Patients who are symptomatic should have imaging study prior to resuming treatment and when clinically indicated. Patients who develop grade 4 symptomatic pancreatitis or diabetes mellitus should be taken off treatment.
Patients may develop symptomatic and radiologic evidence of pancreatitis as well as diabetes mellitus and diabetic ketoacidosis (DKA). Lipase elevation may occur during the period of steroid withdrawal and with other immune-mediated events or associated with colitis, hepatitis, and patients who have asymptomatic lipase elevation typically have self-limited course and may be retreated. For treatment management of symptomatic pancreatitis, please follow the Hepatic AE Management Algorithm.	

Pneumonitis	**Management/Next Dose for Nivolumab and Ipilimumab**
Grade 1	Hold dose pending evaluation and resolution to baseline including baseline pO_2. Restart at same dose after pulmonary and/or infectious disease (ID) consultation excludes lymphocytic pneumonitis.
Grade 2-3	Hold dose pending evaluation. Restart at same dose after pulmonary and/or ID consultation excludes ipilimumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Discontinue treatment if steroids are required.
Grade 3	Discontinue protocol therapy.
Grade 4	Discontinue protocol therapy.
Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified, including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Patients with new lung nodules should be evaluated for sarcoid like granuloma. Please consider recommending seasonal influenza killed vaccine for all patients.	
Recommended management: See Pulmonary Adverse Event Management Algorithm.	

Other GI, nausea, vomiting	**Management/Next Dose for Nivolumab and Ipilimumab**
Grade 1	Continue protocol therapy.
Grade 2	Hold pending evaluation for gastritis duodenitis and other immune adverse events or other causes. Resume at same dose level after resolution to Grade ≤ 1.
Grade 3	Hold pending evaluation until ≤ Grade 1. Resume at same dose level. If symptoms do not resolve within 7 days with symptomatic treatment, patients should discontinue protocol therapy.
Grade 4	Discontinue protocol therapy.
Patients with Grade 2 or 3 N-V should be evaluated for upper GI inflammation and other immune related events.	

Fatigue	**Management/Next Dose for Nivolumab and Ipilimumab**
Grade 1	Continue protocol therapy.
Grade 2	Continue protocol therapy.
Grade 3	Hold until ≤ Grade 2. Resume at same dose level.
Grade 4	Discontinue protocol therapy.
Fatigue is the most common AE associated with immune checkpoint therapy. Grade 2 or greater fatigue should be evaluated for associated or underlying organ involvement including pituitary, thyroid, and hepatic, or muscle (CPK) inflammation.	

Neurologic events	**Management/Next Dose for Nivolumab and Ipilimumab**
Grade 1	Hold dose pending evaluation. Once evaluation is complete, resume at same dose level.
Grade 2	Hold dose pending evaluation and observation. Hold until ≤ Grade 1 and then resume at same dose level. Discontinue therapy if treatment with steroids is required. Resume at same dose level for peripheral isolated n. VII (Bell's palsy).
Grade 3	Discontinue protocol therapy.
Grade 4	Discontinue protocol therapy.
Patients with any grade CNS events of aseptic meningitis, encephalitis, symptomatic hypophysitis, or myopathy, polymyositis. rhabdomyolysis, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, myasthenia gravis should be discontinue therapy once diagnosed.	
Recommended management: See Neurologic Adverse Event Management Algorithm.	

Endocrine Hypophysitis Adrenal Insufficiency	**Management/Next Dose for Nivolumab and Ipilimumab**
Grade 1	Hold pending evaluation for evidence of adrenal insufficiency or hypophysitis. Asymptomatic thyroid stimulating hormone (TSH) elevation may continue treatment while evaluating the need for thyroid replacement.
Grade 2-3	Hold until patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable off steroids for 2 weeks, then resume at same dose level.
Grade 4	Discontinue protocol therapy.
Note all patients with symptomatic pituitary enlargement, exclusive of hormone deficiency, but including severe headache or enlarged pituitary on MRI should be considered Grade 3 events. Isolated thyroid or testosterone deficiency may be treated as Grade 2 if there are no other associated deficiencies and adrenal function is monitored. Please evaluate pituitary function before beginning steroid therapy or replacement therapy of any kind. *Note patients with thyroiditis may be retreated on replacement therapy. Patients must be evaluated to rule out pituitary disease prior to initiating thyroid replacement.	
Recommended management: See Endocrine Management Algorithm.	

Fever	**Management/Next Dose for Nivolumab and Ipilimumab**
Grade 1	Continue protocol therapy. May hold if needed for evaluation, then resume at same dose level.*
Grade 2-3	Hold until ≤ Grade 1. Resume at same dose level.*
Grade 4	Discontinue protocol treatment.

Fever	**Management/Next Dose for Nivolumab and Ipilimumab**
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever.	
See Appendix IV regarding infusion reactions.	

Renal Toxicity	**Management/Next Dose for Nivolumab and Ipilimumab**
Grade 1	Monitor closely and continue protocol therapy.
Grade 2-3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Discontinue protocol therapy.
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever.	
Recommended management: AE management guidelines.	

Infusion Reaction	**Management/Next Dose for Nivolumab and Ipilimumab**
Grade 1	Monitor closely and continue protocol therapy.
Grade 2-3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Discontinue protocol therapy.
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever.	
Recommended management: See Section 8.1.9 and Appendix IV management guidelines.	

Cardiac *	**Management/Next Dose for Nivolumab and Ipilimumab Cardiac Toxicities**
< Grade 2	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize without evidence of myocarditis may resume therapy. If labs worsen or symptoms develop, then treat as below.
Grade ≥2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone and immune suppression as clinically indicated. If no improvement within 24 hours consider adding either infliximab, ATG or tacrolimus. May resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.

Grade ≥2 with confirmed myocarditis	Discontinue protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone. Add ATG or tacrolimus if no improvement.

*Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin

**Patients with evidence of myositis without myocarditis may be treated according as "other event"

Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.

ALL OTHER EVENTS	**Management/Next Dose for Nivolumab and Ipilimumab**
Grade 1	No change in dose.
Grade 2*	Hold until ≤ Grade 1 or baseline, then resume nivolumab/ipilimumab at same dose level.
Grade 3	Hold until ≤ Grade 1 OR baseline and patient no longer on steroid treatment if initiated (exceptions as noted below). Permanently discontinue for events with a high likelihood of morbidity or mortality with recurrent events.
Grade 4	Discontinue protocol therapy.

Modifications are applicable to toxicity that is deemed related to study drug (attribution of possible, probable, or definite).

*For any grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment, nivolumab and ipilimumab should be discontinued.

Recommended management: As clinically indicated.

- Any Grade 3 or 4 drug-related laboratory abnormality or electrolyte abnormality, that can be managed independently from underlying organ pathology with electrolyte replacement, hormone replacement, insulin or that does not require treatment **does not** require discontinuation.

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued study drug dosing should go off protocol treatment.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse

Events (CTCAE), Version 5.0. The CTCAE is available at ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

Clinician graded CTCAE is the AE safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items, but no protocol directed action will be taken. PRO-CTCAE is not intended for expedited reporting, real time review, or safety reporting.

Alliance A151804, "Establishment of a National Biorepository to Advance Studies of Immune-Related Adverse Events (irAEs)," is an NCI effort to obtain clinical data and biospecimens from patients who experience irAEs after treatment with immuno-oncology (IO) therapeutics. Sites who have this study open are encouraged to enroll patients to the study when they experience eligible irAEs.

9.1 Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0.

9.1.1 Rave-CTEP-AERS integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. Sites must initiate all AEs for this study in Medidata Rave.

Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 days after the last administration of the investigational study agent/intervention are collected using the Late Adverse Event form.

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

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query-free.

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

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form (i.e., checking the box *Send All AEs for Evaluation* and save the form). Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence that internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

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

- Study specific documents: *Protocols > Documents > Protocol Related Documents > Adverse Event Reporting*; and
- Additional resources: *Resources > CTSU Operations Information> User Guides & Help Topics.*

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

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

9.1.2 Solicited adverse events

The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

CTCAE v5.0 Term	**CTCAE v5.0 System Organ Class (SOC)**
Anemia	Blood and lymphatic system disorders
Hypothyroidism	Endocrine disorders
Pneumonitis	Respiratory, thoracic and mediastinal disorders
Neutrophil count decreased	Investigations
Platelet count decreased	Investigations
Rash maculo-papular	Skin and subcutaneous tissue disorders
Hyperglycemia	Metabolism and nutrition disorders

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a) **Adverse Events: Other CRF** - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) **Adverse Events: Late CRF** - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at: ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE. All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

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

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

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

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

Grade 1-3 Timeframes	Grade 4-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

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

Expedited AE reporting timeframes are defined as:

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

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

- Within 5 calendar days for Grade 4-5 SAEs
- Within 10 calendar days for Grade 1-3 SAEs

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

Effective Date: August 30, 2024

9.3.2 Expedited AE reporting timelines defined

- "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.
- "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.

Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under an IND.

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

9.3.3 Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements

All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.

Alliance A082002 uses a drug under a CTEP IND. The reporting requirements for investigational agents under a CTEP IND should be followed for all agents (any arm) in this trial.

Treatment expected adverse events include those listed in Section 10.0 and in the package insert.

CTEP-AERS reports should be submitted electronically.

Exclusions

≤ Grade 4 hematosuppression and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.

Grade 1-3 nausea or vomiting and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting

Grade 3 nausea or vomiting does not require AERS reporting, but should be reported via routine AE reporting.

Death

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

Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.

Pregnancy loss and neonatal death

Pregnancy loss is defined in CTCAE as "Death in utero." Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

New Malignancies

All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors.

Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

Secondary Malignancy

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

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

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

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via Rave.

Second Malignancy

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

9.4 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Nivolumab (NSC 748726)

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

presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2069 patients.* Below is the CAEPR for Nivolumab.

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

Version 2.5, June 10, 2023[1]

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

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

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

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Encephalopathy[3]	
		Facial nerve disorder[3]	
		Guillain-Barre syndrome[3]	
		Myasthenia gravis[3]	
		Nervous system disorders - Other (demyelination myasthenic syndrome)	
		Nervous system disorders - Other (encephalitis)[3]	
		Nervous system disorders - Other (meningoencephalitis)	
		Nervous system disorders - Other (meningoradiculitis)[3]	
		Nervous system disorders - Other (myasthenic syndrome)	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
		Reversible posterior leukoencephalopathy syndrome[3]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury[3]	
		Renal and urinary disorders - Other (Immune-related nephritis)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleural effusion[3]		
	Pneumonitis[3]		
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia (BOOP))[3]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme[3]	
	Pruritus[3]		***Pruritus[3] (Gr 2)***
	Rash maculo-papular[3]		***Rash maculo-papular[3] (Gr 2)***

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Skin and subcutaneous tissue disorders - Other (bullous pemphigoid)	
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)[3]		
	Skin hypopigmentation[3]		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

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

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

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

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

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

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

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis

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

EAR AND LABYRINTH DISORDERS - Vestibular disorder

EYE DISORDERS - Eye disorders - Other (iridocyclitis); Optic nerve disorder; Periorbital edema

GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Flatulence; Gastrointestinal disorders - Other (mouth sores); Vomiting

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Pain

HEPATOBILIARY DISORDERS - Bile duct stenosis

IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic microangiopathy); Immune system disorders - Other (limbic encephalitis)

INFECTIONS AND INFESTATIONS - Bronchial infection; Lung infection; Sepsis; Upper respiratory infection

INVESTIGATIONS - Blood lactate dehydrogenase increased; GGT increased; Investigations - Other (protein total decreased); Lymphocyte count increased; Weight loss

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Histiocytic necrotizing lymphadenitis)

NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Intracranial hemorrhage

PSYCHIATRIC DISORDERS - Insomnia

RENAL AND URINARY DISORDERS - Hematuria; Renal and urinary disorders - Other (tubulointerstitial nephritis)

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm; Cough; Dyspnea; Hypoxia

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Pain of skin; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea)

VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Vasculitis

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

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

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

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

Version 2.10, March 29, 2019[1]

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

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Testosterone deficiency[2]		
EYE DISORDERS			
	Eye disorders - Other (episcleritis)[2]		
	Uveitis[2]		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		***Colitis[2] (Gr 3)***
		Colonic perforation[3]	
	Constipation		
Diarrhea			***Diarrhea (Gr 3)***
	Enterocolitis		
	Esophagitis		
		Ileus	
Nausea			***Nausea (Gr 3)***
	Pancreatitis[2]		
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
		General disorders and administration site conditions - Other (Systemic inflammatory response syndrome [SIRS])	
		Multi-organ failure	
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
	Autoimmune disorder[2]		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Immune system disorders - Other (GVHD in the setting of allotransplant)[4]	
INFECTIONS AND INFESTATIONS			
		Infections and infestations - Other (aseptic meningitis)[2]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
		Lymphocyte count decreased	
	Neutrophil count decreased		
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		
	Hyperglycemia		
		Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Arthritis		
		Generalized muscle weakness	
	Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]		
NERVOUS SYSTEM DISORDERS			
		Ataxia	

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Facial nerve disorder[2]		
	Guillain-Barre syndrome[2]		
	Headache		
	Myasthenia gravis[2]		
		Nervous system disorders - Other (immune-mediated encephalitis)[2]	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
	Trigeminal nerve disorder		
PSYCHIATRIC DISORDERS			
		Psychiatric disorders - Other (mental status changes)	
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
	Renal and urinary disorders - Other (granulomatous tubulointerstitial nephritis)		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis		
		Respiratory failure	
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)	
		Respiratory, thoracic and mediastinal disorders - Other (lung infiltration)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Pruritus		***Pruritus (Gr 3)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
	Urticaria		
VASCULAR DISORDERS			
	Hypotension		

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

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

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

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

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

[6]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage,

Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (pure red cell aplasia)[2]; Febrile neutropenia

CARDIAC DISORDERS - Conduction disorder; Restrictive cardiomyopathy

EYE DISORDERS - Extraocular muscle paresis[5]; Eye disorders - Other (retinal pigment changes)

GASTROINTESTINAL DISORDERS - Colonic ulcer; Dyspepsia; Dysphagia; Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal hemorrhage[6]; Proctitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Non-cardiac chest pain

HEPATOBILIARY DISORDERS - Hepatic failure[2]

IMMUNE SYSTEM DISORDERS - Allergic reaction

INFECTIONS AND INFESTATIONS - Infection[7]

INVESTIGATIONS - Creatinine increased; Investigations - Other (rheumatoid factor); Lipase increased; Platelet count decreased; Serum amylase increased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Tumor lysis syndrome

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Joint range of motion decreased; Myalgia; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain

NERVOUS SYSTEM DISORDERS - Dizziness; Dysphasia; Ischemia cerebrovascular; Seizure

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia

RENAL AND URINARY DISORDERS - Proteinuria

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Cough; Dyspnea; Laryngospasm

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Skin hypopigmentation

VASCULAR DISORDERS - Flushing; Hypertension; Vascular disorders - Other (temporal arteritis)

Note: Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.0 DRUG INFORMATION

10.1 General Considerations:

The total administered dose of chemotherapy may be rounded up or down within a range of 10% of the actual calculated dose.

It is not necessary to change the doses of the drugs due to changes in weight unless the calculated dose changes by ≥10% or pre institutional practice.

All study agents are to be administered at the registering institution.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

10.2 Nivolumab (BMS-936558, MDX-1106, ONO-4538 NSC #748726, IND #129803, IND holder: DCTD, NCI)

Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB AURORA application. Access to AURORA requires the establishment of credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems, maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

Procurement

Nivolumab is an investigational agent supplied by the National Cancer Institute (NCI). Bristol-Myers-Squibb (BMS) will supply nivolumab to the DCTD/NCI and it will be distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI.

Drug Ordering

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

Study agent must be ordered after patient is registered to the treatment arm as no starter supplies are being provided for this study.

Submit agent requests through the PMB AURORA application. Access to AURORA requires the establishment of credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems, maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time or use the dialog function in AURORA to communicate with PMB staff. Refer to the PMB's website for specific policies and guidelines related to agent management.

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

Product Quality Complaint (PQC): A product quality complaint is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a study subject. Lot or batch numbers are of high significance and need to be provided where and when possible. PQC must be reported to the PMB as soon as the PQC is identified. Report PQC to PMB at PMBAfterHours@mail.nih.gov or by using the dialog function in AURORA to communicate with PMB staff.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- AURORA (formerly PMB Online Agent Order Processing (OAOP) application): https://ctepcore.nci.nih.gov/AURORA/
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

Formulation

Nivolumab Injection, 100 mg/10 mL (10 mg/mL), is a clear to opalescent, colorless to pale yellow liquid; light (few) particulates may be present. The drug is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated in sodium citrate, sodium chloride, mannitol, diethylenetriamine pentacetic acid (pentetic acid) and polysorbate 80 (Tween 80®), and water for injection. Dilute solutions of hydrochloric acid and/or sodium hydroxide may be used for pH adjustment (pH 5.5-6.5). Nivolumab injection is supplied as 100 mg vials (10 mg/mL) with a 0.7 mL overfill. It is supplied in 10 mL Type I flint glass vials, with fluoropolymer film-laminated rubber stoppers and aluminum seals.

Storage and Stability

Store intact vials refrigerated at 2º to 8ºC (36º to 46ºF), protected from light. Do not freeze. Do not shake. Unopened vials can be stored at room temperature (up to 25°C, 77°F) and room light for up to 48 hours. **Refer to the package label for expiration. If not used immediately, the infusion solution may be stored up to 7 days under refrigeration conditions (2° -8°C, (36°-46°F) and protected from light. The infusion solution may be stored at room temperature (up to 25°C, 77°F) and room light for a maximum of 8-hours, including the product administration period.** Caution: The single-use dosage form contains no antibacterial

preservative or bacteriostatic agent. Therefore, it is advised that the product be discarded 6 hours after initial entry.

Preparation

Withdraw the required volume of Nivolumab and transfer it into an intravenous container. Dilute Nivolumab with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a final volume of not more than 160 mL. For patients with body weight less than 40 kg, do not exceed a total volume of infusion of 4 mL/kg of body weight. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

After preparation, diluted solution may be stored at room temperature and room light for no more than 8 hours from the time of preparation to end of the infusion OR under refrigeration at 2 - 8°C and protected from light for no more than 7 days from the time of preparation to end of infusion.

Administration

Administer via intravenous infusion over approximately 30 minutes through an intravenous line containing a 0.2-micron to 1.2-micron pore size, low-protein-binding polyethersulfone membrane in-line filter. It is not to be administered as an IV push or bolus injection. Flush the intravenous line with 0.9% NaCl after each dose. Do not mix nivolumab with, or administer as an infusion with other medicinal products.

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

Drug Interactions

No drug interaction data is available at this time.

Pharmacokinetics

Single dose nivolumab pharmacokinetics

- **Distribution:** The mean volume of distribution varied between 83 mL/kg and 113 mL/kg across doses.
- **Half-life elimination:** The mean terminal half-life of a single dose of nivolumab ranged between 17 and 25 days across the dose range of 0.3 mg/kg to 10 mg/kg. The mean total clearance varied from 0.13 mL/h/kg to 0.19 mL/h/kg

Multiple dose nivolumab pharmacokinetics

- **Distribution:** Multiple-dose PK of nivolumab following Q2W dosing was linear with dose-proportional increase in Cmax and AUC(TAU) in the studied range of 0.1 mg/kg to 10 mg/kg. Nivolumab accumulation with Q2W dosing frequency was in the range of 2.9 to 3.3 based on AUC(TAU), 2.0 to 2.4 based on Cmax, and 3.1 to 4.8 based on Cmin.
- **Half-life elimination:** The mean of terminal half-life was 25.6 days and the typical clearance was 8.8 mL/h.

Adverse Events

Refer to CAEPR in Section 9.4.

Nursing Guidelines

- Nivolumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids. Additionally, combination therapy (with ipilimumab) tends to have a higher rate of immune mediated side effects.
- Diarrhea can be common and can be very severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.
- Rash/pruritis/dermatitis is seen. Patients should report any rash to the study team. Treat per Section 8.0 and monitor for effectiveness.
- Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.
- Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.
- Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysistis, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and "not feeling well." Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.
- Pancreatitis is possible with nivolumab. Instruct patients to report abdominal pain, nausea and vomiting to the study team.
- Patients who are started on steroid therapy for any side effects of nivolumab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.

Agent Shortages

Specific guidance on how to address agent shortages for patients already enrolled on a clinical study as well as how to manage potential enrollment of new patients is provided at https://ctep.cancer.gov/branches/pmb/drug_shortages.htm.

Treatment plan modifications being made to avoid immediate hazard to patients is permissible under the Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(4)(iii). In accordance with HHS regulations, local investigators must promptly inform the IRB of record of this unanticipated problem and the management plan for the trial.

10.3 Ipilimumab (BMS-734016, MDX-010, NSC#s 732442, IND #129803, IND holder: DCTD, NCI)

Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB AURORA application. Access to AURORA requires the establishment of credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE)

systems, maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

Procurement

Ipilimumab is an investigational agent supplied by the National Cancer Institute (NCI). Bristol-Myers-Squibb (BMS) will supply ipilimumab to the DCTD/NCI and will be distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI.

Drug Ordering

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

Study agent must be ordered after patient is registered to the treatment arm as no starter supplies are being provided for this study.

Submit agent requests through the PMB AURORA application. Access to AURORA requires the establishment of credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems, maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time or use the dialog function in AURORA to communicate with PMB staff. Refer to the PMB's website for specific policies and guidelines related to agent management.

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Product Quality Complaint (PQC): A product quality complaint is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a study subject. Lot or batch numbers are of high significance and need to be provided where and when possible. PQC must be reported to the PMB as soon as the PQC is identified. Report PQC to PMB at PMBAfterHours@mail.nih.gov or by using the dialog function in AURORA to communicate with PMB staff.

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- AURORA (formerly PMB Online Agent Order Processing (OAOP) application): https://ctepcore.nci.nih.gov/AURORA
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

Formulation

Ipilimumab injection, 200 mg/40 mL (5 mg/mL), is formulated as a clear to slightly opalescent, colorless to pale yellow, sterile, non-pyrogenic, single-use, isotonic aqueous solution that may contain particles. Ipilimumab Injection, 200 mg/40 mL, is supplied in 50-cc Type I flint glass vials, respectively, stoppered with gray butyl stoppers and sealed with aluminum seals. The drug product is formulated at a concentration of 5 mg/mL at a pH of 7.0.

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

Storage and Stability

Ipilimumab Injection, 200 mg/40 mL (5 mg/mL), must be stored refrigerated (2ºC to 8ºC) and protected from light. Ipilimumab injection must not be frozen. Partially used vials or empty vials of ipilimumab injection should be discarded at the site according to appropriate drug disposal procedures. **Refer to the package label for expiration.**

Ipilimumab injection may be stored undiluted 5 mg/mL or following dilution in 0.9% Sodium Chloride Injection, USP or 5% Dextrose in PVC, non-PVC/non-DEPH or glass containers for up to 24 hours at (2ºC to 8ºC).

Preparation

Allow the vials to stand at room temperature for approximately 5 minutes prior to preparation of the infusion. Withdraw the required volume of ipilimumab and transfer into an intravenous bag. Ipilimumab injection (5 mg/mL) may be diluted in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to concentrations between 1 mg/mL and 4 mg/mL. Mix the diluted solution by gentle inversion. Store the diluted solution for no more than 24 hours under refrigeration (2ºC to 8ºC, 36ºF to 46ºF) or at room temperature (20ºC to 25ºC, 69ºF to 77ºF).

Administration

Do not mix ipilimumab with, or administer as an infusion with, other products. Administer ipilimumab no sooner than 30 minutes after the nivolumab infusion is completed. Administer the diluted solution over approximately 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding in-line filter. Ipilimumab must not be administered as an IV push or bolus injection. Flush the intravenous line with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP after each dose.

Drug Interactions

No formal pharmacokinetic drug interaction studies have been conducted with ipilimumab.

Pharmacokinetics

Distribution: Vss: 7.21L

Half-life elimination: Terminal: 14.7 days

Renal impairment: The effect of renal impairment on the clearance of ipilimumab was evaluated in subjects with mild (GFR < 90 and >= 60 mL/min/1.73m^2; n=349), moderate (GFR < 60 and >= 30 mL/min/1.73m^2; n=82), or severe (GFR < 30 and > 15 mL/min/1.73m^2; n=4) compared to subjects with normal renal function (GFR >= 90 mL/min/1.73m^2; n=350) in population PK analyses. No clinically important differences in the clearance of ipilimumab were found between subjects with mild to moderate renal impairment and subjects with normal renal function. No specific dose adjustment is necessary in subjects with mild to moderate renal impairment.

Hepatic impairment: The effect of hepatic impairment on the clearance of ipilimumab was evaluated in 76 subjects with mild hepatic impairment (total bilirubin 1 to 1.5 x ULN or AST < ULN) compared to 708 subjects with normal hepatic function (total bilirubin and AST <= ULN). No clinically important differences in the clearance of ipilimumab were found between subjects with mild hepatic impairment and normal hepatic function. Ipilimumab has not been studied in patients with moderate (total bilirubin > 1.5 to 3 x ULN and any AST) or severe hepatic impairment (total bilirubin > 3 x ULN and any AST).

Adverse Events

Refer to CAEPR in Section 9.5.

Nursing Guidelines

- Ipilimumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids.
- Diarrhea can be common and can be very severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.
- Rash/pruritis/dermatitis is seen. Patients should report any rash to the study team. Mild rash may be able to be managed topically. Rarely TENS can be seen. Instruct patients with any rash (especially a blistering/peeling rash) and fever and/or lesions in the mouth to seek immediate medical attention.
- Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.
- Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.
- Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysitis, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and "not feeling well." Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.

- Patients who are started on steroid therapy for any side effects of Ipilimumab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.

Agent Shortages

Specific guidance on how to address agent shortages for patients already enrolled on a clinical study as well as how to manage potential enrollment of new patients is provided at https://ctep.cancer.gov/branches/pmb/drug_shortages.htm.

Treatment plan modifications being made to avoid immediate hazard to patients is permissible under the Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(4)(iii). In accordance with HHS regulations, local investigators must promptly inform the IRB of record of this unanticipated problem and the management plan for the trial.

11.0 MEASUREMENT OF EFFECT

Confirmatory scans should be obtained at least 4 weeks following initial documentation of objective response. This study uses RECIST criteria version 1.1 to confirm responses and to confirm disease progression. RECIST will be used to evaluate the primary endpoint.

11.1 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and will be 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, and should be chosen based on their suitability for accurate repetitive measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible repeated measurements in which case 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 LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease. **The irradiated lesion should not be used for judging response as it can confuse the observer.** Often lung lesions appear larger after radiation due to fibrosis in spite of tumor response as judged by PET

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

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

11.1.3 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 progression).

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

11.2 Non-target Lesions

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

11.2.1 Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis). Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

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

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

11.3 Cytology and Histology

If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

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

11.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see Section 11.6.1)

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

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

* Only for non-randomized trials with response as the primary endpoint.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration" on the Off-treatment Form (C-300) under "other." Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-measurable Disease (i.e., Non-target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

11.5 Guidelines for Evaluation of Measurable Disease

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

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

11.5.1 Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans). Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image

acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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

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

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

11.6 Confirmation Measurement/Duration of Response

11.6.1 Confirmation: To be assigned a status of PR or CR, changes in tumor measurements should be confirmed by repeat studies that should be performed at least 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks.

11.6.2 Duration of Overall Response: The duration of overall response is measured from the time measurement criteria are met for CR/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 complete response is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

11.6.3 Duration of Stable Disease

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

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Protocol Treatment

Protocol treatment is to continue for up to 2 years. Please see the study calendar (Section 5.0) and the treatment section (Section 7.0) for treatment and follow-up time periods. Protocol treatment is to continue until disease progression and no longer benefitting clinically or unacceptable toxicity.

12.2 Criteria for Discontinuation of Protocol Treatment/Intervention

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

- Treatment may continue beyond assessment of progressive disease (PD) provided the patient is clinically stable and felt to be continuing to benefit from therapy. A patient may be deemed clinically stable provided that no worsening of performance status has occurred, there have been no clinically relevant increases in disease-related symptoms such as pain or dyspnea that are thought to be associated with disease progression, and there has been no requirement for intensified management of disease-related symptoms, including increased analgesia, radiotherapy, or other palliative care. Repeat imaging should be obtained within 4-8 weeks if feasible, and no later than 3 months. If the subsequent scan shows additional new lesions or increase in new lesion size (sum of measurements $\geq$ 5 mm), treatment should be discontinued.
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression (if applicable)
- Patient non-compliance
- Pregnancy (if applicable)
- All women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
- The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent (if applicable)
- Surgical intervention, radiotherapy, cryotherapy, ablation, etc., is performed on the primary neoplasm or metastasis (other than radiation prescribed or palliative RT given prior to protocol therapy).

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

12.3 Follow-up

12.3.1 Duration of Follow-up

All patients will be followed until death, early withdrawal from the study or up to 5 years after randomization, whichever occurs first.

12.3.2 Follow-up for All Patients who are Randomized

- Clinical follow-up (e.g., CT scans) for all patients for tumor response and disease progression every 3 months for 3 years, then every 6 months for years 4-5 following randomization until disease progression.
- Survival follow-up for all patients until death or 5 years after randomization.

12.3.3 Follow-up for Specimen Submission

Patients will have an end of treatment submission for specimens. After the end of treatment submission there will be no further submissions.

12.4 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

12.5 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patient

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for ineligible patients who continue with protocol treatment

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for ineligible patients who discontinue protocol treatment

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

Follow-up for patients who are registered, but who never start study treatment

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are specified below.

Randomized phase II and phase III: Baseline, off treatment, and post-treatment follow up (i.e., relapse, progression, and survival) data submission required. See the Data Submission Schedule accompanying the All Forms Packet.

13.0 STATISTICAL CONSIDERATIONS

The primary objective of the phase II/III trial is to determine whether radiation (8Gyx3 every other day) plus IO provides better outcomes than IO alone in patients with stage 4 NSCLC, ECOG PS 0-2 and PD-L1(-). PD-L1 negatives are defined as the patients with PD-L1 expression level <1%. The PD-L1 testing will be performed locally at each enrolling site as standard of care and not at a central laboratory. The primary endpoint of the entire trial is overall survival (OS), which is the time between randomization and death of all causes. Progression-free survival (PFS), which is the time between randomization and progression or death, whichever comes first, will be used in the end of the phase II portion to make a Go/No-Go decision into the phase III portion.

Secondary Endpoint: Secondary endpoints include progression-free survival (PFS) per RECIST objective response rate (ORR, document both irradiated and un-irradiated areas) per RECIST, quality of life (QOL), and treatment-related adverse events.

13.1 Phase II/III seamless design

This trial uses a phase II/III seamless design. In the end of the phase II portion, a Go/No-Go decision will be made on progression-free survival (PFS) of the phase II patients. PFS is defined as the time from randomization to any documented progression per RECIST 1.1 or death due to any cause, whichever occurs first.

We expect to register approximately 427 patients with stage 4 NSCLC, ECOG PS 0-2 and PD-L1(-). Assuming 10% will not proceed to randomization due to ineligibility or early cancellation prior to treatments, we will randomize 384 patients. Assuming approximately 8 patients per month are randomized, it will take approximately 72 months (48 months for accrual and additional 24 months for follow-up after last enrollment) from study activation to observe the required number of deaths for the final analysis if the trial were not terminated early.

In the phase II portion, 100 eligible patients will be enrolled and randomized over approximately 13 months after the first enrollment. Once 74 progression events have been observed among these patients, a Go/No-Go test will be conducted. Under uniform accrual and exponential hazards, it takes approximately 6 months to observe the targeted number of PFS events. If Arm B is not significantly better than Arm A at a one-sided significance level of 0.10, indicating evidence that Arm B is unlikely better than Arm A when the phase II portion is finished, a No-Go decision will be made to terminate the entire trial early. If Arm B has longer PFS than Arm A with a one-sided p-value <0.10 or equivalently the Z-value is >1.28, a Go decision will be made and the trial will move into the phase III portion, in which additional 284 patients will be randomized over approximately 35 months. The final analysis will take place after 298 deaths are observed among the patients of the phase II and phase III portions combined.

As the expected accrual rate for PD-L1 negatives is approximately 8 patients per month, we will not suspend trial accrual to avoid an unnecessary disruption of recruitment momentum given the number of patients accrued over 6 months is relatively small (48 patients or <13% of the total sample size). However, if the average accrual rate of the phase II portion in the last 3 months is greater than 8 patients per month and we have reached 100 patients enrolled, we will temporarily suspend trial enrollment while the PFS data are maturing in the phase II patients over the period of 6 months.

13.2 Stratification

Stratification is based on ECOG PS (0-1 vs. 2) and systemic therapy (IO alone vs. IO plus chemotherapy).

Eligible patients will be randomized with equal allocation to radiation plus IO +/- chemotherapy (Arm B) versus = IO alone +/- chemotherapy (Arm A) with stratification on ECOG PS (0-1 vs. 2) and systemic therapy (IO alone vs. IO plus chemotherapy). Systemic therapy options for IO alone and IO plus chemotherapy can be found in Section 7.2. Randomization will be implemented using stratified permuted block algorithm. [16, 17]

13.3 Provide sample size with power justification

For the phase II portion, we hypothesize a hazard ratio (HR) of 0.55 (Arm A is the reference) to warrant continuing to the phase III trial. In the PEMBRO-RT study of radiation+ IO vs IO, subgroup analyses revealed a benefit for radiation with respect to PFS was seen in the PD-L1–negative subgroup (HR, 0.49, 95%CI 0.26-0.94, p=.03). The sample size of the phase II portion is 100 patients with 50 on each arm. With at least 74 PFS events for Arm A and Arm B combined, the phase II portion has approximately 90% power to detect a HR of 0.55 (λ_B / λ_A), a 81.8% improvement median PFS for Arm B over Arm A from 6 months to 10.9 months, at a one-sided significance level of 0.10. Assuming uniform accrual and exponential distribution for

OS in both arms, it takes approximately 6 months to observe 74 PFS events among the phase II patients. The choice of type I and II errors are justified by viewing the phase II portion as a randomized phase II screen design .[18] The trial will proceed into the phase III portion if the comparison between Arm A and Arm B shows has a positive effect for Arm B.

As reported in Checkmate 227, the median OS and 95%CI is 17.2 months (12.8-22.0) for NIVO+IPI in PD-L1(-) stage IV/recurrent NSCLC and the hazard ratio for IO vs. chemo is 0.62 (0.48-0.78). In the PEMBRO-RT study of radiation+ IO vs IO, subgroup analyses revealed a benefit for radiation with respect to survival only in the PD-L1 negative subgroup (HR=0.48, p=0.046). We are interested in testing a HR of 0.70 (λ_B/λ_A) for Arm B over Arm A, corresponding to approximately a 42.8% increase in median OS from 17 months to 24.3 months. A total of 298 deaths, observed in Arm A and Arm B combined, provides approximately 85% power to detect a HR of 0.70 with a type I error of 0.025 (one-sided) after adjusting for early stopping due to interim analyses (see next section). Assuming approximately 8 PD-L1 negatives per month are randomized, it will take approximately 72 months (48 months for accrual and additional 24 months for follow-up after last enrollment) from study activation to observe 298 deaths for the final analysis. Uniform accrual and exponential distribution for OS in both arms are assumed in the calculation.

With the increased number of Alliance sites and patient/caregiver strong desires for access to immunotherapy, we expect a monthly accrual of approximately 8 patients for randomization. Based on design parameters, the phase II portion accrual is estimated to take 13 months after study initiation, and the first interim analysis of futility (Go/No-Go decision) will take place the same time with at least 74 PFS events observed for Arm A and Arm B combined. Another 35 months from the end of phase II portion will be needed to complete the entire phase III accrual. Under the alternative hypothesis, the phase II/III trial is to take approximately 72 months from the first enrollment to reach the required 298 deaths for the final analysis.

13.4 Formal interim analysis

13.4.1 Interim Analysis Plan

The first interim analysis is to test futility of PFS and to make the Go/No-Go decision at the end of the phase II portion. The phase II analysis will take place when at least 74 PFS events have been observed. The trial will proceed into the phase III portion only if the p-value of the stratified log-rank test is <0.10 for PFS or the Z-value is >1.28.

After entering the phase III portion, two additional interim analyses on OS are to test both superiority and futility. Early stopping could occur for superiority (Arm B is superior to Arm A) or futility (Arm B is equivalent or inferior to Arm A) on OS at these interim analyses. Stratified log-rank test will be used to generate the Z-values and the one-sided p-values for both tests. The efficacy early stopping boundary is based on the Lan-DeMets implementation of O'Brien-Fleming-like boundary and the futility early stopping boundary is based on Freidlin, Korn and Gray (2010).[21,22] The second interim analysis will occur when approximately 195 deaths are available (65% information), which is expected to occur at 48 months of the trial, and has the corresponding early-stopping boundaries for efficacy and futility set at 2.64 and 0.20 (Z-value scale), respectively. The third interim analysis will occur when approximately 256 deaths are available (86% information), which is expected to occur at 60 months of the trial, and has the corresponding early-stopping boundaries for efficacy and futility set at 2.29 and 0.43 (Z-value scale), respectively. The final analysis will be tested with a total 298 deaths and a critical one-sided p-value at 0.0222 or equivalently a Z-value at 2.01. In the calculation, we have assumed that early stopping due to futility is not binding.

13.4.2 Study Monitoring by Alliance DSMB

The Alliance DSMB will review the study twice a year with respect to patient accrual and morbidity. An interim study summary report will be prepared at each meeting accordingly until the study results are released. The interim reports will contain information about patient accrual rate, a projected completion date for the accrual phase, distributions of pretreatment characteristics and important prognostic baseline variables, and the frequencies and severity of treatment-related adverse events. Three interim analyses are planned. Except for these planned interim analyses, the interim reports will not contain the results from the treatment comparisons with respect to the primary or any secondary endpoints, with the exception of the reporting of adverse events. At each DSMB meeting, the Alliance DSMB will review the interim reports and make recommendation regarding next steps of the trial. Unless the study is terminated prior to the final analysis, these interim analyses' results will not be available to the investigators, sponsor or industry collaborator. The Alliance DSMB and the study team will also closely monitor severe adverse events and unexpected adverse events at the semi-annual DSMB meetings. The following severe (grade 4+) adverse events of interest will be closely monitored by the study team: pneumonitis, pericarditis, esophagitis, and encephalitis. If excessive treatment-related severe adverse events have happened in more than 30% of the first forty treated patients who receive at least one cycle of the protocol treatments, the study will be suspended for careful review of all adverse events data.

13.4.3 Statistical Analysis Plan

For both phase II and phase III portions of this trial, the primary analyses for PFS and OS respectively will be performed on an intent-to-treat (ITT) basis, for which all randomized cases will be included in the treatment arm to which they were randomized regardless of what treatment the patients actually received. Depending on whether the trial proceed to the phase III portion, the primary analysis will be based on the data from phase II portion only or both phase II and phase III portions. The comparison of the distributions of OS between treatment arms will be done with a one-sided stratified log-rank test).[24,28] The rates at various time points (e.g., every 6 months after randomization) and medians of OS for each arm will be estimated using the Kaplan-Meier estimator.[22] The associated 95% confidence interval (CI) will be calculated using Greenwood's formula and based on a log-log transformation applied on the survival function. Hazard ratios will be estimated using a stratified Cox regression model. The final phase III analysis of OS will be considered as "positive" if the stratified log-rank test statistics Z-value greater than the critical value adjusted for type 1 error using group sequential methods. Multivariable Cox models will be used to evaluate the treatment effect on survival time and its interaction with baseline covariates, including stage, systemic therapy, histology and performance status.[25] A competing risk model [26]) will be used to explore the effect of treatments on overall survival by taking the competing risk of death due to causes unrelated to treatment into account. Restricted mean survival time (RMST) ratio could be a useful measure to quantify the treatment effect for immunotherapies [27]. We will choose the last observed event time as τ. Regression analyses with baseline prognostic factors adjusted will be conducted for a RMST ratio. All patients who receive at least one dose of any protocol treatment will be included in the safety analysis. Treatment-related toxicity will be summarized by grade, type, and system organ class. Comparisons of the percentages of patients experiencing an adverse event between Arm A and Arm B will be performed using Fisher's exact test. Similar analyses will be conducted for PFS. PFS is defined as the time from randomization to disease progression or death of all causes, whichever comes first. Progression time will

be censored at the last follow-up without progression occurring or initiation of subsequent therapy.

The ORRs between treatments will be compared with Fisher's exact test. The difference of ORR between treatments will be estimated by the Miettinen-Nurminen method and its 95%CI will be given .[29] Multivariable logistic regression will be used to evaluate the treatment effect on ORR while adjusting for significant baseline covariates.[30]

All patients who receive at least one dose of any protocol treatment will be included in the safety analysis. Treatment-related toxicity will be summarized by grade, type, and system organ class. Comparisons of the percentages of patients experiencing an adverse event between Arm A and Arm B will be performed using Fisher's exact test.

13.5 Logistics and Accrual

We expect a monthly accrual of approximately 18 patients for screening and approximately 8 PD-L1 negatives for randomization. Based on design parameters, the phase II portion accrual is estimated to take 13 months after study initiation, and the first interim analysis of futility (Go/No-Go decision) will take place the same time with at least 74 PFS events observed for Arm A and Arm B combined. Another 35 months from the end of phase II portion will be needed to complete the entire phase III accrual. Under the alternative hypothesis, the phase II/III trial is to take approximately 72 months from the first enrollment to reach the required 298 deaths for the final analysis. Patients will be followed until they either withdraw consent, are lost to follow-up, die or for a maximum of 5 years, whichever occurs first.

13.6 Data Mapping Utility Monitoring

Data for this study will be submitted via the Data Mapping Utility (DMU). Cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. DMU Light reporting consists of Patient Demographics, On/Off Treatment Status, Abbreviated Treatment and Course information, and Adverse Events as applicable. Instructions for setting up and submitting data via DMU are available on the CTEP Website: (https://ctep.cancer.gov/protocolDevelopment/dmu.htm).

Note: All adverse events (both routine and serious) that meet the protocol mandatory reporting requirements must be reported via DMU in addition to expedited reporting of serious adverse events via CTEP-AERS.

13.7 Inclusion of Women and Minorities

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

DOMESTIC PLANNED ENROLLMENT REPORT		
Racial Categories	**Ethnic Categories**	**Total**

DOMESTIC PLANNED ENROLLMENT REPORT					
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	1	0	0	0	1
Asian	0	3	0	0	3
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	14	13	0	0	27
White	221	160	2	2	385
More Than One Race	7	3	1	0	11
Total	243	179	3	2	427

13.8 Other Pre-Specified Outcomes: NIH-Required Analyses

Estimates of treatment effect and the corresponding 95% confidence intervals (CIs) will be provided as follows (with an understanding that sometimes the CI or estimate will not be computable because of scant data).

- Estimates of [primary outcome measure] and the corresponding 95% confidence intervals (CIs) by sex.
- Estimates of [primary outcome measure] and the corresponding 95% confidence intervals (CIs) by race.
- Estimates of [primary outcome measure] and the corresponding 95% confidence intervals (CIs) by ethnicity.

14.0 CORRELATIVE AND COMPANION STUDIES

There will be 2 substudies and all patients are encouraged (or required) to participate.

14.1 Quality of Life (Alliance A082002-HO1)

14.1.1 Background

A patient-reported outcome (PRO) is "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."[31] PROs provide information regarding how patients perceive health and treatment effects, and how treatments influence outcomes, and they are useful in evaluating how disease and therapeutic interventions impact many aspects of a patients' life [32]. Compared to PRO data, clinician reporting of symptomatic outcomes has been shown to be incomplete and sometimes inaccurate [33-35]. The incorporation of PROs into therapeutic clinical trials is, therefore, critical to inform medical decision making between patients and their doctors.

In A082002, we will assess QOL and patient-reported symptoms. The rationale for inclusion of each PRO and information about the instruments to be used are briefly described below.

Understanding the impact of treatment and symptoms on patients' daily life is essential in order to balance efficacy vs. safety in clinical trial. It also is critical in explaining to future patient s what they may expect. If a small survival benefit of TRT is detected, but at a cost

of substantial QOL decrements, some patients or clinicians may feel it is not worth the tradeoff. Conversely, if a small survival benefit is detected with no decrement in QOL, then sentiments may be different. Therefore, collecting QOL information in this setting is important for informing multiple stakeholders (patients, clinicians, guideline developers, and investigators).

14.1.2 Objectives

Primary Objective

- To compare QOL at approximately 3 months as assessed by the between patients randomized to Immunotherapy +/- radiation therapy. Hypothesis: QOL will be non-inferior in the IO + radiation therapy arm compared to the IO alone arm at 3 months.

Secondary Objective

- To compare QOL at approximately 12 months as assessed by the between patients randomized to Immunotherapy +/- radiation therapy. Hypothesis: QOL will be non-inferior in the IO + radiation therapy arm compared to the IO alone arm at 12 months.

Exploratory Objectives

- To compare various QOL domains after approximately 3 and 12 months of the study as assessed by the subscales of the EORTC QLQ-C30 and EORTC-QLQ-LC13 questionnaires between patients randomized to Immunotherapy +/- radiation therapy. This analysis is exploratory, though we anticipate the direction of the comparisons to be consistent with Primary and Secondary Hypotheses.
- To compare self-reported symptomatic adverse events assessed by the PRO-CTCAE between patients randomized to Immunotherapy +/- radiation therapy. This analysis is exploratory in nature.

14.1.3 Methods

This trial will incorporate the following QOL instruments:

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30): The EORTC QLQ-C30, a widely used cancer-specific HRQL measure has been used extensively in CALGB treatment trials. It is proposed to use this instrument in this study to assess the patients' quality of life and symptom impact. This is a well-validated scale that assesses the overall quality of life of lung cancer patients. It is composed of six functional scales (physical, role, emotional, cognitive, social, and global health status/quality of life) and nine symptom scales/items (fatigue, nausea and vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, financial impact). This instrument will be used to assess the primary dimensions of quality of life (i.e., physical, social, emotional functioning), as well as to measure cancer-related symptoms.

Lung Cancer Modular Supplement (EORTC-QLQ-LC13): This is a 13-item lung cancer-specific questionnaire that is added to the EORTC QLQ-C30 to obtain additional information about symptoms that are prevalent in lung cancer patients, such as dyspnea, cough, and hemoptysis. The EORTC-QLQ-LC13 is a validated measure.

Patient-Reported Adverse Symptoms:

Patients will be asked to self-report their adverse symptoms at baseline and each follow-up using items from the National Cancer Institute's PRO-CTCAE (Patient-Reported

Outcomes version of the Common Terminology Criteria for Adverse Events). This will involve 10 symptom items from the PRO-CTCAE Core Symptom Set. These items will be administered to patients electronically via their choice of either an automated telephone system (IVRS), or web.

Both the EORTC QLQ-C30 and QLQ-C13 have been validated with published results.

14.1.4 Statistical Analyses

Primary Endpoint

For the primary analysis, a single mixed model of the change in EORTC QLQ-30 Global Health Score will be analyzed. The mixed model will compare the 3 and 12 month time points between randomized arms. In addition to a randomized arm covariate, the model will include a randomized arm-by-time interaction term and will use the planned time point of assessment as the categorical time value. Unstructured covariance will initially be used, though alternative covariance structures will be investigated with the final covariance structure selected based on minimization of the Akaike information criterion. A contrast will be used to compare mean change from baseline at 3 months between arms. If the two-sided 95% confidence interval excludes a difference of 9 favoring the IO alone arm, then non-inferiority will be concluded. The difference of 7 points represents a clinically meaningful effect based on Maringwa et al (35).

A total sample size of 256 patients (128 per arm) achieves 90% power to detect non-inferiority using a one-sided two-sample equal variance t-test with a margin of non-inferiority of -9 at a significance level of 0.025. The power for this substudy was calculated using PASS.

Secondary Endpoint:

For the secondary analysis, the same mixed model as described above will be analyzed. A contrast will be used to compare mean change from baseline at 12 points between arms. Similarly, if the two-sided 95% confidence interval excludes a difference of 9 favoring the IO alone arm, then non-inferiority will be concluded at this time point.

Exploratory Endpoints:

For the exploratory analyses, mixed models will be constructed and analyzed using the subscale scores for the other 5 function subscales associated with the EORTC QLQ-C30 as well as the EORTC QLQ-LC13. Similar contrasts and tests will be analyzed according to the plan mentioned above.

For each of the PRO-CTCAE items assessed, the maximum grade for each patient will be recorded and analyzed. Frequency tables will be reviewed to determine the patterns for each of the adverse events across between arms.

14.2 Correlative Science (Alliance A082002-ST1)

14.2.1 Background

We will test how immunotherapy with or without radiation therapy affects the immune cell repertoire and immune system activation. We will conduct biomarker assays on available peripheral blood potentially including, but not limited to, multi-color flow cytometry immunophenotyping to assess diverse immune cell populations (CD4/CD8+ T cells, T regulatory cells, myeloid derived suppressor cells, natural killer cells, macrophages, etc.), flow cytometry T cell receptor phenotyping, multiplex cytokine profiling, T cell receptor sequencing, and circulating (cell-free) DNA/RNA analysis. From available pre-therapy

tumor biopsy tissue remaining after PD-L1 testing and pathologic confirmation of NSCLC, we will isolate RNA and DNA and potentially perform DNA sequencing (including tumor mutation burden), RNA analysis (e.g., T cell effector/inflammatory immune signatures), and potentially multiplex immunohistochemistry to determine if baseline tumor mutation burden, certain T cell clones, RNA molecular signature, and tumor immune cell infiltration predict for response to immunotherapy or immunotherapy and radiation therapy. These studies will facilitate identification of potential biomarkers of response to the treatment combination, understand how the treatment combination is affecting the immune system, and monitor response to the treatment over time.

14.2.2 Objectives

- To determine if baseline tissue-based immune-related biomarkers predict for response to the treatment arms.
- To determine if baseline and intra-treatment blood-based immune-related biomarkers predict for response to the treatment arms.

14.2.3 Methods

This study will include collection of biospecimens for future analyses. An amendment for any correlative science studies to be performed on biological samples will be submitted to CTEP, NCI for review and approval according to NCTN guidelines or via the Navigator portal after the trial has been reported. Amendments to the protocol and/or proposals for use of banked tissue or blood samples will include the appropriate background, experimental plans with assay details, and a statistical section. Samples for testing will not be released for testing until funding and the appropriate NCI approvals have been obtained.

Tissue-based correlative assays may include the following assays, but will be dependent on tissue availability and funding:

DNA sequencing (e.g., targeted panel, whole exome sequencing): DNA will be isolated from available tumor biopsy tissue and targeted vs. whole exome sequencing will be performed. Tumor mutational burden (TMB) is a measure of tumor neo-antigenicity and has shown clinical utility in predicting outcomes for patients treated with anti-PDL1/PD1 therapies across a range of tumor types. We will calculate tumor mutation burden for each patient and correlate TMB with response to protocol therapy and clinical outcomes.

RNA-based expression profiling (e.g., RNA-Seq, NanoString): RNA will be isolated from available tumor tissue and RNA expression profiling will be performed. RNA signatures measuring levels of T cell effector presence/activity or inflammatory tumor micro-environment have been shown to predict response to immunotherapy. We will measure and determine whether high T cell effector signature correlates with response to protocol therapy and clinical outcomes.

Blood-based correlative assays may include the following assays, but will be dependent on sample availability and funding:

Circulating cell-free DNA (cfDNA): Studies have shown that tumor-related cell-free DNA can track response to therapy and clinical outcomes. We hypothesize that we can identify presence of cfDNA mutations in circulating cfDNA of peripheral blood, and that changes in cfDNA levels during therapy will serve as an early predictor of response to therapy and clinical outcomes (e.g., progression-free and overall survival). We will determine cfDNA levels from peripheral blood on patients before and during therapy at various time points using available assays (e.g., Avenio, Natera, Archer etc.). We may also

determine blood TMB using this assay. We hypothesize that patients with high bTMB levels at baseline will correlate with improved response from the protocol therapy.

Flow cytometry immunophenotyping (e.g. CYTOF, other custom immune monitoring panels): We will perform flow cytometry immunophenotyping by multicolor flow cytometric analysis of peripheral blood samples procured at the baseline and additional time points. Samples of anticoagulated peripheral blood procured via venipuncture at different time points prior, during and following treatment will be used for this analysis. In addition, flow cytometric analysis of TCR-Vb repertoire provides accurate, reliable and reproducible profiling of T lymphocyte clonality in blood samples, allowing detection of monoclonal, oligoclonal and mildly expanded T cell populations in real time. This method is well suited to measure and to monitor changes in T cell repertoire in patients exposed to immunomodulating agents in real time. Thus, we hypothesize that flow cytometry immunophenotyping of T cell and other immune cell subsets will identify changes in immunologic subsets of cells that are predictive of response and clinical outcomes.

T cell receptor (TCR) sequencing/phenotyping (e.g. Immunoseq): High-throughput sequencing of T cell receptors has now provided the opportunity for accurate identification and quantification of every distinct T cell clone. It allows the assessment of the diversity of the TCR repertoire and the kinetics of each antigen-specific T cell clone over time. We will perform TCR sequencing on genomic DNA isolated from PBMCs from peripheral blood samples isolated before and during therapy in order to determine how protocol therapy alters TCR repertoire diversity and clones of neoantigen-specific T cells. We hypothesize that T cell receptor repertoire and clonal diversity will be altered by protocol therapy.

Cytokine assays (e.g. Luminex): We will assess cytokine/inflammatory markers from peripheral blood (plasma) samples using ELISA based methods isolated before and during therapy using standard laboratory protocols. We hypothesize that the addition of immunotherapy to standard chemoradiation therapy will alter cytokine/inflammatory marker levels, such as interferon gamma, IL-2, and other interleukins/cytokines.

15.0 GENERAL REGULATORY CONSIDERATIONS AND CREDENTIALING

IROC Institutional Requirements

Institutions participating on this study must be credentialed. See the table below for specific requirements. IROC-Houston will notify you when all requirements have been met.

<table>
<tr><td rowspan="2">RT Credentialing Requirements</td><td colspan="2">Web Link for Procedures and Instructions:
http://irochouston.mdanderson.org</td></tr>
<tr><td>Treatment Modality</td><td>Key Information</td></tr>
</table>

	Photons	
Facility Questionnaire	X	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link.
Credentialing Status Inquiry Form	X	To determine whether your institution needs to complete any further credentialing requirements, please complete the "Credentialing Status Inquiry Form" found under credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org)
Phantom Irradiation	X	A lung phantom study (with motion table as appropriate) provided by the IROC Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (http://irochouston.mdanderson.org). Note that only the most sophisticated technique needs to be credentialed, e.g., if credentialed for IMRT, 3DCRT may be used.
IGRT Verification Study	X	Institutions must be credentialed for soft tissue IGRT by IROC Houston. Find details on the IROC Houston QA Center website (http://irochouston.mdanderson.org) Institutions that have previously been approved for IGRT may not need to repeat credentialing.
Credentialing Notification Issued to:		
Institution	X	IROC Houston QA Center will notify the institution that all desired credentialing requirements have been met.

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APPENDIX I: REGISTRATION FATIGUE/UNISCALE ASSESSMENT

At patient registration, this form is to be administered by a nurse/CRP, completed by the patient, and entered into Medidata Rave at the time of registration.

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

How would you describe:

your level of fatigue, on the average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No Fatigue									Fatigue as bad as it can be	

your overall quality of life in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

APÉNDICE I: EVALUACIONES DE FATIGA/UNISCALE EN EL MOMENTO DEL REGISTRO

Evaluaciones de fatiga/Uniscale en el momento del registro

At patient registration, this form is to be administered by a nurse/CRP, completed by the patient, and entered into Medidata Rave at the time of registration.

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

¿Cómo describiría:

su nivel de fatiga, en promedio, durante la semana pasada, incluido el día de hoy?

0	1	2	3	4	5	6	7	8	9	10
Sin fatiga										Fatiga tan mala como sea posible

su calidad de vida en general durante la semana pasada, incluido el día de hoy?

0	1	2	3	4	5	6	7	8	9	10
Tan mala como sea posible										Tan buena como sea posible

APPENDIX II: PATIENT CLINICAL TRIAL WALLET CARD

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

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

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: A021804

Study Drug(S):

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov

APPENDIX III: NCI/DCTD COLLABORATIVE AGREEMENTS

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

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

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

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

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

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

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to

Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

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

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

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

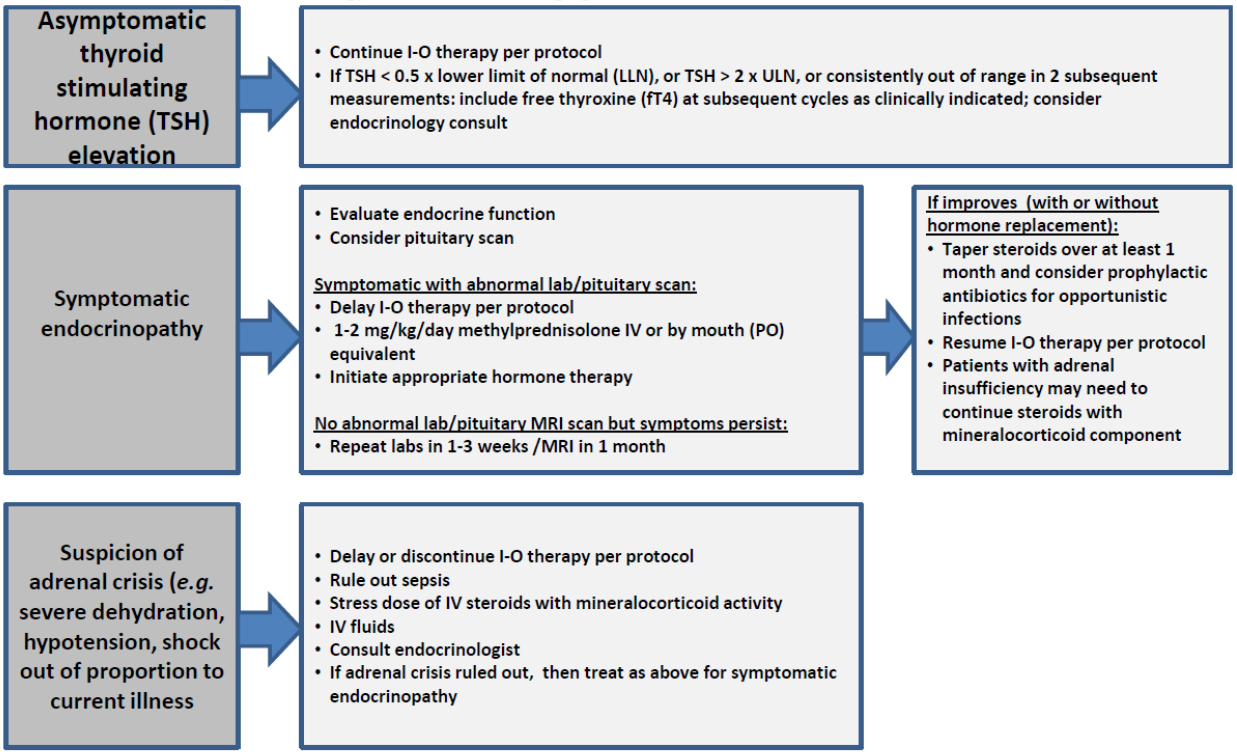
Email: ncicteppubs@mail.nih.gov

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

APPENDIX IV: MANAGEMENT ALGORITHMS FOR ENDOCRINOPATHY, GI, HEPATIC, NEUROLOGICAL, PULMONARY, RENAL AND SKIN ADVERSE EVENTS

Endocrinopathy Management Algorithm

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



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

GI Adverse Event Management Algorithm

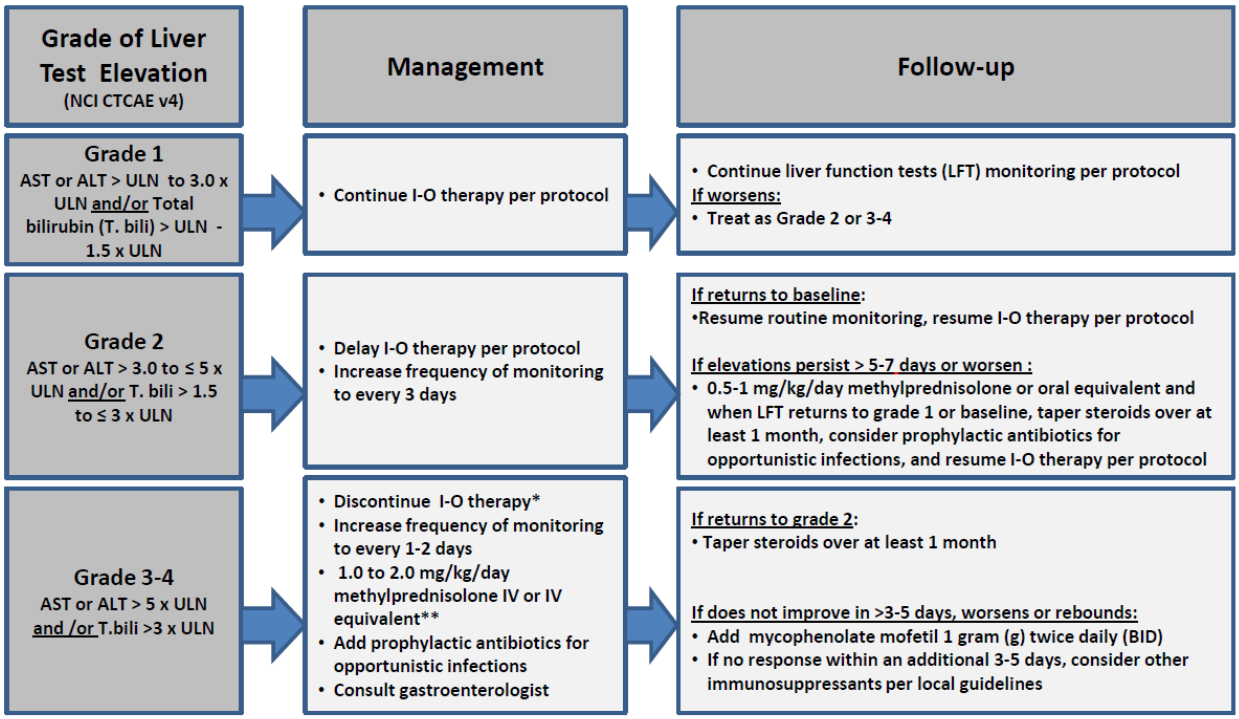
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

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

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

Hepatic Adverse Event Management Algorithm

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



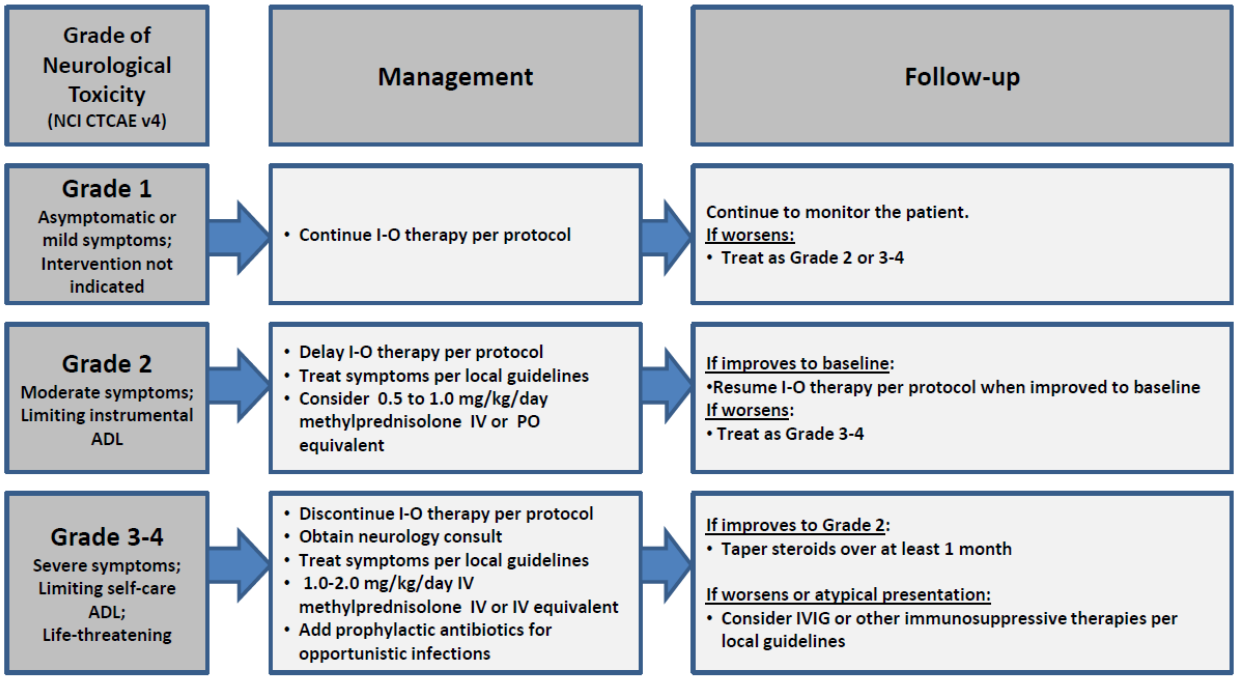
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Neurological Adverse Event Management Algorithm

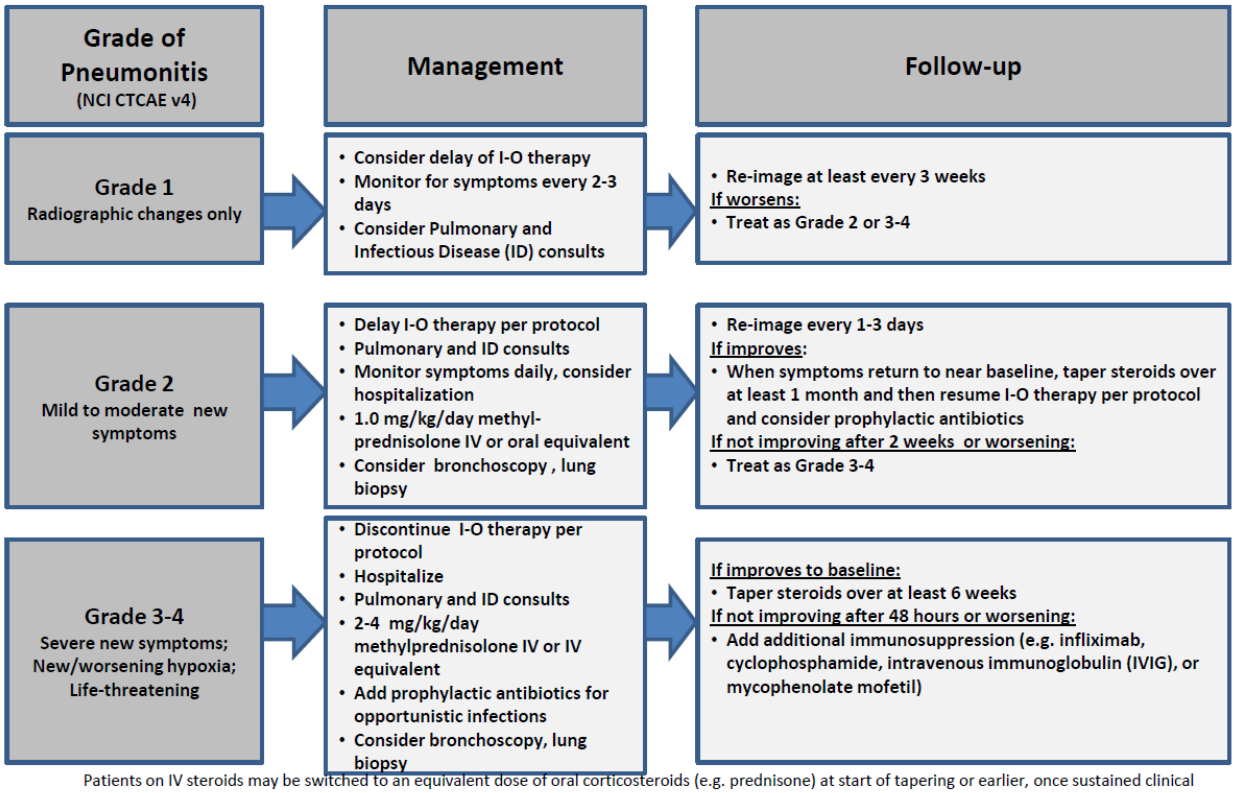
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

Pulmonary Adverse Event Management Algorithm

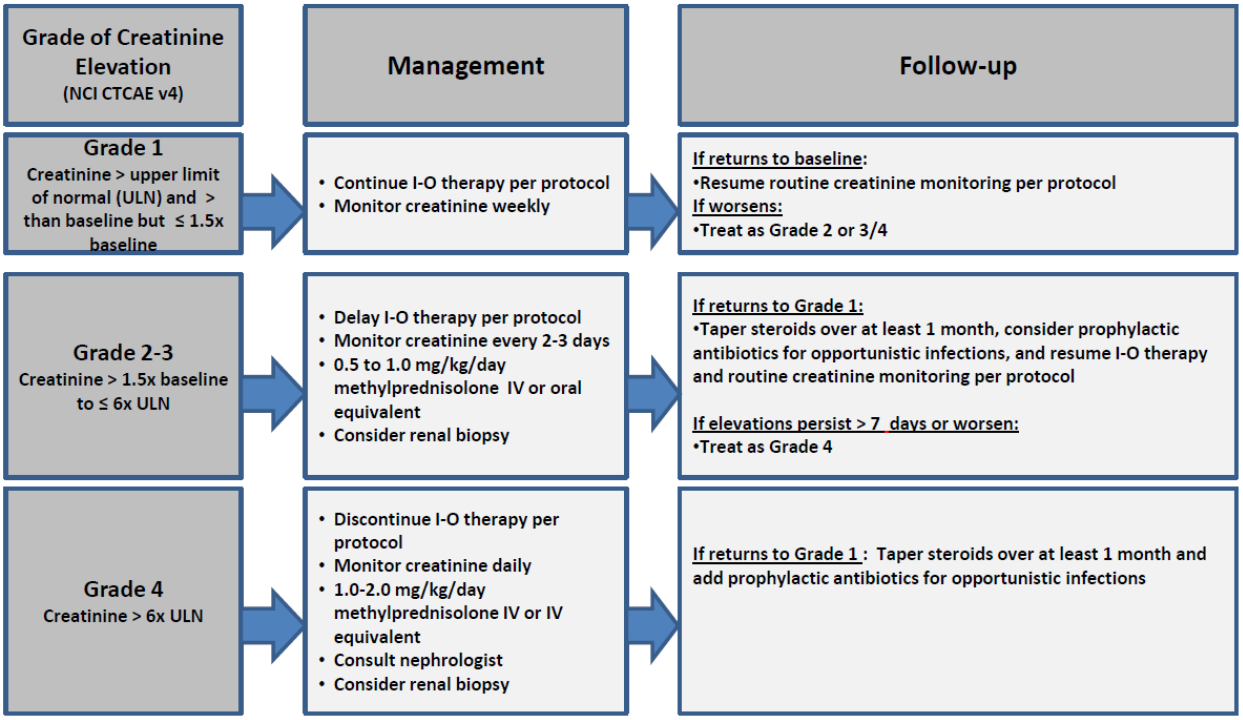
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

Renal Adverse Event Management Algorithm

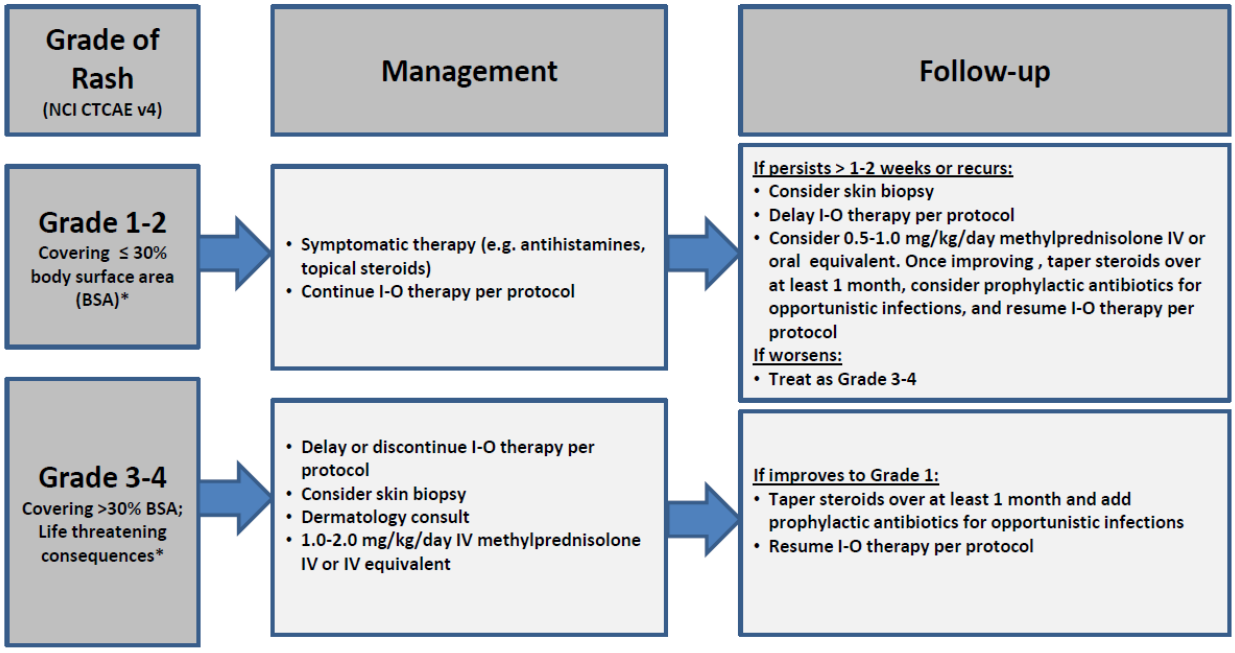
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

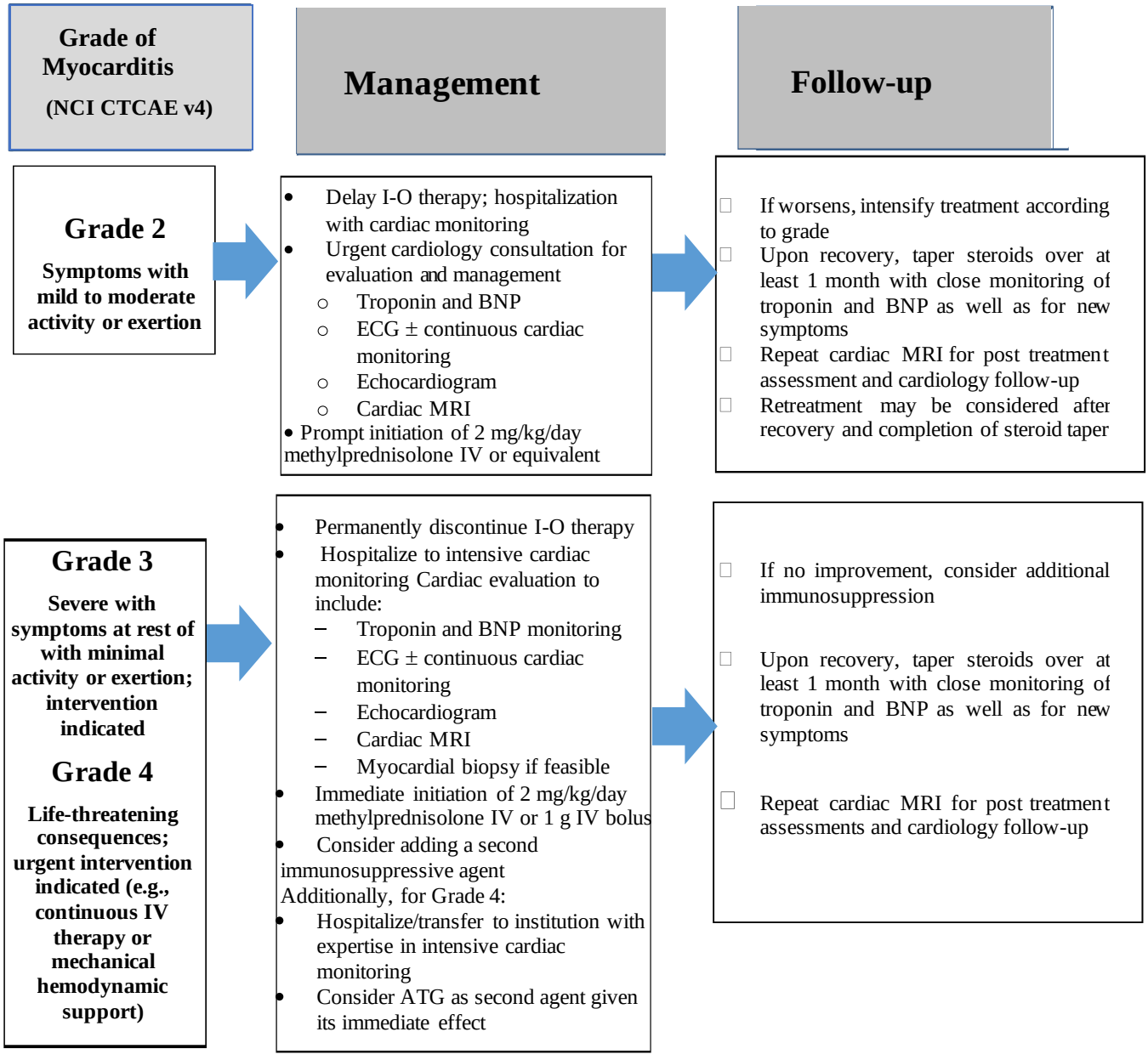
Skin Adverse Event Management Algorithm

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



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

Myocarditis Adverse Event Management Algorithm



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

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging