ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A032002

PHASE II RANDOMIZED TRIAL OF IMMUNOTHERAPY VERSUS IMMUNOTHERAPY AND RADIATION THERAPY FOR PLATINUM INELIGIBLE/REFRACTORY METASTATIC UROTHELIAL CANCER (IMMORTAL)

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

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.

UPDATES TO THE PROTOCOL:

Cover Page

- The phone numbers and institution names have been removed from the co-chairs' contact information.
- Drs. [redacted] and [redacted] have replaced Dr. [redacted] as the new GU Committee Co-chairs. With this change, Dr. [redacted] Bladder Cancer [redacted] title has been removed.
- The Primary Statistician's email has been updated.

Protocol Contacts (Page 2)

- The institution name and phone number for the A032002 Nursing Contact have been removed.
- [redacted] has replaced [redacted] as the A032002 Pharmacy Contact.

Section 4.1 Investigator and Research Associate registration with CTEP

This section has been revised in its entirety to align with current CTEP boilerplate language.

Section 4.2 Cancer Trials Support Unit registration procedures

This section has been revised in its entirety to align with current CTEP boilerplate language.

Section 4.2.2 Protocol specific requirements for A032002 site registration

This section has been revised in its entirety to align with current CTEP boilerplate language.

Section 4.4 Patient Registration Procedures

This section has been revised in its entirety to align with current CTEP boilerplate language.

Section 6.1.2 (Medidata Rave)

This section has been revised in its entirety to align with current CTEP boilerplate language.

Section 6.1.4 (Rave-CTEP-AERS integration)

This section has been completely removed as this study will no longer be using the Rave-CTEP-AERS system for reporting serious adverse events. Subsequent sections have been renumbered accordingly.

Section 6.3.1 TRIAD Access Requirements

The second bullet has been revised its entirety to align with current CTEP boilerplate language.

Section 8.2.1 General AE Management and Dose Modification Guidelines for Pembrolizumab (MK-3475)

In the "Table for Dose Modification and Toxicity Management Guidelines for Immune-related AEs and Infusion Reactions Associated with Pembrolizumab", item #3 under 'General Instructions' has been revised to the following: "Generally, when corticosteroids (prednisone) are used, investigators should begin a taper when the irAE is ≤Grade 1 and continue at least 4 weeks."

Section 9.1.1 CTEP-AERS integration

The section entitled "Rave-CTEP-AERS integration" has been completely removed as the trial is now IND exempt due to the change in drug from "atezolizumab" to "pembrolizumab." Subsequent sections have been renumbered accordingly.

Section 9.3 Expedited Adverse Event Reporting (Rave-CTEP-AERS)

The section heading has been updated to the following as this study will no longer be using the Rave-CTEP-AERS system for reporting serious adverse events: "Expedited Adverse Event Reporting (~~Rave~~ CTEP-AERS)."

-This section has been completely updated as this study will no longer be using the Rave-CTEP-AERS system for reporting serious adverse events.

UPDATES TO THE MODEL CONSENT:

There have been no changes made to the model consent.

A replacement protocol document and model consent form have been issued

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ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A032002

PHASE II RANDOMIZED TRIAL OF IMMUNOTHERAPY VERSUS IMMUNOTHERAPY AND RADIATION THERAPY FOR PLATINUM INELIGIBLE/REFRACTORY METASTATIC UROTHELIAL CANCER (IMMORTAL)

Commercial agent: Pembrolizumab (MK-3475) (NSC # 776864)
This trial is IND Exempt.
ClinicalTrials.gov Identifier: NCT04936230

Study Chair
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Weill Cornell Medicine
1283 York Avenue
New York, NY 10065
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GU Committee Chair
[redacted], MD

GU Committee Chair
[redacted], MD

Community Oncology Co-Chair
[redacted], MD

Correlative Co-chair
[redacted], MD

NRG Study Champion
[redacted], MD

Immuno-Oncology Co-Chair
[redacted] MD, PhD

Medical Onc Co-Chair
[redacted], MD

Imaging Co-Chair
[redacted], MD

Radiation Oncology Committee Chair
[redacted] MD

Primary Statistician
[redacted], Ph. D

Secondary Statistician
[redacted]

Health Outcomes Statistician
[redacted] Ph.D

Health Outcomes Co-Chair
[redacted] MD

Health Outcomes Co-Chair
[redacted], MD

Protocol Coordinator
[redacted], MPH

[redacted]

Participating Organizations:
Alliance/Alliance for Clinical Trials in Oncology (lead), ECOG-ACRIN/ECOG-ACRIN Cancer Research Group, NRG/NRG Oncology, SWOG/SWOG

Study Resources:

Expedited Adverse Event Reporting https://ctepcore.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

Protocol Contacts:

A032002 Nursing Contact
[redacted]

A032002 Pharmacy Contact
[redacted]

Alliance Biorepository at Washington University (WUSTL)
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alliance032002@irocohio.org or 614-293-2929
For RT QA: IROC Rhode Island,
IROCRI@QARC.org or 401-753-7600
For RT Credentialing: IROC Houston,
irochouston@mdanderson.org, or 713-745-8989

Protocol-related questions may be directed as follows:

Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
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 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) or 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.

PHASE II RANDOMIZED TRIAL OF IMMUNOTHERAPY VERSUS IMMUNOTHERAPY AND RADIATION THERAPY FOR PLATINUM INELIGIBLE/REFRACTORY METASTATIC UROTHELIAL CANCER (IMMORTAL)

Key Eligibility Criteria

Eligibility Criteria (see Section 3.2)

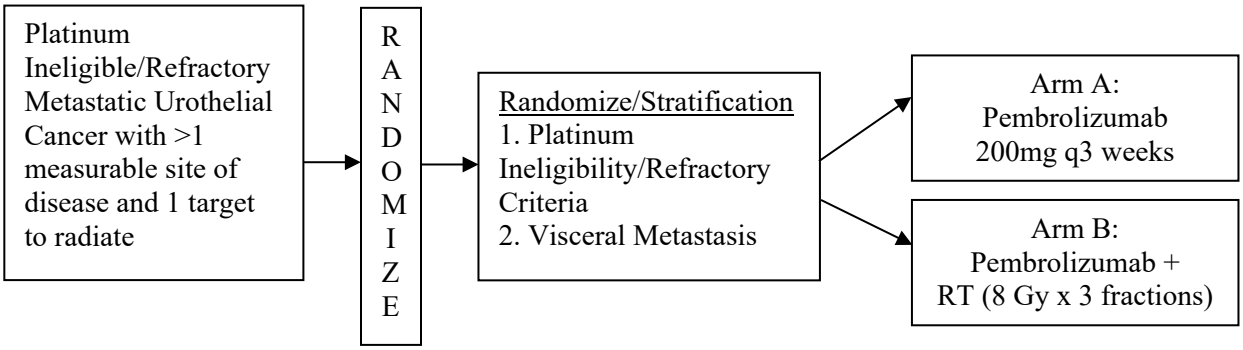
- Men and women, ages ≥18 years of age.
- ECOG performance status ≤2
- No prior treatment per Section 3.2.7
- No comorbid conditions per Section 3.2.8
- No active infections requiring systemic antibiotics within 2 weeks prior to registration. See Section 3.2.8
- No live vaccine within 30 days. See Section 3.2.8

Required Initial Laboratory Values	
ANC	≥ 1500/mm^3
Platelet count:	≥ 100,000/mm^3
Leukocytes	≥2,500/mm^3
Hemoglobin	≥8 g/dL
Total bilirubin:	≤ 1.5 x ULN*
AST/ALT:	≤ 3.0 x ULN**
Alk Phos	≤2.5 × ULN***
INR, PTT	≤1.5 x ULN†

* pts w/Gilbert disease ≤ 3 are eligible
** ≤ 5 ULN for pts w/liver involvement
*** ≤ 5 ULN for pts w/liver involvement or if due to bone metastases primarily in absence of liver disease, no limitation

Schema

1 Cycle = 21 Days



Treatment is to continue until disease progression and no longer benefiting clinically or unacceptable adverse event. Patients will be followed for 3 years or until death, whichever comes first.

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

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

Table of Contents

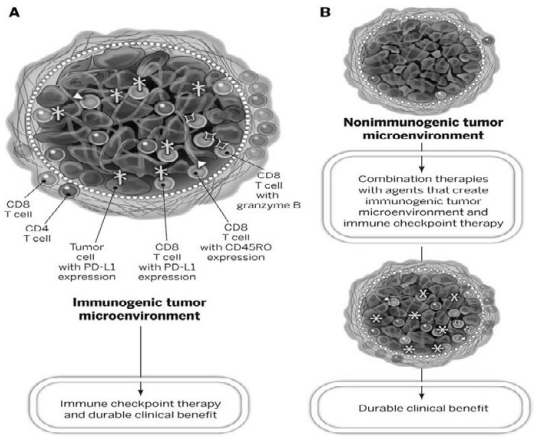
1.0 BACKGROUND

1.1 Rationale for selected approach and trial design

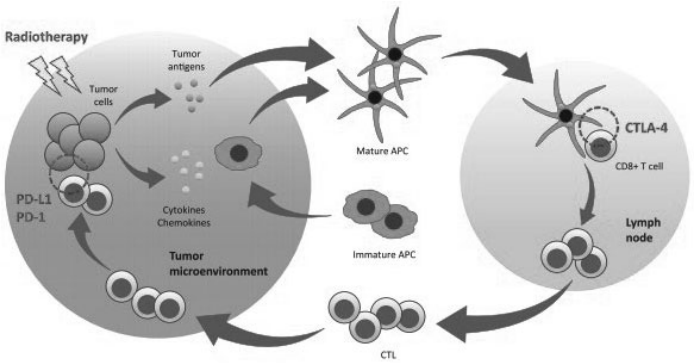
Treatment for metastatic urothelial carcinoma has remained mostly unchanged over the past 3 decades. The estimated 5-year survival for metastatic disease has been approximately 5% [2]. Platinum-based chemotherapy regimens was the current standard of care for first-line treatment. Responses for patients that received platinum-based chemotherapy tend to be short-lived (median survival with cisplatin-based therapy is ~14 months) and nearly all patients experience disease progression after treatment [3]. Until recently, the standard-of-care second-line therapies of docetaxel and paclitaxel (in the USA) and vinflunine (in Europe) resulted in only short survival, often resulting in only single digit response rates[4]. There have been few exciting advances with regards to systemic therapy for urothelial cancer until the approval of atezolizumab in 2016, quickly followed by four more immunotherapy options in 2017 (pembrolizumab, nivolumab, durvalumab, avelumab).

The KEYNOTE-045 phase III trial that compared pembrolizumab and investigator's choice of chemotherapy (paclitaxel, docetaxel, or vinflunine) reported a median overall survival (OS) of 10.3 months (95%CI 8.0-11.8) in the pembrolizumab group, compared with 7.4 months (95%CI 6.1-8.3) in the chemotherapy group (HR 0.73, 95%CI 0.59-0.91) [6].

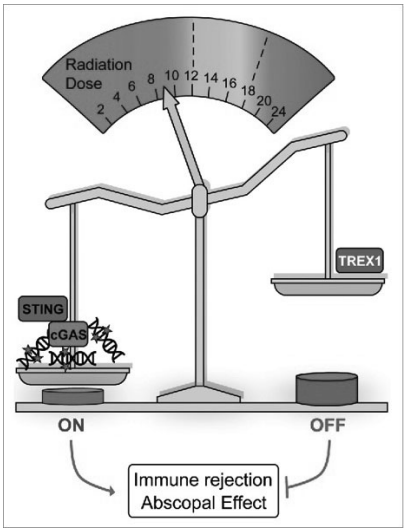
As such, immunotherapy has clear activity in urothelial cancer, but the clinical benefit can be improved upon. The pre-existing immune infiltrate of tumors likely dictate response to immunotherapy and prognosis [7]. Combining therapies with methods to create an immunogenic tumor microenvironment may potentially increase the durable clinical benefit with immunotherapy [8].



Tumor-targeted radiotherapy can generate immune-stimulating effects and not immune suppression as was previously thought. Moreover, it has become clear that radiotherapy can induce profound effects on tumor cells and on the tumor microenvironment that can enhance or trigger an anticancer immune response. Radiotherapy triggers antigen release from tumor cells, and the release of cytokines and chemokines from the tumor and its microenvironment. Immature antigen-presenting cells (APCs) are recruited to the tumor microenvironment, where they uptake tumor antigens and mature. These mature APCs then traffic to tumor-draining lymph nodes, where they prime CD8+ T lymphocytes that recognize the presented tumor antigens. Activated CD8+ T cells expand into effector cytotoxic T lymphocytes (CTLs), which home to the tumor site where they recognize and kill the tumor cells [9]. The current immune checkpoint blocking agents utilized in the clinical setting focus on the blockade of cytotoxic T lymphocyte antigen-4 (CTLA-4) at the CD8+ T-cell priming phase, and blockade of the programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) interaction at the CTL effector phase.



As radiotherapy is under investigation for its ability to enhance responses to immunotherapy, the mechanisms by which radiation induces anti-tumor T cells is being elucidated. The DNA exonuclease Trex1 is induced by radiation doses above 12–18 Gy in different cancer cells, and attenuates their immunogenicity by degrading DNA that accumulates in the cytosol upon radiation. Cytosolic DNA stimulates secretion of interferon-beta by cancer cells following activation of the DNA sensor cGAS and its downstream effector STING. Repeated irradiation at doses that do not induce Trex1 amplifies interferon-beta production, resulting in recruitment and activation of Batf3-dependent dendritic cells. This effect is essential for priming of CD8 T cells that mediate systemic tumor rejection in the context of immune checkpoint blockade. Thus, Trex1 is an upstream regulator of radiation-driven anti-tumor immunity and can guide the selection of radiation dose and fractionation in patients treated with immunotherapy [10].



Based on promising preclinical data and enticing clinical case reports, there are more than 100 accruing clinical trials combining radiation therapy with various forms of immune checkpoint inhibitors. This randomized phase II trial is unique and crucial for the following reasons:

1) Testing the hypothesis of immune rejection and the abscopal effect needs to move beyond single institution, academic center efforts into a cooperative group setting involving patients treated in academic and community-based settings. As immune checkpoint blockade has activity, although limited, in urothelial cancer, this is an ideal setting to further test this phenomenon to improve upon its efficacy given that many patients will lack additional therapies. Until this phenomenon is tested in a cooperative group setting on a national level with homogeneity in radiotherapy and immunotherapy and without industry bias of single or combinatorial untested agents, thousands of patients will continue to be accrued to early stage studies hinting at an effect but providing no clinical guidance.
2) Unlike many other trials testing this phenomenon, this trial strictly adheres to one specific radiation dose (8 Gy x 3) in one disease site with specific criteria (platinum ineligible or refractory metastatic urothelial cancer).

The data from this randomized phase II trial (clinical and correlative) is a necessary step to guide other phase II trials in this and other disease settings and potentially the first step to a larger phase III design. There are 3 envisioned outcomes for this trial: 1) positive - evaluate in a phase 3 trial, 2) positive utilizing iRECIST in aforementioned point 1, 3) evaluate to propose a phase 3 design with iRECIST as primary endpoint and

3) negative - ending further investigation as this question would be answered in this disease site with this therapy.

Recently, Sundahl and colleagues reported on a randomized phase 1 trial of pembrolizumab with sequential versus concomitant stereotactic body radiotherapy (8 Gy x 3) in metastatic urothelial carcinoma [28]. Safety was the primary outcome, with dose limiting toxicity defined as any grade 3–5 metabolic or hematological toxicity or any grade 3–5 non-hematological toxicity that was (probably or possibly) related to SBRT, and that occurred between the start of SBRT and 12 weeks after the end of SBRT. No DLTs occurred in any of the 18 patients. Secondary endpoints included best overall objective response as per Response Evaluation Criteria in Solid Tumors v1.1, progression-free survival, OS, and local response in the irradiated lesion as per RECIST 1.1. A response rate of 0% (RECIST 1.1) was observed in the sequential arm, with all patients experiencing progressive disease as the best overall objective response in non-irradiated lesions. Two patients had an initial partial response (PR) at first evaluation, which progressed shortly afterward and therefore does not qualify as a PR according to RECIST 1.1. In the concomitant arm, a response rate of 44% was noted in non-irradiated lesions, with three patients experiencing a PR and one patient experiencing a complete response. Although not powered to detect a difference in OS, median OS was 4.5 and 12.1 months in sequential and concomitant arms, respectively.

1.2 Registration Patient Reported Outcomes (PROs) and Quality of Life (QOL) Measurements

PROs, particularly involving symptomatic toxicities, provide discrepant yet complementary information compared with clinician interpreted data[12-16]. In particular, greater sensitivity for adverse event reporting, auxiliary characterization of performance status and earlier detection of symptoms[12,14,17-20]. Implementation of PRO systems has shown feasibility in the clinical trial setting demonstrating 78% to 96% adherence[21,22] and several studies report that baseline PRO and QOL data may prognosticate survival better than performance status in clinical trials[23-25]. A landmark prospective study also now suggests that serial monitoring of patient reported symptoms may improve median overall survival by up to 5 months for patients undergoing treatment of solid malignancies[22].

QOL measurements of fatigue and overall perception of QOL are routinely included in Alliance studies and will be assessed upon registration in this study. Baseline single-item assessments of fatigue and overall QOL are strong prognostic indicators for survival in cancer patients, independent of performance status[26-28]. Routine inclusion of these measures should be considered similar to that of including performance status, either as stratification or prognostic covariates.

2.0 OBJECTIVES

2.1 Primary objective

The primary objective is to compare the overall response rates by 6 months in patients with advanced urothelial carcinoma when treated with immunotherapy alone and immunotherapy plus radiotherapy to a single site.

2.2 Secondary objectives

2.2.1 To compare the response rates using iRECIST as assessed by central review

2.2.2 To compare progression-free survival (PFS) and overall survival (OS) for patients treated with immunotherapy and immunotherapy plus radiotherapy

2.2.3 To compare the rates of treatment discontinuation at 1 year

2.2.4 To assess adverse events experienced by patients treated with immunotherapy and immunotherapy plus radiotherapy via the CTCAE and PRO-CTCAE.

2.2.5 To determine whether treatment effects are similar for key subgroups including those defined by the stratification variables.

2.3 Quality of Life Correlative Study Objectives

2.3.1 To compare patient-reported fatigue as assessed by the PROMIS-Fatigue 8a from baseline through 24 months between patients treated with immunotherapy alone and immunotherapy plus radiotherapy to a single site.

2.3.2 To compare health-related quality of life (HRQOL) as assessed by the EORTC QLQ-C30 from baseline through 24 months between patients treated with immunotherapy alone and immunotherapy plus radiotherapy to a single site.

2.3.3 To compare urinary symptoms as assessed by the EORTC QLQ-BLM30 from baseline through 24 months between patients treated with immunotherapy alone and immunotherapy plus radiotherapy to a single site.

2.3.4 To compare patient-reported diarrhea, shortness of breath and pain as assessed by the EORTC QLQ-C30 from baseline through 24 months between patients treated with immunotherapy alone and immunotherapy plus radiotherapy to a single site.

2.3.5 To compare health utilities and quality-adjusted survival between patients treated with immunotherapy alone and immunotherapy plus radiotherapy to a single site.

2.3.6 To compare other scale scores of the EORTC QLQ-C30 (global health status and quality of life; physical, role, emotional, cognitive, and social function; symptoms) and EORTC QLQ-BLM30 (urostomy problems, catheter problems, future perspectives, abdominal bloating and flatulence, body image, sexual function) at 45 days, and at 6, 12, and 24 months between patients treated with immunotherapy alone and immunotherapy plus radiotherapy to a single site.

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:

- Patients with life expectancy of less than 6 months
- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical conditions such as uncontrolled infection, uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
    - HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
    - For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.
    - Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.
- Patients with a “currently active” second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a “currently active” malignancy if they have completed therapy and are free of disease for ≥ 3 years.

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 4 months (120 days) after the last dose of study agent due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

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 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.

___ **3.2.1 Documentation of disease**

- Histologically confirmed metastatic urothelial carcinoma

___ **3.2.2 Patients must be either ineligible for platinum treatment or platinum refractory as defined below:**

Platinum-ineligible: If patients meet any one of the following criteria:

1. Impaired renal function [creatinine clearance (CrCl) of <30 mL/min]
2. Grade >2 peripheral neuropathy
3. NYHA Heart Failure of >3

Platinum-refractory: If patients meet any one of the following criteria:

1. Prior platinum-based perioperative chemotherapy within 12 months of relapse
2. Prior platinum-based chemotherapy for metastatic disease

___ **3.2.3 Measurable disease as defined in Section 11.0.**

Patients must have at least one measurable site ≥1 cm in diameter per RECIST 1.1 and a site targetable for radiotherapy. Measurable site must not overlap with radiated site such that measurable site cannot receive >2 Gy per fraction.

Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions). See Section 11.0 for the evaluation of measurable disease.

___ **3.2.4 Men and women, ages ≥ 18 years of age**

___ **3.2.5 ECOG performance status ≤ 2**

___ **3.2.6 Required Initial Lab Values**

- Leukocytes ≥2,500/mm^3
- Absolute neutrophil count ≥1,500/mm^3
- Platelets ≥100,000/mm^3

- Hemoglobin ≥8 g/dL
- Total bilirubin ≤1.5 × institutional upper limit of normal (ULN) (however, patients with known Gilbert disease who have serum bilirubin level ≤3 × ULN may be enrolled)
- AST(SGOT)/ALT(SGPT) ≤3 × ULN*
- Alkaline phosphatase ≤2.5 × ULN**

* AST and/or ALT ≤5 × ULN for patients with liver involvement

** ≤5 × ULN for patients with documented liver involvement or if due to bone metastases primarily in absence of liver disease, no limitation.

___ **3.2.7 Prior Treatment**

- No prior allogeneic bone marrow transplantation or prior solid organ transplantation.
- No Prior radiotherapy to targetable site or measurable site.
- No chemotherapy or radiotherapy within 4 weeks prior to entering the study or those who have not recovered from adverse events (other than alopecia) due to agents administered more than 4 weeks earlier. However, the following therapies are allowed:
    - Hormone-replacement therapy or oral contraceptives
    - Palliative radiotherapy for bone metastases >2 weeks prior to registration
- No prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies.
- No treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
- No prior treatment with any other investigational agent within 4 weeks prior to registration.
- No prior treatment with systemic immunostimulatory agents (including, but not limited to, interferon [IFN]-α or interleukin [IL]-2) within 6 weeks prior to registration.
- Any prior systemic therapy is permitted except therapy with PD1/PDL1 inhibitor.
- Patients who have received acute, low dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled.
- The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.

___ **3.2.8 Comorbid conditions**

- **No active tuberculosis** (TB)
- **No known additional malignanc**y that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
- Patients with known primary **central nervous system (CNS) malignancy or symptomatic CNS metastases** are excluded, with the following exceptions:

  Patients with asymptomatic untreated CNS disease may be enrolled, provided all of the following criteria are met:

  - Evaluable or measurable disease outside the CNS
  - No metastases to brain stem, midbrain, pons, medulla, cerebellum, or within 10 mm of the optic apparatus (optic nerves and chiasm)
  - No history of intracranial hemorrhage or spinal cord hemorrhage
  - No ongoing requirement for dexamethasone for CNS disease; patients on a stable

dose of anticonvulsants are permitted.
- No neurosurgical resection or brain biopsy within 28 days prior to registration

- Patients with asymptomatic treated CNS metastases may be enrolled, provided all the criteria listed above are met as well as the following:
  - Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study
  - No stereotactic radiation or whole-brain radiation within 28 days prior to registration
  - Screening CNS radiographic study ≥4 weeks from completion of radiotherapy and ≥2 weeks from discontinuation of corticosteroids

- No active **autoimmune disease** that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
- Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone are eligible.
- No known history of, or any evidence of active, non-infectious **pneumonitis or colitis**.
- No known **hypersensitivity** to Chinese hamster ovary cell products or other recombinant human antibodies.
- No history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
- No known clinically significant **liver disease**, including active viral, alcoholic, or other hepatitis; or inherited liver disease causing decompensated cirrhosis.
- No history of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (*i.e.*, bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- No significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina.
- No other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications.
- No history of leptomenigeal disease.
- No uncontrolled tumor-related pain.
- Patients requiring pain medication must be on a stable regimen at study entry.
- Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.
- Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.

- No uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently).

  Patients with indwelling catheters (e.g., PleurX®) are allowed.

- Patients with controlled Type 1 **diabetes mellitus** on a stable insulin regimen are eligible.
- **Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations** only (*e.g.*, patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
  - Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations
  - Rash must cover less than 10% of body surface area (BSA)
  - Disease is well controlled at baseline and only requiring low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%).
- No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids).
- **No uncontrolled intercurrent illness** including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- No active infections requiring systemic antibiotics within 2 weeks prior to registration. Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.
- **No Major surgical procedure** within 28 days prior to registration or anticipation of need for a major surgical procedure during the course of the study.
- No administration of a live, attenuated vaccine within 30 days before registration or anticipation that such a live, attenuated vaccine will be required during the study and up to 5 months after the last dose of immunotherapy.
- Patients who have received live attenuated vaccines within 30 days of the first dose of trial treatment are eligible at the discretion of the investigator. All seasonal influenza vaccines and vaccines intended to prevent SARS-CoV-2 and coronavirus disease 2019 (COVID-19) are allowed.

4.0 PATIENT REGISTRATION

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 a 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 six person registration types.

- 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;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
CTEP-IAM Account with ID.me credentials	✓	✓	✓	✓	✓
FDA Form 1572 • Practice sites, IRBs, and labs	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, certification, licensure, ABMS certification, GCP Training, personal statement, memberships, honors, publications, research support)	✓	✓	✓		
GCP Training Certificated (mandatory file upload)	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional file upload)	✓	✓	✓		
Annual Re-registration	✓	✓	✓	✓	✓

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 through 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).

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

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

In addition, the Site-Protocol 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 (applies to US and Canadian sites only) 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 on CIRB Signatory Institution (US sites only); and

Compliance with all protocol-specific requirements (PSRs).

4.2.2 Protocol specific requirements for A032002 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 its associated investigators and staff or 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 *A032002*.

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 in order 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.

4.3 Patient Registration Requirements

4.3.1 Informed consent

The patient must be aware of the neoplastic nature of his/her 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.

4.3.2 Patient questionnaire booklets

Patient-completed booklets should be downloaded prior to the pre-registration of any patients. These booklets can be downloaded from the CIRB Approved Documents tab on the CTSU website. Patient-completed booklets will only be available in English.

4.4 Patient Registration 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;
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the 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 is 1 substudy within Alliance A032002. This correlative science study must be offered to all English-speaking patients enrolled on Alliance A032002 (although patients may opt to not participate). This substudy does not require separate IRB approval. The substudies included within Alliance A032002 are:

- Quality of Life, Alliance A032002-HO1 (Section 14.1)

If a patient 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 14.1. The patient should be registered to Alliance A032002-HO1 at the same time they are registered to the treatment trial (A032002). Questionnaires should be submitted per Section 14.1.

4.6 Stratification Factors and Treatment Assignments

4.6.1 Stratification Factors

1) Platinum Status: Ineligible vs. Refractory
    - Platinum ineligible is defined as meeting any one of the following criteria: Impaired renal function [creatinine clearance (CrCl) of <30 mL/min], >2 peripheral neuropathy, or NYHA Heart Failure of >3.
    - Platinum-refractory is defined as prior platinum-based perioperative chemotherapy within 12 months of relapse or prior platinum-based chemotherapy for metastatic disease.
2) Visceral Metastasis: Yes vs. No

4.6.2 Treatment Assignments

Patients will be randomized 1:1 to the two treatment arms. The factors defined in Section 4.8.1 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 randomized to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups.

1) Immunotherapy
2) Immunotherapy + Single Site Radiotherapy

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: Any X-ray, scan of any type or ultrasound which is utilized for tumor measurement per protocol.

To be completed ≤ 60 DAYS before registration: Any baseline exams used for screening, or any X-ray, scan of any type or ultrasound of uninvolved organs which is not utilized for tumor measurement.

	Prior to Registration*	Day 1 of each cycle*	Post-treatment follow up**	At PD, withdrawal, or removal**
Tests & Observations				
History and physical, weight, PS***	X	X	X	X
Pulse, Blood Pressure	X	X		
ECG	X(6)			
Adverse Event Assessment-CTCAE		X	X	
Adverse Event Assessment-PRO-CTCAE	X(1)	X(1)	X	
Registration Fatigue/Uniscale Assessment	X(2)			
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 with reflex T4		X		
Serum or Urine hCG	X(3)			
UPC ratio/urine protein	X	A		
Staging				
Tumor Measurement	X	C	X	
CT chest/abd/pelvis	X(5)	D	D	
Correlative studies				
QOL assessment	*From baseline through 24 months, see Section 6.5.*			
Tissue, blood, and urine 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 ≤ 72 hours prior to day of treatment.

** Physical examination and staging scans are required ≤ 12 weeks after the end of treatment, then every 12 weeks until disease progression; thereafter, survival information is required every 3 months until 3 years following registration. See also Section 12.0.

*** Patients receiving immunotherapy will be assessed for pulmonary signs and symptoms throughout the study.

1 The PRO-CTCAE assessment is required for all patients. If the PRO-CTCAE assessment completed prior to registration is obtained ≤ 14 days prior to treatment, then the PRO-CTCAE assessment on day 1 of cycle 1 may be skipped. The PRO-CTCAE patient-completed booklet for this protocol can be found on the 'CIRB Approved Documents' tab on the CTSU website.

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

3 For women of childbearing potential. Must be done ≤ 14 days prior to initiation of study treatment.

4 See Section 6.2.

5 Baseline scans can include either: 1) a CT, spiral CT, or MRI and bone scan, 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.
6 ECG prior to registration should be performed if clinically indicated.
A. All patients receiving immunotherapy will have a urinalysis or urine protein performed ≤ 72 hours prior to every dose. If urine protein is ≥ 2+, 24-hour urine collection or UPC ratio will be required.
B. Required only if signs or symptoms suggestive of metastases develop.
C. ≤ 2 days prior to each treatment if accessible to physical examination.
D. Every 3 months until evidence of progression or relapse. If the baseline scans were a CT or MRI and bone scan, follow-up bone scans are required only for patients with bone metastases as the only site of evaluable disease, and are optional for other patients. Response assessment should include assessment of all sites of disease and use the same imaging method as was used at baseline. Bone imaging (after baseline) is required only if indicative of metastases at baseline or 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 Alliance study webpage, within the Case Report Forms section. The Data Submission Schedule is also available on the CTSU site within the study-specific Case Report Forms folder.

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.

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 ICAREdata® Project

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.

6.1.5 IRB Termination

Until institutions receive a formal notice from the Alliance regarding termination to patient follow-up, institutions must not close this trial with the IRB of record for the study. Please contact the Alliance Regulatory team at regulatory@alliancenctn.org with any questions.

6.2 Specimen collection and submission

6.2.1 Correlative Science Manual (CSM)

The Alliance A032002 Correlative Science Manual (CSM) contains instructions for specimen collection, processing and shipping. The manual can be found on the BioMS and CTSU websites. Questions regarding the CSM should be addressed to the contacts specified in the manual.

6.2.2 Central Pathology Review

Retrospective central pathology review using patient diagnostic material is required for all patients registered to this study.

6.2.3 A032002 Biobanking

All participating institutions must ask patients for their consent to participate in the biobanking planned for Alliance A032002, although patient participation is optional. For patients who consent to participate (model consent question, "I agree that my samples and related health information may be kept in a biobank for use in future health research"). Biomarker studies will be performed. Rationale and methods for the scientific components of these studies are described in Section 14.2.

6.2.4 Overview of Specimen Requirements

	After registration & prior to C1D1*	6 weeks after registration	3 months after registration	Disease progression**
Mandatory for all patients:				
Diagnostic H & E slides for histopathology review	X			
For patients consented to A032002 biobanking:				
FFPE tumor tissue	X			
Peripheral Whole blood (EDTA tubes)	2 x 10 mL	2 x 10 mL	2 x 10 mL	2 x 10 mL
Urine (EDTA tubes)	X	X	X	X

* Blood and urine samples should be collected before patient receives first dose of study drug, recommend on the same day of registration

** Progression samples may be collected and submitted up to 1 month after progression. Continue peripheral **Whole Blood (EDTA tubes)** for ct-DNA specimen submission if there is early discontinuation of protocol therapy until disease progression

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 type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR; and
- 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

See Section 7.2.1 for details regarding data to be submitted via TRIAD for patients receiving radiation therapy.

6.4 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 ALLIANCE032002@irocohio.org.

6.4.1 Detailed Steps of Data Submission

Collection of images is required. Alliance A032002 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, PET/CT, CT, MRI and bone scans must be acquired at the following times and subsequently submitted. Supporting documentation must accompany all submissions for this trial. Images will be collected digitally for central archiving and curation. Imaging studies will be collected digitally at the following time points:

1. Baseline – within 42 days before registration
    a. CT of the chest/abdomen/pelvis
        i. Intravenous and oral contrast unless contraindicated
        ii. 5mm of less slice thickness
    b. Substitutions allowed:
        i. CT of the chest and MRI of the abdomen/pelvis
            1. Must be diagnostic quality
            2. Intravenous and oral contrast unless contraindicated
            3. 5mm or less slice thickness
        ii. FDG-PET/CT of the whole body or limited whole body
            1. CT must be of diagnostic quality
            2. Intravenous and oral contrast unless contraindicated
            3. 5mm or less slice thickness
    c. Bone scan of the whole body
2. Restaging – every 3 months +/- 14 days
    a. Same imaging as acquired at baseline
    b. Bone imaging only required if indicative of metastases at baseline or if signs or symptoms develop
3. Progression

4. Confirmatory Follow-up – 12 weeks after evidence of objective response

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.

If not using TRIAD, 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., ALLIANCE032002), 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 ALLIANCE032002@irocohio.org per the request by participating sites before their first data submission.

2. Web Transfer

   (http://upload.IROCOhio.org or https://moveit.imres.med.ohio-state.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 ALLIANCE032002@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 ALLIANCE032002@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 A032002
   The Ohio State University
   395 W. 12th Avenue, Suite [redacted]
   Columbus, Ohio, 43210
   Phone: (614) 293-2929
   Fax: (614) 293-9275

Once the imaging data submission is done, send an e-mail to IROC Ohio at the specific trial email ALLIANCE032002@irocohio.org to inform that the study has been submitted from the institution. IROC Ohio will notify site and ALLIANCE A032002 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 ALLIANCE032002@irocohio.org or call (614) 293-2929 for help.

6.5 Submission of Patient Completed Measures

All participating institutions must ask English-speaking patients for their consent to participate in the correlative study planned for Alliance A032002, although patient participation is optional. For patients registered to correlative study A032002-HO1 (model consent question, "I choose to take part in the Quality of Life study and will fill out these forms") the quality of life evaluations will be performed. For patients who consent to participate the questionnaires will be completed at the time points listed in the table below (quality of life evaluations should continue in patients who have experienced disease progression, it may be mailed or e-mailed to patients who do not have a planned clinic visit at the specified QOL time point).

Please note that PRO-CTCAE is contained in a separate booklet and is required for all patients per the study calendar. The schedule below only pertains to patients who consent to participate in the Quality of Life study.

Patient-completed booklets for this study are to be ordered prior to the pre-registration of any patients (see Section 4.3.2). These booklets can be downloaded from the CIRB Approved Documents tab on 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. 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. Booklet administration schedule is provided below.

Treatment Arm	≤ 21 days prior to treatment	45 days after registration (+/- 14 days)	6 months after registration (+/- 14 days)	12 months after registration (+/- 14 days)	24 months after registration (+/- 14 days)
For patients registered to A032002-HO1, submit patient-completed questionnaires* at the following time points:					
EORTC QLQ-C30	X	X	X	X	X
EORTC QLQ-BLM30	X	X	X	X	X
PROMIS-Fatigue 8a	X	X	X	X	X
EQ-5D-5L	X	X	X	X	X

* Download EORTC QLQ-C30, QLQ-BLM30, PROMIS-Fatigue 8a and EQ-5D-5L questionnaires for IRB submission and review from the 'CIRB Approved Documents' tab on the CTSU website. 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.

6.5.1 Patient Language Considerations

The PROMIS-Fatigue 8a, EORTC QLQ-BLM30, EORTC QLQ-C30, and EQ-5D-5L are available in English only.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 14 days of registration.

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

Patients must have completed last systemic cancer therapy within 4 weeks prior to the start of protocol treatment.

It is acceptable for individual chemotherapy 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 chemotherapy 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.

7.1 Immunotherapy with Pembrolizumab

Protocol therapy will consist of 1 cycle administered every 21 days. 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 ≥ 5 mm), treatment should be discontinued.

Arm	Agent	Dose	Route	Day	Rx
A	Pembrolizumab	200 mg	IV*	Day 1	Every 3 weeks
B	Pembrolizumab + RT	200 mg + RT**	IV*	Day 1	Every 3 weeks***

* Infused over approximately 30 minutes (range: 25-40 minutes).

** Patients will receive 3 fractions of radiation to a total dose of 24 Gy (8 Gy x 3 fractions).

Administration of radiotherapy will occur to a single site for subjects randomized to the pembrolizumab and radiotherapy group.

***Radiotherapy can be initiated after the first dose of immunotherapy and must be completed before 12 weeks after first dose of immunotherapy administered.

7.2 Radiotherapy

Administration of radiotherapy will occur to a single site for subjects randomized to the pembrolizumab and radiotherapy group.

Radiotherapy can be initiated after the first dose of immunotherapy and must be completed before 12 weeks after first dose of immunotherapy administered.

There is no size criterion for irradiated site and should follow this priority list:

1. Growing area that may cause symptoms.
2. Area that can tolerate the highest dose prescription (8 Gy x 3) based on normal tissue constraints.
3. If all above equal, then order would be Pelvis, Abdomen, Liver, Lung, Bone.

The goal of RT treatment is to deliver appropriate radiotherapy while minimizing exposure of surrounding normal tissues. Many different ways of delivering RT exist, and all are acceptable as long as the treating institution has completed the necessary credentialing. Most commercially available electron and photon-producing treatment units are allowed. As such, conventional linear accelerators and specialized linear accelerators with image guidance (e.g., Novalis, Trilogy, Synergy, Artiste, TrueBeam, Unity, ViewRay) are allowed. These units can be used with conformal dose delivery or IMRT. Specialized dose painting accelerators (e.g., Cyberknife, or Tomotherapy) are allowed provided they meet the technical specifications of the protocol and are used in a fashion that passes the

credentialing required by the protocol. Conventional linear accelerators without add-on IGRT must have some other IGRT capability like CT-on-rails in the treatment room.

IGRT is required for this study. Either 3DCRT or IMRT (including VMAT) are acceptable planning techniques. IMRT (including VMAT) can result in dosimetric inaccuracies in circumstances where tumor motion is not properly considered. Planning techniques may differ for each lesion to be treated provided that the tumor motion is properly accounted for with each technique when the target or targets are in or near the thorax region.

i. Dose Fractionation

Patients will receive 3 fractions of radiation to a total dose of 24 Gy.

For each metastatic location, Variation Acceptable range is described for plan scoring. Doses falling outside the range of Per Protocol and Variation Acceptable will be scored as Deviation Unacceptable.

There should be a minimum of 40 hours between treatments to any single metastasis.

ii. Technical Factors

Physical Factors

Only photon (x-ray) beams with photon energies ≥ 6MV or electron beam with electron energies 4 MeV – 20 MeV will be allowed. For metastases located within 3 cm of the lungs, photon energies of 6-10MV are required. Cobalt-60 and charged particle beams (including proton and heavier ions) are not allowed.

For lung central and lung peripheral metastases, photon beam energies > 10 MV are allowed only for a limited number (≤ 50% of all beams or all beam angles) of beams that must travel more than a cumulative distance of 10 cm through soft tissue (not lung) to reach the isocenter OR a shorter distance if the tumor abuts the chest or abdominal wall (i.e., to spare skin dose).

FFF photon beams are allowed if the institution has performed SBRT credentialing with FFF beams.

Treatment Technology

This protocol requires photon or electron treatment. Techniques including 3DCRT, IMRT, VMAT are allowed. Delivery on LINACs, Tomotherapy, or CyberKnife are acceptable.

Minimum Field Aperture (Field Size) Dimension

Because of uncertainties in beam commissioning resulting from electronic disequilibrium within small beam apertures, an equivalent square field dimension of 3 cm is required for any field used for treatment delivery for sites using standard 3-D conformal technique where nearly all of the PTV is encompassed for each beam. It is understood that this may exceed the technical requirements for small lesions. In such cases, the prescription dose is still prescribed to the edge of the defined planning treatment volume (PTV). For sites using dose painting including IMRT techniques, whereby design the entire PTV is not encompassed for each beam, smaller beam apertures are allowed. In addition, if the site has specifically commissioned the beams for smaller field sizes, and if these same beams have been employed in IROC Houston QA Center credentialing, they may reduce the minimum field aperture requirement to the size that has been commissioned and credentialed.

All institutions must use heterogeneity correction dose calculation algorithms approved by the IROC Houston QA Center independent of the treatment planning technique.

Stereotactic Targeting

For the purposes of this protocol, the term 'stereotactic' implies the targeting, planning, and directing of radiation beams along any trajectory in 3-D space toward a target of known 3-D coordinates. The coordinate system is defined by reliable 'fiducials.' A fiducial may be external or internal to the patient's body. External fiducials may relate to a frame or treatment device. Internal fiducials may be implanted markers OR reliably identifiable anatomy that is clearly visible on orthogonal kV imaging, including the tumor itself. In all cases, the relationship between the fiducial and the actual tumor position in real-time should be reliably understood for both planning and treatment.

Isocenter Placement

When using a gantry mounted linear accelerator for this protocol, the isocenter is defined as the common intersection point of gantry, collimator, and couch rotation for the treatment unit. For other types of treatment units (e.g., Tomotherapy or CyberKnife), a reference point in space that is typically positioned at the center of the target is used instead of a mechanical isocenter.

iii. Localization, Simulation, and Immobilization

Patient Positioning (Immobilization)

Patients will be positioned in a stable pose conducive to allowing accurate reproducibility of the target position throughout treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. Patient immobilization must be reliable enough to ensure that the gross tumor volume (GTV) does not deviate beyond the confines of the planning treatment volume (PTV).

Positioning patients directly on the couch and relying solely on image-guidance for reproducible set-up is strongly discouraged.

Simulation

All patients will undergo CT-based treatment planning in custom made immobilization devices. CT scan range must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting (if used), and be adequate to ensure contouring of all targeted metastases, as well as necessary organs at risk (OAR), defined below. High- resolution CT scans should be obtained with uniform slice thickness of ≤ 3mm throughout. If a single CT scan cannot be obtained due to a large spatial separation between metastases (i.e., cervical and femoral metastases), or planning system slice number limitation, multiple CT scans are allowed provided that OAR are entirely encompassed in a single CT scan.

Use of Contrast Agents

The use of IV contrast will be required for liver metastases unless using an MRLinac. For other metastases (central & peripheral lung, cervical/mediastinal, abdominal-pelvic, and spinal/paraspinal), the use of IV contrast is encouraged but will be left to the discretion of the treating physician.

The use of other contrast agents is left to the discretion of the treating oncologist. Vascular contrast from the planning dataset is recommended to be converted to water equivalent density if used for planning. Duplicate planning datasets obtained prior to injection of intravenous contrast may be used for dose calculation.

Respiratory Motion Assessment and Management

All metastases with potential for respiratory motion should be evaluated by appropriate means including 4D CT scan, implanted fiducial marker, or fluoroscopy at the time of simulation.

Respiratory motion management (RMM) including abdominal compression, active breathing control, breath hold, end expiratory gating, or fiducial marker tracking, is recommended for any metastasis to be treated with motion > 5mm. A recommended approach would be to use an ITV technique for motion < 1cm, but for motion > 1cm (typically too large for a free breathing ITV) motion management including but not limited to abdominal compression, active-breathing control (ABC), gating, breath hold, etc. should be used.

Localization Using Daily IGRT

As an RT protocol, this study requires the use of IGRT. IGRT is a computer assisted process that uses imaging devices that generate a series of coordinates for shifting the patient support system in three orthogonal directions (sometimes also including rotational changes) to position the treatment beams relative to target regions. The allowed technologies are as follows: cone-beam CT (CBCT) using either a specially mounted kV imaging head or the MV treatment beam with an opposed electronic imaging panel, dual fixed-position in-room kV imaging systems that are orthogonal or near orthogonal, an in-room standard diagnostic CT scanner that is geometrically linked to the treatment unit, and the Tomotherapy or MRLinac approach. Although all of these units are allowed, some might not be appropriate for some disease sites. For example, orthogonal imaging techniques result in overlapping structures that are not as easily visualized compared to 3D cone-beam approaches. Simple portal imaging approaches that do not use computer assistance are not considered suitable for this study.

When the treatment equipment does not include any device that allows direct visualization of anatomical structures using the treatment beam, the recommendations of AAPM Task Group Report 142 for testing the coincidence of the imaging and treatment reference points must be implemented. When specialized units such as Tomotherapy or Cyberknife are employed, the relevant AAPM guidance documents should be followed for testing the coincidence of imaging and treatment systems.

IGRT Requirements

The minimum IGRT requirement for each metastatic location is listed in Table 5-3. Volumetric imaging refers to 3D modalities (e.g., kV cone-beam, MV cone-beam, CT onrails, MRLinac), while orthogonal imaging refers to 2D modalities (e.g., kV OBI, ExacTrac). For volumetric imaging, appropriate CT window/level thresholds must be employed for registration at each metastatic location as outlined in Table 5-4. Additional IGRT may be employed at the discretion of the treating physician (i.e., orthogonal kV imaging prior to required volumetric imaging or volumetric imaging even if only orthogonal kV imaging is required). Note that when orthogonal kV imaging is employed for sites where respiratory motion is expected and not controlled via motion management techniques, care must be taken to ensure accurate targeting of the ITV within the treatment. For example, static kV imaging at an undetermined breath hold position would not be adequate IGRT for treating a free-breathing lung tumor.

Metastatic Location	Minimum IGRT Requirement	
	No Fiducials	**With Fiducials****
Lung--Peripheral+	Volumetric (3D)	Orthogonal kV (2D)
Lung—Central+	Volumetric (3D)	Orthogonal kV (2D)
Mediastinal/Cervical LN	Volumetric (3D)	N/A
Liver+	Volumetric (3D)	Orthogonal kV (2D)
Spinal	Orthogonal kV (2D)	Orthogonal kV (2D)
Osseous*	Orthogonal kV (2D)	N/A
Abdominal-pelvic+	Volumetric (3D)	Orthogonal kV (2D)

*NOTE: When osseous/rib metastases are classified into another metastatic location, follow the IGRT guidelines for that site.

**NOTE: When a metastasis contains an implanted fiducial that is clearly visible on kV orthogonal or volumetric imaging, either method can be used.

+NOTE: Registration to a soft tissue surrogate for the tumor is recommended for lung, liver, and abdominal-pelvic metastases for both 3D and 2D IGRT datasets.

Use of a shortened CT planning scan for registration may be important for IGRT systems that cannot handle a large number of CT slices. A subset of the planning CT scan can be uploaded to the IGRT system for localization of each metastasis. The CT data should include the metastasis of interest plus at least 5 cm superiorly and inferiorly.

iv. Target Volumes

Site Location Definition:

Site to be treated will be assigned to one of the seven “Metastasis Locations” as described below.

Site Locations:

Lung Central: GTV within 2 cm of proximal bronchial tree as described in RTOG 0813/0915:

Tumor within or touching the zone of the proximal bronchial tree, defined as a volume 2 cm in all directions around the proximal bronchial tree (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) [See Figure 5-1]. Tumors that are immediately adjacent to mediastinal or pericardial pleura (PTV touching the pleura) also are considered central tumors and are eligible for this protocol. A visual representation is shown below in Figure 5-1.

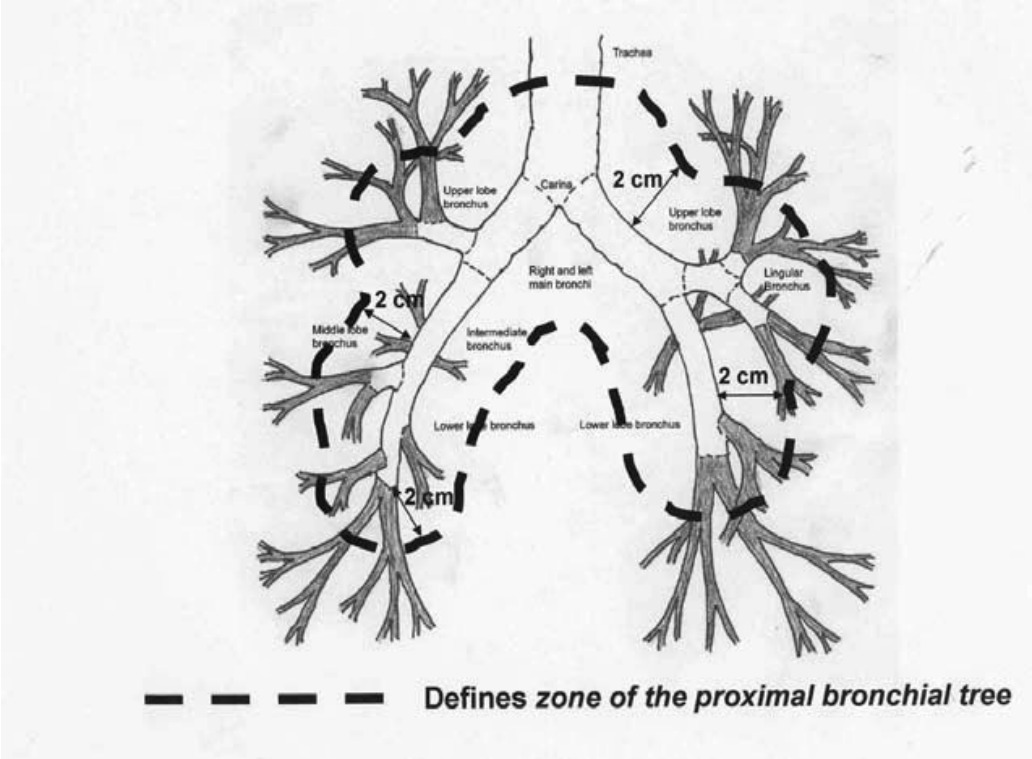


Figure 5-1

Lung Peripheral: Metastases within the lung parenchyma with GTV outside of the proximal bronchial tree as described above.

Mediastinal/Cervical LN: Mediastinal: GTV arising within the anatomic space between the lungs, above the diaphragm, and below the thoracic inlet at the level of the top of the sternal notch. Cervical Lymph nodes: GTV occurring within cervical lymph node Levels I-VI and/or retropharyngeal spaces.

- Sternal metastases will be assigned to the mediastinal/cervical lymph node location based on potential for normal tissue toxicity.

Liver: GTV arising within the liver.

- Rib metastases immediately adjacent to the liver will be assigned to the liver metastasis location based on potential for normal tissue toxicity.

Spinal: Metastases will be assigned to the spinal/paraspinal site if the GTV arises within the vertebral bodies expanded by 1 cm. Spinal metastases, shown in Figure 5-2 in black, can involve:

(a) The vertebral body only **OR**
(b) The vertebral body and pedicle **OR**
(c) Posterior elements only

Figure 5-2

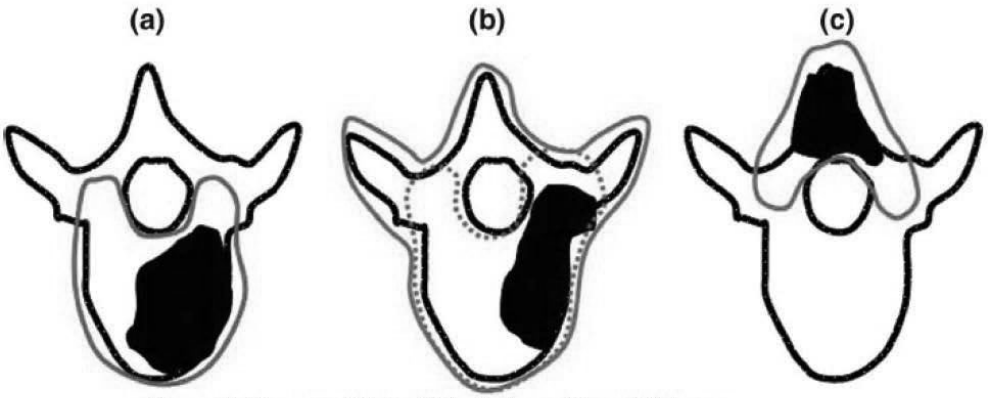


Figure 2: Diagram of Spine Metastasis and Target Volume

For each of these metastases, the PTV delineation will include:

(a) the involved vertebral body and both pedicles (solid red line in Figure 5-2a) **OR**

(b) a more generous delineation of the involved vertebral body and both pedicles (dashed red line in Figure 5-2b) **OR**

(c) the involved vertebral body, both pedicles, and the anterior and posterior elements of the spine (solid red line in Figure 5-2b) **OR**

(d) the spinous process and laminae (solid red line in Figure 5-2c)

- The target volume may be chosen at the discretion of the treating Radiation Oncologist based on the extent of tumor involvement.
- Spinal metastases with epidural extension will only be included if there is > 3 mm gap between the edge of the epidural metastasis and edge of the spinal cord.
- Metastases arising in the ribs within 1 cm of the edge of the vertebral body should be included in the spinal metastasis location, but osseous metastases planning guidelines are to be used.

Osseous: GTV arising within an osseous structure, part of the axial skeleton, not included in the spinal definition.

- Rib metastases that are within 1 cm of the vertebral bodies will be classified into the spinal metastasis location given the similar normal tissues at risk.
- Rib/scapular metastases within the thorax adjacent to lung parenchyma will be classified into the lung metastasis location given the similar normal tissues at risk.
- Rib/osseous metastases adjacent (≤ 1cm) to mediastinal or cervical structures will be classified into the mediastinal/cervical lymph node location given the similar normal tissues at risk.
- Rib metastases adjacent (≤ 1cm) to the liver will be classified into the liver location given the similar normal tissues at risk.
- Rib metastases adjacent to the stomach/abdominal wall will be classified into the intra-abdominal location given the similar normal tissues at risk.
- Sternal metastases will be considered part of the

mediastinal/cervical lymph nodes location given the similar normal tissues at risk.

Abdominal-pelvic: GTV arising within the anatomic space defined by the diaphragm superiorly, the genitourinary diaphragm inferiorly including the peritoneal and retroperitoneal spaces, not including liver, osseous, or spinal metastases.

Target Volume Definition Based on Metastatic Location:

Specific RT planning parameters depend on the location of the treated metastasis as well as mechanism used for motion management/evaluation. The table below defines appropriate planning CT window/leveling, recommended additional modality scans to be fused, as well as how to define the GTC, ITV, CTV, and PTV for each metastatic location. Only rigid registration will be permitted for multi-modality fusion. In general, the GTV is defined as the entirety of the metastasis as seen on planning CT scan aided by additional diagnostic imaging studies (i.e., PET/CT or MRI). Use of additional diagnostic studies is left to the discretion of the treating physician. The CTV=GTV; there is no margin added for microscopic extension. In general, either a helical CT or 4DCT will be used for defining the GTV/ITV depending upon the tumor motion encountered, although both scans may be acquired at the time of simulation. Typically, the ITV is generated using either expiratory/inspiratory phase scans or from reconstructed maximum intensity projection (MIP) scans. Maximum/minimum intensity projections (MIP/MinIP) should be used with caution because the MIP reconstruction for lung or MinIP reconstruction for liver may erroneously define an ITV in cases of significant irregular breathing or when tumors abut soft tissue structures (e.g., the diaphragm for MIP) or fat (for the MinIP).

	Metastatic Location						
Planning Parameter	**Lung Central**	**Lung Peripheral**	**Liver**	**Abdominal -pelvic**	**Mediastinal /Cervical Lymph Nodes**	**Osseos**	**Spinal**
CT window/level	Pulmonary/ Mediastinal	Pulmonary/ Mediastinal	Hepatic	Soft tissue	Pulmonary / Mediastinal	Bone/ soft tissue	Bone/ soft tissue
Additional Studies	PET/CT	PET/CT	PET/CT MRI	PET/CT MRI	PET/CT	PET/CT MRI	PET/CT MRI
Multiphase CT	N/A	N/A	N/A	Yes	N/A	N/A	N/A
Anatomy of focus for multi-modality fusion	Bony Anatomy	Bony Anatomy	Liver	Bony Anatomy	Bony Anatomy	Bony Anatomy	Bony Anatomy
GTV definition	Metastasis	Metastasis	Metastasis	Metastasis	Metastasis	Metastasis	Metastasis
CTV definition	= GTV/ITV*	= GTV/ITV*	= GTV/ ITV*	=GTV/ ITV*	=GTV/ ITV*+	= GTV	= GTV
PTV axial expansion	= CTV + 5mm**	= CTV + 5mm**	= CTV + 5mm**	= CTV + 5mm**	= CTV + 5mm**	= CTV + 5mm**	= PTV in RTOG 0631** (see Figure 5-2)

PTV craniocaudal expansion	= CTV + 7mm**	= CTV + 7mm**	= CTV + 7mm**	= CTV + 7mm**	= CTV + 7mm**	= CTV + 7mm**	= PTV in RTOG 0631** (see Figure 5-2)

***NOTE:** A GTV to ITV expansion of greater than 1cm in any one direction is strongly discouraged and alternative respiratory management technique is suggested.

****NOTE:** When osseous/rib metastases are classified into other specific metastatic locations, the planning guidelines for that metastatic location should be used. If rib metastases are grouped into the spinal metastasis location, then the metastasis should be contoured as defined for osseous metastases, but the prescription doses for the spinal region should be used.

[+]**NOTE:** Mediastinal lymph nodes should undergo motion assessment and an ITV should be generated to account for motion.

v. Treatment Planning

Planning Techniques

General Considerations: A variety of planning techniques can be used to deliver RT. General guidelines include the following:

- Multiple coplanar or non-coplanar beam arrangements are acceptable.
- Typically 7-13 static radiation beams with equal weighting are used. It is recommended that at least 10 beams be used when possible.
- A minimum field dimension of 3 cm should be observed while treating small metastases with 3D-CRT.
- Dynamic conformal arcs are acceptable. It is recommended that arcs span a total for all beams of 340 degrees.
- For non-IMRT or dose painting techniques, the conformal field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e., no additional "margin" for dose buildup at the edges of the blocks or MLC jaws beyond the PTV). The only exception will be when observing the minimum field dimension of 3 cm when treating small lesions.
- The prescription isodose line covering 95% the PTV will generally be 80-90%, but may range from 60-90% where the maximum dose is 100%. As a result, a "hotspot" will exist within the PTV that is equal to the prescription dose divided by the prescription isodose line (i.e., 45 Gy/0.6 = 75 Gy when 45 Gy is prescribed to the 60% isodose).
- Doses higher than the prescription isodose (i.e., hotspots) should be manipulated to occur within the target.

Dose calculations: All dose distributions shall include corrections for tissue heterogeneities. The approved algorithms to be used are found on the IROC Houston website (http://irochouston.mdanderson.org).

Successful treatment planning will require accomplishment of all of the following criteria:

1. Normalization: The treatment plan should be initially normalized such that 100% corresponds to the maximum dose within the PTV (MAXPTV). While this point will typically correspond to the PTV center of mass, it can be located elsewhere within the PTV.
2. Prescription Isodose Surface Coverage: The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is

conformally covered by the prescription isodose surface. Doses less than 95% of the prescription dose are restricted to the outside edges of the PTV as shown in Figure 5-3. The prescription isodose surface selected MUST be ≥ 60% and ≤ 90% of the dose maximum within the PTV (MAXPTV). The MAXPTV corresponds to the normalization point (100%) of the plan as noted in number 1 above.

3. Target Dose Heterogeneity: Rather than prioritizing target dose homogeneity, RT treatment planning prioritizes adequate minimum target coverage and rapid dose fall-off gradients outside of the target. Hot spots within targets are generally accepted without consequence since targets are mostly tumor. The only exception is when the hotspot within the PTV also intersects an OAR (see Figure 5-3).

4. Critical Organ Doses: Respect all critical organ dose-volume limits.

5. High-Dose Spillage:

    a. *Location*: Any dose > 105% of the prescription dose should occur within the PTV and not within the normal tissues outside the PTV. See Figure 5-3.

    b. *Volume:* Acceptable isodose distributions should be as conformal as possible. To this end, the ratio of prescription isodose volume to PTV should be as small as possible.

        i. The ratio of the prescription isodose volume to the PTV volume should be < 1.2. Acceptable variations include a ratio of 1.2-1.5. Ratios above 1.5 will be considered unacceptable deviations. The prescription line for each lesion will be contoured for calculation of this ratio. The prescription line will be labelled as V_5000 with the 5000 changing to reflect the prescription dose in cGy. Contours with identical doses should be distinguished.

        ii. Guidelines for the ratio of the 50% prescription isodose volume to the PTV volume (R50%) and for the maximum dose at 2cm (D2cm) from the PTV are given in Table 5-5. Additionally, the 50% isodose volume may be elongated deliberately in order to avoid OAR, thereby making it difficult to meet the guidelines in Table 5-5. This is acceptable as long as normal tissue constraints are met.

        iii. Given that conformal tumor coverage is often more difficult to achieve in lung than in more homogeneous organs, these ratios should serve as a guide for liver, abdominal-pelvic, mediastinal/cervical metastases as well.

        iv. Elliptically shaped metastases as well as extremity metastases may not meet these guidelines. This is acceptable as long as normal tissue constraints are respected. These criteria will not be required in treating very small tumors (< 2.5 cm axial GTV dimension or < 1.5 cm craniocaudal GTV dimension) in which the required minimum field size of 3 cm results in the inability to meet a conformity ratio of 1.5.

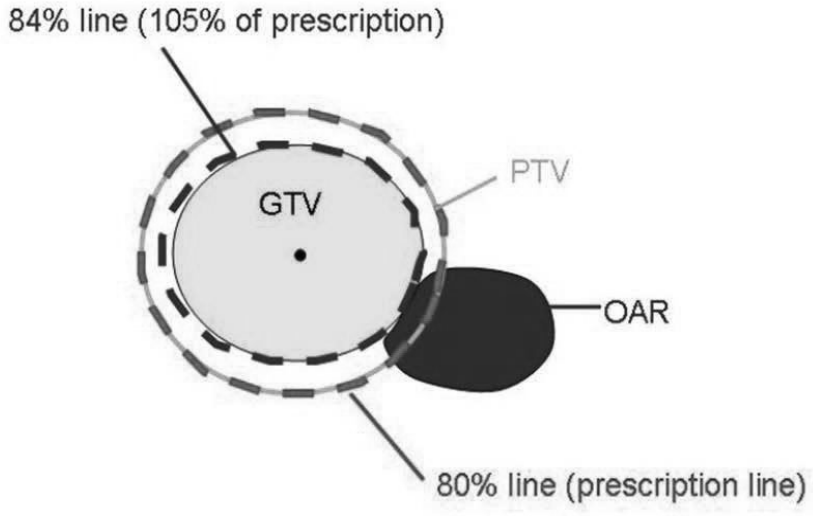
Table 5-5

PTV Volume (cc)	Ratio of 50% Prescription Isodose Volume to PTV Volume, R50%	Maximum Dose at 2cm (D2cm) from PTV in any direction as % of Prescribed Dose
1.8	< 7.5	<57.0
3.8	< 6.5	<57.0
7.4	< 6.0	<58.0
13.2	< 5.8	<58.0
22.0	< 5.5	<63.0
34.0	< 5.3	<68.0
50.0	< 5.0	<77.0
70.0	< 4.8	<86.0
95.0	< 4.4	<89.0
126.0	< 4.0	<91.0
163.0	< 3.7	<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 used.

Figure 5-3



1. Prescription dose 50 Gy
2. Prescription isodose 80%
3. 105% of prescription dose 52.5 Gy (corresponds to 84% isodose line)
4. Maximum dose (normalization) at isocenter is 62.5 Gy

Planning Priorities

Every attempt should be made to successfully satisfy all of the planning goals and OAR criteria without receiving a plan score of Deviation Unacceptable. In some circumstances, it may not be possible to meet all the ideal criteria, leading

to plans in the Variation Acceptable range. Thus, suggested priority of planning goals in order of importance is:

1. Respect spinal cord, cauda equina, sacral plexus and brachial plexus dose constraints.
2. Meet dose "compactness" constraints including the prescription isodose surface coverage, high-dose spillage (location and volume), and intermediate dose spillage (D2cm, and R50%) as these define the aim in using RT. Dose compactness should be assessed for plans based on treatment dose for a single lesion.

   Meet critical structure constraints other than those listed in 1. The OAR constraints are last in priority (except for nervous system tolerance) because they are the least validated. The aim of a RT plan is captured mostly in the dose compactness criteria, thereby justifying their higher priority. As an example, in a case where not all goals can be met, it would be suggested to meet dose compactness goals without deviation, even at the expense of a non- spinal cord normal tissue having an acceptable variation. Unacceptable deviations should be avoided in all cases.

3. In cases where PTV coverage cannot be achieved while avoiding unacceptable deviations to OARs coverage of a section of PTV including or immediately adjacent to the OAR may be as low as 70% of the prescription dose ONLY in this situation.

vi. Critical Structures

<u>Note</u>: All required structures must be labeled as listed below in Table 5-6 for digital RT data submission.

The following table outlines the required naming of the various normal and critical structures.

Table 5-6

Standard Name	***Description***
Group 1 : Lung- Peripheral	
PTV_2400_1	For peripheral lung tumors.
GTV_2400_1	For peripheral lung tumors
PTV_20_1	PTV with 2cm expansion
NonPTV_1	External minus PTV
NonPTV_20_1	External minus PTV_20 (PTV with a 2 cm expansion)
SpinalCord	Spinal cord
BrachialPlexus	Brachial plexus
BrachialPlex_L	Left Brachial Plexus
BrachialPlex_R	Right Brachial Plexus
BronchialTree	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
Esophagus	Esophagus
GreatVessels	Great Vessels
BronchTree_20	proximal bronchial tree expanded by 2cm

Larynx	Larynx
ChestWall	Chest wall
Rib	Ribs within 5 cm of the PTV should be contoured
Heart	Heart
External	Body surface
SkinOAR	skin will be defined as the outer 0.5 cm of the body surface
Lungs	Combined Left and Right Lungs
Lung_R	Right Lung
Lung_L	Left Lung
Trachea	Trachea
Stomach	Stomach
Liver	Liver
BileDuct	Bile duct
Kidney_R	Right Kidney
Kidney_L	Left Kidney
Kidneys	Total kidneys
Group 2 : Lung - Central	Description
PTV_2400_2	For central lung tumors
GTV_2400_2	For central lung tumors
PTV_20_2	PTV with 2cm expansion
NonPTV_2	External minus PTV
NonPTV_20_2	External minus PTV_20 (PTV with a 2 cm expansion)
SpinalCord	Spinal cord
BrachialPlexus	Brachial plexus
BrachialPlex_L	Left Brachial Plexus
BrachialPlex_R	Right Brachial Plexus
BronchialTree	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
Esophagus	Esophagus
GreatVessels	Great Vessels
BronchTree_20	proximal bronchial tree expanded by 2cm
Larynx	Larynx
ChestWall	Chest wall
Rib	Ribs within 5 cm of the PTV should be contoured
Heart	Heart
External	Body surface
SkinOAR	skin will be defined as the outer 0.5 cm of the body surface
Lungs	Combined Left and Right Lungs
Lung_R	Right Lung
Lung_L	Left Lung
Trachea	Trachea
Stomach	Stomach
Kidney_R	Right Kidney
Kidney_L	Left Kidney

Kidneys	Total kidneys
Esoph_NonAdj	Esophagus (Non-adjacent wall)
Trachea_NonAdj	Trachea (Non-adjacent wall)
GrVess_NonAdj	Great vessels (Non-adjacent wall)
Group 3 : Mediastinal/ Cervical Lymph Node	Description
PTV_2400_3	For mediastinal and cervical lymph node tumors.
GTV_2400_3	For mediastinal and cervical lymph node tumors.
PTV_20_3	PTV with 2cm expansion
NonPTV_3	External minus PTV
NonPTV_20_3	External minus PTV_20 (PTV with a 2 cm expansion)
SpinalCord	Spinal cord
BrachialPlexus	Brachial plexus
BrachialPlex_L	Left Brachial Plexus
BrachialPlex_R	Right Brachial Plexus
BronchialTree	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
Esophagus	Esophagus
GreatVessels	Great Vessels
BronchTree_20	proximal bronchial tree expanded by 2cm
Larynx	Larynx
ChestWall	Chest wall
Rib	Ribs within 5 cm of the PTV should be contoured by outlining the bone and marrow
Heart	Heart
External	Skin
SkinOAR	skin will be defined as the outer 0.5 cm of the body surface
Lungs	Combined Left and Right Lungs
Lung_R	Right Lung
Lung_L	Left Lung
Trachea	Trachea
Stomach	Stomach
Kidney_R	Right Kidney
Kidney_L	Left Kidney
Kidneys	Total kidneys
Esoph_NonAdj	Esophagus (Non-adjacent wall)
Trachea_NonAdj	Trachea (Non-adjacent wall)
GrVess_NonAdj	Great vessels (Non-adjacent wall)
Group 4 : Liver	Description
PTV_2400_4	For liver tumors.
GTV_2400_4	For liver tumors.
PTV_20_4	PTV with 2cm expansion
NonPTV_4	External minus PTV
NonPTV_20_4	External minus PTV_20 (PTV with a 2 cm expansion)

SpinalCord	Spinal cord
ChestWall	Chest wall
Heart	Heart
External	Skin
SkinOAR	skin will be defined as the outer 0.5 cm of the body surface
Stomach	Stomach
Kidney_R	Right Kidney
Kidney_L	Left Kidney
Kidneys	Total kidneys
Femurs	Both Femurs
Duodenum	Duodenum
Bladder	Bladder
Liver	Liver
BileDuct	Bile duct
Ureter	Ureter
Bowel	Large and Small Bowel
Group 5 : Spinal/ Paraspinal	Description
PTV_2400_5	For spinal/paraspinal tumors.
GTV_2400_5	For spinal/paraspinal tumors.
NonPTV_5	External minus PTV
NonPTV_10_5	External minus PTV_10 (PTV with a 1 cm expansion)
NonPTV_20_5	External minus PTV_20 (PTV with a 2.0 cm expansion)
SpinalCord	Spinal cord
SpinalCord_Prt	A portion of the spinal cord contoured near a target
BrachialPlexus	Brachial plexus
BrachialPlex_L	Left Brachial Plexus
BrachialPlex_R	Right Brachial Plexus
CaudaEquina	Cauda equine
SacralPlexus	Sacral plexus
Esophagus	Esophagus
GreatVessels	Great Vessels
BronchialTree	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
BronchTree_20	Proximal bronchial tree expanded by 2cm
ChestWall	Chest wall
Rib	Ribs within 5 cm of the PTV should be contoured by outlining the bone and marrow
Heart	Heart
External	Skin
SkinOAR	skin will be defined as the outer 0.5 cm of the body surface
Lungs	Combined Left and Right Lungs
Lung_R	Right Lung

Lung_L	Left Lung
Trachea	Trachea
Stomach	Stomach
Kidney_R	Right Kidney
Kidney_L	Left Kidney
Kidneys	Total kidneys
Liver	Liver
BileDuct	Bile duct
Duodenum	Duodenum
Bowel	Large and Small Bowel
Rectum	Rectum
Bladder	Bladder
Femurs	
Esoph_NonAdj	Esophagus (Non-adjacent wall)
Trachea_NonAdj	Trachea (Non-adjacent wall)
GrVess_NonAdj	Great vessels (Non-adjacent wall)
Group 6 : Osseous	Description
PTV_2400 _6	For non-spinal osseous tumors.
GTV_2400_6	For non-spinal osseous tumors.
NonPTV _6	External minus PTV
NonPTV_10 _6	External minus PTV_10 (PTV with a 1 cm expansion)
NonPTV_20 _6	External minus PTV_20 (PTV with a 2.0 cm expansion)
SpinalCord	Spinal cord
SpinalCord_Prt	A portion of the spinal cord contoured near a target
BrachialPlexus	Brachial plexus
CaudaEquina	Cauda equine
BrachialPlex_L	Left Brachial Plexus
BrachialPlex_R	Right Brachial Plexus
SacralPlexus	Sacral plexus
Esophagus	Esophagus
GreatVessels	Great Vessels
BronchialTree	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
BronchTree_20	Proximal bronchial tree expanded by 2cm
ChestWall	Chest wall
Rib	Ribs within 5 cm of the PTV should be contoured by outlining the bone and marrow
Heart	Heart
External	Skin
SkinOAR	skin will be defined as the outer 0.5 cm of the body surface
Lungs	Combined Left and Right Lungs
Lung_R	Right Lung

Lung_L	Left Lung
Trachea	Trachea
Stomach	Stomach
Kidney_R	Right Kidney
Kidney_L	Left Kidney
Kidneys	Total kidneys
Liver	Liver
BileDuct	Bile duct
Duodenum	Duodenum
Bowel	Large and Small Bowel
Rectum	Rectum
Bladder	Bladder
Femurs	
Esoph_NonAdj	Esophagus (Non-adjacent wall)
Trachea_NonAdj	Trachea (Non-adjacent wall)
GrVess_NonAdj	Great vessels (Non-adjacent wall)
Group 7 : Abdominal-pelvic metastases (lymph node/ adrenal gland)	Description
PTV_2400 _7	For abdominal-pelvic tumors.
GTV_2400 _7	For abdominal-pelvic tumors.
PTV_20 _7	PTV with 2cm expansion
NonPTV _7	External minus PTV
NonPTV_20 _7	External minus PTV_20 (PTV with a 2 cm expansion)
SpinalCord	Spinal cord
CaudaEquina	Cauda equina
SacralPlexus	Sacral plexus
ChestWall	Chest wall
Heart	Heart
External	Skin
SkinOAR	skin will be defined as the outer 0.5 cm of the body surface
Stomach	Stomach
Kidney_R	Right Kidney
Kidney_L	Left Kidney
Kidneys	Total kidneys
Femurs	Both Femurs
Duodenum	Duodenum
Bladder	Bladder
Liver	Liver
BileDuct	Bile duct
Bowel	Large and Small Bowel

Planning RT Near Prior Radiotherapy Volumes

The toxicity of delivering RT to an area in close proximity to prior conventionally fractionated external beam radiotherapy (EBRT) volumes is not known. Therefore, overlap of protocol treatment SBRT isodoses with prior fractionated external beam volumes must be minimized.

Organs at Risk

For all metastases, specific organs at risk (OAR) must be contoured. The specific OAR to be contoured will depend on the location of the metastasis to be treated. The contour of structures that have a lumen (bronchus, trachea, esophagus, etc.) will include both the “wall” and the

"lumen" to result in a cylindrical structure. In general, OAR within 3 cm of any single metastasis should be contoured. To identify these OARs, all PTVs will be expanded by 3cm and any OAR that overlaps with PTV + 3cm must be contoured.

Lung Central/Lung Peripheral/Mediastinal/Cervical Lymph Node metastases:

- Proximal tracheobronchial tree (as defined by Timmerman et al. 2006)
- Lungs, left/right/combined
- Heart
- Great vessels
- Trachea
- Esophagus
- Spinal cord
- Chest wall
- Brachial plexus
- Skin
- Liver
- Bile duct
- Kidney, left/right
- Larynx
- Stomach
- Rib

Liver/Abdominal-pelvic metastases:

- Heart
- Stomach
- Duodenum
- Spinal cord
- Kidney, left/right
- Bowel
- Rectum
- Bladder
- Skin
- Lungs, left/right/combined
- Liver
- Bile duct
- Chestwall
- Sacral plexus
- Cauda equine
- Femurs

Spinal Metastases:

- For all spinal metastases, the partial spinal cord volume as per RTOG 0631 should be defined as follows: the partial spinal cord should be contoured starting from 5-6 mm above the superior extent of the target volume to 5-6 mm below the inferior extent of the target volume.
- For thoracic and cervical spinal metastases, follow guidelines for pulmonary/ mediastinal/cervical metastases depending upon nearby organs at risk.
- For lumbar metastases, follow guidelines for abdominal-pelvic

metastases.

Osseous Metastases:

- OAR for osseous metastases will depend on the location of the osseous metastasis.

NOTE: OARs listed above should be contoured in their entirety if a portion of that organ is located within 3 cm of the osseous metastases.

Contouring of Normal Tissue Structures

In order to verify each of these limits, the organs must be contoured such that appropriate volume histograms can be generated. 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 ending at L2. 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 cm 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, lumen, 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 the 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, as indicated in Figure 5-1. 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."

Whole Lung

Both the right and left lungs should be contoured as one structure. 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 in this structure.

Proximal Bronchial Tree Plus 2 cm

As part of determining if lung metastases are central or peripheral, adhering to the eligibility of the zone of the proximal bronchial tree, the RTOG SBRT protocols defined an artificial structure 2 cm larger in all directions from the proximal bronchial tree. If the GTV falls within this structure, the patient is eligible for this protocol. Most treatment planning systems have automatic contouring features that will generate this structure without prohibitive effort at the time of treatment planning. This structure is not required by the protocol, but its construction is suggested to facilitate appropriateness of patient selection. Alternately, participating sites may use ruler tools in the treatment planning software to ensure protocol compliance.

Skin

The external contour of the patient will be contoured. The skin OAR 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.

Bowel (Large/Small)

The bowel should be contoured 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 should be contoured.

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 should be contoured.

Bile ducts

To contour the bile ducts, 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 should be contoured.

Rib

Ribs within 5 cm of the PTV should be contoured by outlining the cortical bone including the intramedullary space. 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. Most treatment planning systems have automatic contouring features that will generate this structure without prohibitive effort at the time of treatment planning. If possible, this structure should be constructed as a single contour that is 2 cm larger than the PTV.

Other Structures

The constraints tables above contain other structures. These are required if the structure is within 3 cm of the PTV.

Planning priorities for Organs at Risk:

The spinal cord doses are absolute limits, and treatment delivery that exceeds these limits will constitute an unacceptable deviation. However, some OAR (i.e., the esophagus, trachea, bronchi and heart within the lung) may be situated adjacent to the treated GTV/PTV. As such, there is no specified limit as tumors that are immediately adjacent to that organ will not be able to be treated to the prescription doses without irradiating a small volume of that organ to the prescribed dose. In such a case, the planning must be accomplished so that there is no hot spot within that organ, even if that organ is part of the GTV/PTV, i.e., that no part of any serial OAR receives more than 105% of the prescribed dose (deviation unacceptable). In addition, the volume of the OAR in question needs to be minimized, both in length and in the width (i.e., circumference), with efforts made to reduce the dose to the contralateral wall of the organ. For parallel OAR, exceeding the doses in Table 5-7 by more than 110% of the prescribed dose will be considered an unacceptable deviation.

For non-spinal cord OAR with known sensitivity to high doses of radiation (including the bowel, esophagus, and stomach) included within a PTV or immediately adjacent to PTVs, a prescription dose at the lower end of acceptable variation should be used.

Additionally, every effort should be made to cover the GTV with the prescription dose while ensuring rapid falloff to the organ at risk. Coverage of a section of PTV including or immediately adjacent to the OAR may be as low as 70% of the prescription dose ONLY in this situation. Every effort should be made to cover 100% of the GTV by the prescription dose at the lower end of acceptable variation. Since the tumor and normal tissue may not allow strict avoidance, the larger volume limits will not be scored as unacceptable deviations if exceeded.

For tumors that are not immediately adjacent to any OAR, centers are encouraged to observe prudent treatment planning principles in avoiding unnecessary radiation exposure to critical normal structures; we expect that the OAR doses will be as low as achievable (ideally, < 6 Gy/fraction).

Table 5-7

Serial Organ	DVH Metric	Per Protocol Dose (Gy)	Variation Acceptable Dose (Gy)	Avoidance Endpoint
Spinal Cord	D1.2cc[Gy]	<13	-----	Myelitis (Timmerman)
	D0.03cc[Gy]	<22.5	-----	Myelitis (Timmerman)
Ipsilateral Brachial Plexus	D3cc[Gy]	<22	<25.2	Brachial Plexopathy (Timmerman)
	D0.03cc[Gy]	<26	-----	Brachial Plexopathy (Timmerman)

Cauda Equina	D0.03cc[Gy]	<25.5	-----	Neuritis (Timmerman)
	D5cc[Gy]	<21.9	-----	Neuritis (AAPM TG-101)
Sacral Plexus	D0.03cc[Gy]	<24	-----	Neuropathy (AAPM TG-101)
	D5cc[Gy]	<22.5	-----	Neuropathy (AAPM TG-101)
Trachea and Ipsilateral Bronchus *	D5cc[Gy]	<25.8	-----	Stenosis/Fistula (Timmerman)
	D0.03cc[Gy]	<30	-----	Stenosis/Fistula (Z4099)
Esophagus *	D5cc[Gy]	<17.7	<25.2	Stenosis/Fistula (Z4099)
	D0.03cc[Gy]	<27	-----	Stenosis/Fistula (Timmerman 2006/RTOG0618)
Heart	D15cc[Gy]	<24	<25.2	Pericarditis (Z4099)
	D0.03cc[Gy]	<30	-----	Pericarditis (Z4099)
Great Vessels	D10cc[Gy]	<39	-----	Aneurysm (Z4099)
	D0.03cc[Gy]	<45	-----	Aneurysm(Z4099)
Skin	D10cc[Gy]	<31	-----	Ulceration (Timmerman)
	D0.03cc[Gy]	<33	-----	Ulceration (Z4099)
Stomach	D10cc[Gy]	<22.5	<25.2	Ulceration/Fistula (Timmerman)
	D0.03cc[Gy]	<30	-----	Ulceration/Fistula (Timmerman)
Duodenum *	D10cc[Gy]	<15	<25.2	Ulceration (Timmerman 2006)
	D0.03cc[Gy]	<24	<25.2	Ulceration(Timmerman 2006)
Bowel *	D20cc[Gy]	<24	<25.2	Colitis/Fistula (Z4099)
	D0.03cc[Gy]	<34.5	-----	Ulceration (Timmerman)
Rectum*	D0.03cc[Gy]	<49.5	-----	Ulceration (Timmerman)
	D3.5cc[Gy]	<45	-----	Proctitis/Fistula (Timmerman)
	D20cc[Gy]	<27.5	-----	Proctitis/Fistula (Timmerman)
Bladder	D0.03cc[Gy]	<33	-----	Cystitis/Fistula (Timmerman)
	D15cc[Gy]	<16.8	<25.2	Cystitis/Fistula (AAPM TG-101)
Ureter	D0.03cc[Gy]	<40	-----	Stenosis (Timmerman)
Penile bulb	D3cc[Gy]	<25	<25.2	Impotence (Timmerman)
Femoral heads	D10cc[Gy]	<24	<25.2	Necrosis (Timmerman)
Bile duct	D0.03cc[Gy]	<36	-----	Stenosis (Timmerman)
Renal hilum/vascular trunk	D15cc[Gy]	<19.5	<25.2	Malignant Hypertension (Timmerman)
Rib	D5cc[Gy]	<40	-----	Pain/Fracture (Timmerman)
	D0.03cc[Gy]	<50	-----	Pain/Fracture (Timmerman)
Parallel Organ				
Lung Total	D15%[Gy]	<20	<22	Pneumonitis (RTOG0618)

	D37%[Gy]	<11	<12.1	Pneumonitis (Timmerman)
	CV10.5Gy[cc]**	>1500 cc	-------	Basic Lung Function (Z4099)
	CV11.4Gy[cc]**	>1000 cc	-------	Pneumonitis (Z4099)
Total Kidney	CV15Gy[cc]**	>200 cc	-------	Basic Kidney Function (Timmerman)
Liver	CV17.1Gy[cc]**	>700 cc	-------	Liver Function (Timmerman 2006, Z4099)

* **NOTE: 1)** Every effort should be made to avoid circumferential irradiation.

NOTE: **2)** Doses to serial OARs up to and including 105% of the dose prescribed to the PTV will be scored as Variation Acceptable. Doses to parallel OARs up to 110% of the values listed in the table will be scored as Variation Acceptable. Doses above these values will be scored as Deviation Unacceptable.

** **NOTE**: **3)** A complementary volume (CV) or "cold volume" is the volume of tissue receiving the indicated dose or less. CVxGy[cc] are complementary or cold volume objectives for parallel tissues, where "xGy" is the threshold dose and the critical volumes are displayed in the table.

Rib/Chest Wall Dose Constraints

Recent reports have highlighted that the rib and chest wall in proximity to the treated lesion may represent an organ at risk for complication. Tumor location, particularly when located peripherally, will enhance the potential risk for chest wall toxicity. While target coverage should not be compromised to limit dose to the rib/chest wall, every effort should be made to minimize dose to this OAR.

vii. Documentation Requirements

Treatment Interruptions

In general, treatment interruptions should be avoided by preventative medical measures and supportive therapies. Treatment breaks, including indications, must be clearly documented on the treatment record.

Quality Assurance Documentation

See Section 7.2.1 for the list of items to be submitted for review.

viii. Compliance Criteria

Treatment Duration

Treatment Duration will be defined per metastasis

Per Protocol:

- 3 fraction treatment: All 3 fractions of SBRT should be completed within 2 weeks of first SBRT dose

Acceptable Variation: Treatment completing > 2 but < 3 weeks

Unacceptable Deviation: Treatment completed > 3 weeks

PTV Dosimetry Compliance

Per Protocol: The entire PTV receives >95% of the prescription dose.

Variation Acceptable: The entire PTV receives 70-95% of the prescription dose.

Deviation Unacceptable: The entire PTV receives <70% of the prescription dose.

Conformity Compliance

Per Protocol: The ratio of the prescription isodose volume to the PTV volume is <1.2.

Variation Acceptable: The ratio of the prescription isodose volume to the PTV volume is <1.5.

Deviation Unacceptable: The ratio of the prescription isodose volume to the PTV volume is >1.5.

Organ at Risk Dosimetry Compliance

Respect spinal cord, cauda equina, sacral plexus and brachial plexus dose constraints. Any dose to spinal cord, cauda equina, sacral plexus above that listed in Table 5-7 will be considered an unacceptable deviation. For all other serial OARs, when OAR dose criteria provided in Table 5-7 cannot be accomplished by following planning priorities listed above, doses to the OARs of more than 105% of the dose prescribed to the PTV will be scored as Deviations Unacceptable. For serial OARs with per protocol limits greater than 105% of the prescribed dose, there are no variation acceptable criteria, and exceeding the per protocol limit will be considered an unacceptable deviation. Doses to parallel OARs exceeding 110% of the doses listed in Table 5-7 will be scored as unacceptable deviations.

Radiation Therapy Adverse Events

All Radiation Therapy AEs will be scored according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.

Adverse events related to SBRT for the treatment of metastases are dependent on the location of the metastases treated, as well as from exposure of surrounding normal tissues.

For all treated metastases, fatigue is likely to occur and should be transient, lasting < 8 weeks. Other adverse events are likely to be related to the specific metastatic location receiving SBRT.

Lung (Central and Peripheral), Mediastinal/Cervical Lymph Node Metastases:

Cardiac and Pericardial Injury

Although cardiac and pericardial injury is uncommon in the conventionally fractionated course of RT, with large doses per fraction of RT a number of possible side-effects can be seen.

Gastrointestinal/Esophageal Injury

The radiation effects on the esophagus can be acute: esophagitis (i.e., dysphagia, causing pain on swallowing, typically relatively soon after RT course is completed, and typically resolves on its own within days to a week or longer), or chronic, typically manifesting with dysphagia due to stenosis, or esophageal ulceration, with perforation in the extreme cases.

Central Airway/Bronchial Injury

This bronchial injury with subsequent focal collapse of lung may impair overall pulmonary status. It also makes further assessment of tumor response more difficult as the collapsed lung approximates the treated tumor. Because atelectatic lung and tumor have similar imaging characteristics, radiology reports will often describe the overall process as progressive disease, while the actual tumor may be stable or shrinking.

The consequences of bronchial toxicity, e.g., cough, dyspnea, hypoxia, impairment of pulmonary function test parameters, pleural effusion or pleuritic pain (associated with collapse), should all be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), v. 4; MedDRA, v. 12.0.

Lung Injury

Radiation pneumonitis is a subacute (weeks to months from treatment) inflammation of the end bronchioles and alveoli. Radiation fibrosis is a late manifestation of radiation injury to the irradiated lung. Given the small amount of lung that is typically included in the SBRT portals, lung toxicity has

not been as dose-limiting as in conventionally fractionated, large-field RT, but it is nevertheless seen, can be symptomatic, and may be confused with other causes of respiratory deterioration, including infections, and tumor recurrence**.**

Given that larger volumes of lung may be irradiated in this protocol compared to SBRT for primary tumors, it is very important that a Radiation Oncologist participate in the care of the patient, as the clinical picture may be very similar to acute bacterial pneumonia, with fatigue, fever, shortness of breath, nonproductive cough, and a pulmonary infiltrate on chest x-ray. The infiltrate on chest x-ray should include the area treated to high dose, but may extend outside of these regions. The infiltrates may be characteristically "geometric" corresponding to the radiation portal, but may also be ill defined.

Patients reporting symptoms as above will be promptly evaluated and treated. Mild radiation pneumonitis may be treated with nonsteroidal anti-inflammatory agents or steroid inhalers. More significant pneumonitis will be treated with systemic steroids, bronchodilators, and pulmonary hygiene. Supra- and concurrent infections should be treated with antibiotics. Consideration of prophylaxis of opportunistic infections should be considered in immunocompromised patients.

Liver/abdominal-pelvic metastases

Very likely (80-90%): Patients may experience fatigue (which generally goes away after the radiation therapy is completed), skin irritation, redness, itchiness, discomfort, temporary changes in blood work (decrease in blood counts, increase in liver enzymes), without symptoms.

Less likely (30%): Patients may experience nausea, vomiting (during therapy) – more common if stomach or gastrointestinal tract irradiated, gastric, esophagus, small bowel or large bowel irritation/ulceration, bleeding, fistula, obstruction or changes in motility following therapy (may require medications or surgery) (<10% permanent changes), chest wall pain, and rib fracture (< 10%).

Less likely, but serious (<20%): Patients may experience radiation-induced liver disease (RILD) (<5%). Classic RILD is a clinical diagnosis of anicteric ascites, hepatomegaly and elevation of alkaline phosphatase relative to other transaminases that may occur 2 weeks to 3 months following radiation to the Liver; non-classic RILD includes elevation of liver enzymes and/or any decline in liver function within 12 weeks from start of therapy (~20%). RILD can lead to liver failure that could lead to death. There is an increased risk of liver toxicity in patients with large tumors and in patients with pre-existing liver disease. In addition, permanent thrombocytopenia (<1%) may lead to bleeding, and kidney injury (<1%) may lead to changes on imaging and more rarely the need for medication.

Spinal metastases

Radiation Myelitis

Given the proximity and position of the spinal cord in relation to the radiosurgery target, every effort should be made to minimize the radiation dose to the spinal cord. Radiation myelitis is a subacute or chronic clinical syndrome after radiation. The symptoms may include paresthesia, sensory changes, and motor weakness including paralysis. There is no active treatment for radiation myelitis; therefore, it is important to prevent any injury to the spinal cord. Corticosteroids are used when clinical symptoms develop.

Radiation Esophagitis

Patients with thoracic spine treatment will likely develop esophageal mucositis within the first 2 weeks. These symptoms subside with time; however, adequate symptomatic treatment including hydration is advised. There are no long-term adverse events reported with spine radiosurgery. However, it is prudent to minimize the radiation spillage in the normal esophagus. The consequences of esophageal toxicity, e.g., swallowing difficulty, dysphagia, cough, dehydration, and fistula, should be documented.

Radiation Laryngitis or Pharyngitis

Patients with cervical spine treatment will likely develop laryngopharyngeal mucositis within the first 2 weeks. These symptoms subside with time; however, adequate symptomatic treatment including hydration is advised. No long-term laryngopharyngeal toxicity has been reported with spine radiosurgery. However, it is prudent to minimize the radiation spillage in the normal larynx and

pharynx. The consequences of toxicity, e.g., swallowing difficulty, dysphagia, cough, dysphonia dehydration, and fistula, should be documented.

Tracheal Injury

Although no cases of tracheal injury have been reported with spine radiosurgery, it is prudent to minimize the radiation spillage in the normal trachea. The consequences of tracheobronchial toxicity, e.g., cough, dyspnea, hypoxia, impairment of pulmonary function test parameters, pleural effusion or pleuritic pain (associated with collapse), should be documented.

Radiation Pneumonitis

There have been no reported cases of symptomatic radiation pneumonitis with spine radiosurgery. However, it is prudent to minimize the radiation spillage in the lung tissue. It is strongly recommended to use radiation beams directed from the posterior to avoid passage of radiation through the lungs. Patients with symptoms of pneumonitis will be promptly evaluated and treated. Mild radiation pneumonitis may be treated with non- steroidal anti-inflammatory agents or steroid inhalers. More significant pneumonitis will be treated with systemic steroids, bronchodilators, and pulmonary hygiene. Supra- and concurrent infections should be treated with antibiotics. Consideration of prophylaxis of opportunistic infections should be considered in immunocompromised patients.

Compression Fracture of Treated Vertebra

Radiation doses in excess of 19 Gy for a single fraction are associated with higher rates of vertebral body compression (Saghal 2013). In this protocol, doses per fraction this high are not used, so that the estimated rate of vertebral body compression fracture following spinal metastases treatment should be approximately 10%.

Other Adverse Events

Short-term or long-term injury to the kidney or upper airway has not been reported. If other severe adverse events occur, details should be documented.

Osseous:

Erythema, desquamation and alopecia are common side effects from radiation therapy for osseous metastases; other effects are determinate on location of metastasis, and may include pain, edema and neuralgia.

7.2.1 Radiation Therapy Quality Assurance

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). 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. https://irocri.qarc.org/

Within one week following the completion of radiotherapy, the following data must be submitted for all patients:

- RT treatment plans including treatment planning 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.
- RT-1 Dosimetry Summary Form
- Motion Management Reporting Form (if applicable)
- 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.

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

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 neoplasm or impact the primary endpoint.

This includes any surgical intervention, radiotherapy, cryotherapy, ablation, etc.

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 in solid tumor protocols. Use of dexamethasone and other steroidal antiemetics is prohibited in leukemia and lymphoma protocols.

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.

8.1.6 **Palliative radiation therapy** may not be administered.

Patients who require radiation therapy during protocol treatment will be removed from protocol therapy due to disease progression.

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 permitted at the discretion of the treating physician.

Filgrastim (G-CSF) tbo-filgrastim, and sargramostim (GM-CSF) are prohibited OR permitted at the discretion of the treating physician.

Use of white blood cell growth factors (which includes: filgrastim (G-CSF), pegfilgrastim) and other FDA approved white blood cell growth factor biologics) should adhere to the following guidelines:

1. White blood cell growth factor treatment for patients on protocols that do not specify their use is discouraged.
2. White blood cell growth factor may not be used:

a. To avoid dose reductions, delays or to allow for dose escalations specified in the protocol.

b. For the treatment of febrile neutropenia the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting. The use of CSF (filgrastim/pegfilgrastim) must be documented and reported. (e.g. on CRFs per protocol requirements)

c. If white blood cell growth factors are used, they must be obtained from commercial sources. Selection of white blood cell growth factor products should be per institutional guidelines.

8.2 Dose Modification and Treatment Modifications

- Any patients with autoimmune toxicity who require additional immune suppressive treatment beyond steroids should go off treatment.
- Dose delays may occur for toxicity with re-initiation of treatment as per protocol.
- Any patient started on corticosteroids initially for a presumed autoimmune adverse event, and subsequently found to not have an autoimmune etiology of their adverse event, may resume therapy after a 2-week observation period without recurrence of symptoms.
- No dose reductions will be made for MK-3475 (pembrolizumab) during this study, only dose delays.

8.2.1 General AE Management and Dose Modification Guidelines for Pembrolizumab (MK-3475)

Dose Modifications

Adverse events (both nonserious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as described below.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for interruption should be documented in the patient's study record.

Dose Modification and Toxicity Management for Immune-related Adverse Events Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and

symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines for irAEs and infusion reactions associated with pembrolizumab are provided in the table below.

Note that non-irAEs will be managed as appropriate, following clinical practice recommendations.

Table for Dose Modification and Toxicity Management Guidelines for Immune-related AEs and Infusion Reactions Associated with Pembrolizumab

General instructions:

1. For non-endocrine-related severe and life-threatening irAEs, investigators should consider the use of IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. Some non-endocrine irAEs do not require steroids. For example, celiac disease induced by pembrolizumab can be controlled by diet alone.
2. For non-endocrine-related toxicities, pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab-treatment.
3. Generally, when corticosteroids (prednisone) are used, investigators should begin a taper when the irAE is ≤Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld due to a non-endocrine irAE, pembrolizumab may generally resume after the irAE has decreased to ≤Grade 1 after a corticosteroid taper.

irAEs	**Toxicity grade (CTCAE V5.0)**	**Action with pembrolizumab**	**Corticosteroid and/or other therapies**	**Monitoring and follow-up**
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper Add prophylactic antibiotics for opportunistic infections	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper Patients who do not respond to corticosteroids should be seen by a gastroenterologist for confirmation of the diagnosis and consideration of secondary immune suppression	Monitor participants for signs and symptoms of enterocolitis (*i.e.*, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (*i.e.* peritoneal signs and ileus) Specifically assess for celiac disease serologically, and
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

				exclude *Clostridium difficile* infection Participants with ≥Grade 2 diarrhea suspecting enterocolitis should consider GI consultation and performing endoscopy to rule out enterocolitis and assess mucosal severity Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Grade 1 or 2	Continue		Investigate for diabetes. In the absence of corticosteroids or diabetes medication non-adherence, any grade hyperglycemia may be an indication of beta-cell destruction and pembrolizumab-induced diabetes

				akin to type 1 diabetes. This should be treated as a Grade 3 event. Given this risk, exercise caution in utilizing non-insulin hypoglycemic agents in this setting. After a thorough investigation of other potential causes, which may involve a referral to an endocrinologist, follow institutional guidelines. Monitor glucose control.
	New onset T1DM (evidence of β-cell failure) or Grade 3 or 4 hyperglycemia	Withhold [d] Resume pembrolizumab when symptoms resolve and glucose levels are stable	Initiate treatment with insulin If patient is found to have diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, treat as per institutional guidelines with appropriate management and laboratory values (*e.g.* anion gap, ketones, blood pH, *etc.*) reported	Monitor for glucose control Strongly consider referral to endocrinologist Obtain C-peptide level paired with glucose, autoantibody levels (*e.g.* GAD65, islet cell autoantibodies), and hemoglobin A1C level
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency) Provide adrenal insufficiency precautions including indications for stress dose steroids and medical alert jewelry
	Grade 3 or 4	Withhold or permanently discontinue [d]		

				Strongly consider referral to endocrinologist
Hyperthyroidism	Grade 2	Consider withholding. Resume pembrolizumab when symptoms are controlled, and thyroid function is improving	Treat with nonselective beta-blockers (*e.g.*, propranolol) or thionamides as appropriate Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed	Monitor for signs and symptoms of thyroid disorders Strongly consider referral to endocrinologist
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	Initiate thyroid replacement hormones (*e.g.*, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function Strongly consider referral to nephrologist
	Grade 3 or 4	Permanently discontinue		
Cardiac Events (including myocarditis, pericarditis, arrhythmias, impaired ventricular function, vasculitis)	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1), or Grade 1	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes Strongly consider referral to cardiologist and cardiac MRI Consider endomyocardial biopsy If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month
	Grade 2, 3 or 4	Permanently discontinue	Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or	Ensure adequate evaluation to confirm etiology and/or exclude other causes Strongly consider referral to

			equivalent upon improvement If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent Initiate treatment per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, extracorporeal membrane oxygenation (ECMO), ventricular assist device (VAD), or pericardiocentesis as appropriate	cardiologist and cardiac MRI Consider endomyocardial biopsy If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes Strongly consider referral to dermatologist Consider skin biopsy for evaluation of etiology
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

Infusion-Related Reactions

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Mild reaction; infusion interruption not indicated;	Grade 1	Increase monitoring of vital signs as medically indicated until the participant	None

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
intervention not indicated		is deemed medically stable in the opinion of the investigator.	
Requires therapy or infusion interruption but responds promptly to symptomatic treatment (*e.g.*, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	Grade 2	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (*e.g.* from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Prolonged (*i.e.*, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Grade 3	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids (*e.g.* methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours) • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing.
Life-threatening; pressor or ventilator support indicated	Grade 4	Admit participant to intensive care unit (ICU) and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. Follow Grade 3 recommendations as applicable.	No subsequent dosing.

Infusion Reactions	NCI CTCAE Grade	Treatment	Premedication at subsequent dosing

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; ECMO=extracorporeal membrane oxygenation; GI=gastrointestinal; ICU=intensive care unit; IO=immuno-oncology; ir=immune related; IV=intravenous; MRI=magnetic resonance imaging; PO=per os; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal; VAD=ventricular assist device.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (*e.g.* vasculitis and sclerosing cholangitis).

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov.

Neurological Toxicities

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue pembrolizumab. • Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.

Immune-mediated neuropathy, including facial paresis, Grade 2	• Withhold pembrolizumab for up to 12 weeks after event onset. [a]
	• Investigate etiology and refer patient to neurologist.
	• Initiate treatment as per institutional guidelines.
	• For general immune-mediated neuropathy:
	  o If event resolves to Grade 1 or better, resume pembrolizumab. [b]
	  o If event does not resolve to Grade 1 or better while withholding pembrolizumab, permanently discontinue pembrolizumab. [c]
	• For facial paresis:
	  o If event resolves fully, resume pembrolizumab. [b]
	  o If event does not resolve fully while withholding pembrolizumab, permanently discontinue pembrolizumab. [c]

Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue pembrolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue pembrolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

[a] Pembrolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before pembrolizumab can be resumed.

[c] Resumption of pembrolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with pembrolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

Event	Management
Immune-mediated myelitis, Grade 1	• Continue pembrolizumab unless symptoms worsen or do not improve. • Investigate etiology and refer patient to a neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue pembrolizumab. • Investigate etiology and refer patient to a neurologist. • Rule out infection. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue pembrolizumab. • Refer patient to a neurologist. • Initiate treatment as per institutional guidelines.

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue pembrolizumab. [a] • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Resumption of pembrolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with pembrolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

8.2.2 Pembrolizumab (MK-3475) Supportive Care

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are also outlined in the table in Section 8.2.1. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below).

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- **Pneumonitis:**
  - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  - **For Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
  - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- **Diarrhea/Colitis:**

  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
  - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For Grade 2 diarrhea/colitis that persists greater than 3 days, administer oral corticosteroids.
  - For Grade 3 or 4 diarrhea/colitis that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
- **For T1DM or Grade 3-4 Hyperglycemia**
  - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
  - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis:**
  - For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For Grade 3-4 events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hyperthyroidism or Hypothyroidism:**

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - **Grade 2 hyperthyroidism events (and Grade 2-4 hypothyroidism):**

- In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
- In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.

o **Grade 3-4 hyperthyroidism**

- Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic:**
  - **For Grade 2 events**, monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - Treat with IV or oral corticosteroids
  - **For Grade 3-4 events**, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal Failure or Nephritis with relationship to study therapy:**
  - For Grade 2 events, treat with corticosteroids.
  - For Grade 3-4 events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Management of Infusion Reactions:** Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

  The table below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of MK-3475 (pembrolizumab).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of MK-3475 (pembrolizumab) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

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. The PRO-CTCAE patient-completed booklet for this protocol can be downloaded from the CIRB Approved Documents tab on the CTSU website. PRO-CTCAE is not intended for expedited reporting, real time review, or safety reporting. All dose interruptions and treatment modifications will be guided by clinician interpreted CTCAE. PRO-CTCAE should not be used for determining dose delays or dose modifications or any other protocol directed action.

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 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. Symptomatic adverse events reported by patients through PRO-CTCAE are not safety reporting and may be presented with other routine Adverse Event data.

CTCAE v5.0 Term	CTCAE v5.0 System Organ Class (SOC)	PRO-CTCAE Term
Neutrophil count decreased	Investigations	N/A
Platelet count decreased	Investigations	N/A
Diarrhea	Gastrointestinal Disorders	Diarrhea
Colitis	Gastrointestinal Disorders	Diarrhea, Abdominal Pain
Rash maculo-papular	Skin and subcutaneous tissue disorders	Rash
Hyperglycemia	Metabolism and nutrition disorders	N/A
Electrocardiogram QT corrected interval prolonged	Investigations	N/A

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, b	a, b	a, b
Probable			a, b	a, b	a, b
Definite			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** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

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

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

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

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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

Effective Date: May 5, 2011

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 Adverse Events of Special Interest in Pembrolizumab Studies

Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
    - Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN
    - Treatment-emergent ALT or AST > 3 × ULN in combination with clinical jaundice
- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

The Pembrolizumab Events of Special Interest Are:

- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, macrophage activating syndrome, hemophagocytic lymphohistiocytosis
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

9.3.4 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 A032002 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.

9.4 CAEPRs

9.4.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Pembrolizumab (MK-3475, NSC 776864)

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 3097 patients.* Below is the CAEPR for Pembrolizumab (MK-3475).

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 2.7, December 13, 2022[1]

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia[2]	
		Blood and lymphatic system disorders - Other (immune thrombocytopenic purpura)[2]
	Lymph node pain[2]	
CARDIAC DISORDERS		
		Myocarditis[2]
		Pericarditis[2]
ENDOCRINE DISORDERS		
	Adrenal insufficiency[2]	
		Endocrine disorders - Other (hypoparathyroidism)

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Endocrine disorders - Other (thyroiditis)[2]	
	Hyperthyroidism[2]	
	Hypophysitis[2]	
	Hypopituitarism[2]	
	Hypothyroidism[2]	
EYE DISORDERS		
		Uveitis[2]
		Eye disorders - Other (Vogt-Koyanagi-Harada syndrome)
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Colitis[2]	
	Diarrhea[2]	
	Mucositis oral[2]	
	Nausea	
	Pancreatitis[2]	
	Small intestinal mucositis[2]	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills[2]	
Fatigue		
	Fever[2]	
HEPATOBILIARY DISORDERS		
	Hepatobiliary disorders - Other (autoimmune hepatitis)[2]	
		Hepatobiliary disorders - Other (sclerosing cholangitis)
IMMUNE SYSTEM DISORDERS		
		Anaphylaxis[2]
		Cytokine release syndrome[2]
		Immune system disorders - Other (acute graft-versus-host-disease)[2,3]
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[2]
	Immune system disorders - Other (sarcoidosis)[2]	
		Serum sickness[2]

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
		Infusion related reaction
INVESTIGATIONS		
	Alanine aminotransferase increased[2]	
	Alkaline phosphatase increased	
	Aspartate aminotransferase increased[2]	
	Blood bilirubin increased	
		GGT increased
		Serum amylase increased
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
	Hyponatremia	
		Metabolism and nutrition disorders - Other (diabetic ketoacidosis)[2]
		Metabolism and nutrition disorders - Other (type 1 diabetes mellitus)[2]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia[2]	
	Arthritis[2]	
	Back pain	
	Joint range of motion decreased	
	Myalgia[2]	
	Myositis[2]	
NERVOUS SYSTEM DISORDERS		
		Guillain-Barre syndrome[2]
		Nervous system disorders - Other (myasthenic syndrome)[2]
		Nervous system disorders - Other (neuromyopathy)[2]
		Nervous system disorders - Other (non-infectious encephalitis)[2]
		Nervous system disorders - Other (non-infectious meningitis)[2]
		Nervous system disorders - Other (non-infectious myelitis)
		Nervous system disorders - Other (optic neuritis)

Adverse Events with Possible Relationship to Pembrolizumab (MK-3475) (CTCAE 5.0 Term) [n= 3793]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Nervous system disorders - Other (polyneuropathy)[2]
		Paresthesia
		Peripheral motor neuropathy[2]
RENAL AND URINARY DISORDERS		
		Renal and urinary disorders - Other (autoimmune nephritis)[2]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Pneumonitis[2]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Bullous dermatitis[2]	
		Erythema multiforme[2]
	Erythroderma	
		Palmar-plantar erythrodysesthesia syndrome
	Pruritus[2]	
	Rash acneiform[2]	
	Rash maculo-papular[2]	
	Skin and subcutaneous tissue disorders - Other (dermatitis)[2]	
	Skin hypopigmentation[2]	
		Stevens-Johnson syndrome[2]
		Toxic epidermal necrolysis
	Urticaria[2]	
VASCULAR DISORDERS		
		Vasculitis[2]

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]Immune-mediated adverse reactions have been reported in patients receiving Pembrolizumab (MK-3475). Adverse events potentially related to Pembrolizumab (MK-3475) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of Pembrolizumab (MK-3475), administration of corticosteroids and supportive care.

[3]Acute graft-versus-host disease has been observed in patients treated with Pembrolizumab (MK-3475) who received hematopoeitic stem cell transplants.

Adverse events reported on Pembrolizumab (MK-3475) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Pembrolizumab (MK-3475) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Hemolysis

CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocardial infarction; Pericardial effusion; Pericardial tamponade; Ventricular arrhythmia

EYE DISORDERS - Eye pain

GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Constipation; Duodenal hemorrhage; Dysphagia; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intussusception); Oral pain; Rectal hemorrhage; Small intestinal perforation; Upper gastrointestinal hemorrhage; Vomiting

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema limbs; Facial pain; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); Generalized edema; Malaise; Non-cardiac chest pain; Pain

INVESTIGATIONS - CPK increased; Cholesterol high; Creatinine increased; Fibrinogen decreased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Weight loss; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Joint effusion[2]; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity

NERVOUS SYSTEM DISORDERS - Aphonia; Depressed level of consciousness; Dysarthria; Edema cerebral; Encephalopathy; Headache; Hydrocephalus; Lethargy; Meningismus; Nervous system disorders - Other (brainstem herniation); Seizure; Syncope; Tremor

PSYCHIATRIC DISORDERS - Agitation; Confusion

RENAL AND URINARY DISORDERS - Acute kidney injury; Nephrotic syndrome; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); Urinary incontinence; Urinary tract pain

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia; Laryngeal inflammation; Pleural effusion; Pleuritic pain[2]; Pneumothorax; Respiratory failure

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (drug eruption)

VASCULAR DISORDERS - Hypertension; Peripheral ischemia; Thromboembolic event

Note: Pembrolizumab (MK-3475) 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 Pembrolizumab (MK-3475, NSC 776864)

Availability

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Pembrolizumab is commercially available. Pembrolizumab (MK-3475) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution for intravenous use.

Each vial contains 100 mg of pembrolizumab (MK-3475) in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab (MK-3475) and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

Preparation

Follow institutional standards.

MK-3475 (pembrolizumab) solution for infusion must be diluted prior to administration. Do not shake the vials. Do not use if opaque or extraneous particulate matter other than translucent to white proteinaceous particles is observed. Do not use if discolored. To prepare the infusion solution add the dose volume of MK-3475 (pembrolizumab) to an infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. The final concentration must be between 1 mg/mL to 10 mg/mL.

Compatible IV bag materials: PVC plasticized with DEHP, non-PVC (polyolefin), EVA, or PE lined polyolefin.

Storage

Store intact vials between 2°C - 8°C (36°F - 46°F). Do not freeze. Protect from light by storing in the original box.

Stability

Store the diluted solution at room temperature for no more than 6 hours from the time of dilution, including room temperature storage of the diluted solution and the duration of infusion, or under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 96 hours from the time of dilution. Do not shake. Discard after 6 hours at room temperature or after 96 hours under refrigeration.

Administration

IV infusion only. Do not administer as an IV push or bolus injection. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Infuse over approximately 30 minutes (range: 25 - 40 minutes) using an infusion set containing a low-protein binding 0.2 to 5 micron in-line filter made of polyethersulfone or polysulfone. A central line is not required; however, if a subject has a central venous catheter in place, it is recommended that it be used for the infusion. Do not co-administer other drugs through the same infusion line. Following the infusion, flush the IV line with normal saline.

Adverse Events

See Comprehensive Adverse Events and Potential Risks list (CAEPR) for MK-3475 (pembrolizumab, NSC 776864) CAEPRs in Section 9.4.

Nursing Guidelines

1) MK-3475 (pembrolizumab) 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.

2) Diarrhea can be seen however is less common than that seen with anti-CTLA-4 agents. However it can be 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.

3) Rash/pruritus/dermatitis is seen. Patients should report any rash to the study team. Treat per section 8.0 and monitor for effectiveness.

4) 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.

5) 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.

6) 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.

7) Patients who are started on steroid therapy for any side effects of MK-3475 (pembrolizumab) 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.

8) Fatigue is common and may or may not be associated with immune related side effects. Assess patient's fatigue level prior to each cycle of therapy and report any changes to the study team.

9) Patients should avoid receiving live vaccines within 30 days of study drug administration or per other study guidelines.

10) Patients who have undergone an allogenic bone marrow transplant, have an increased risk of severe complications including early GVHD, and venoocclusive disease, if they have previously been treated with MK-3475.

11) Myocarditis has been reported and associated with MK-3475. Instruct patients to report chest pain, SOB, or dyspnea to study team immediately and/or seek emergency medical attention.

11.0 MEASUREMENT OF EFFECT

Disease should be re-evaluated every 12 weeks after C1D1. Disease response will be made by institutional investigator assessment, based on local radiology review and RECIST v1.1 criteria. Refer to the Study Calendar to determine the allowable scan windows (Section 5.0). This study uses iRECIST guidelines to guide treatment beyond progressive disease. Irradiated lesion will not be included in RECIST v1.1 or iRECIST evaluation.

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.

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).

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

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

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

11.5.3 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.

11.5.4 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.

11.5.5 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.

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

11.5.7 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 must 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.

11.7 iRECIST guidelines

Since A032002 includes the main treatment backbone with immunotherapy, this trial will adopt iRECIST guidelines for assessments of radiographic responses (31), one of the secondary endpoints of the trial. This section gives a summary of iRECIST guidelines and the application to A032002.

The following table, adapted from the iRECIST guidelines, is a snapshot of changes between RECIST 1.1 and iRECIST guidelines.

	RECIST 1.1	iRECIST
Measurable and non-measurable disease, number and site of target disease	Measurable: >10mm for visceral disease, >15mm for LN lesions, Maximum 5 lesions (2 per organ) All other disease non-target (>10mm for LN disease)	Measurability as per RECIST 1.1 New lesions assessed per RECIST 1.1 but recorded separately for target vs non-target
CR, PR, or SD	Cannot have met criteria for PD before CR, PR, or SD	Can have had iUPD (one or more) but not iCPD, before iCR, iPR, or iSD
Confirmation of CR or PR	Not required for randomized trials	As per RECIST 1.1
Confirmation of SD	Not required	As per RECIST 1.1
After initial progression (iUPD) but then iCR, iPR, or iSD	Any PD precludes later CR, PR, or SD	iCR/iPR/iSD can be achieved after initial iUPD. Sum of target lesion diameters at time of iCR/iPR/iSD should be noted and status should be reset. Subsequent progression after iCR/iPR/iSD should be another iUPD, until confirmation iCPD
New lesions	Result in PD; recorded but not measured	Results in iUPD at first occurrence iCPD only assigned on basis of new lesions if at next assessment additional new lesions appear or an increase in size of new lesions seen (>5mm of sum of new lesion target or any increase in new lesion non-target) If non-target or target lesions have unequivocal PD, iCPD can be assigned at time of first progression
Independent blinded review and central scan collection	Collection of scans required on A031704	Collection of scans required on A031704
Confirmation of progression	Not required unless equivocal	Required
Consideration of clinical status	Not included in assessment	**Clinical stability is considered** when deciding whether treatment should continue after iUPD

In general, iRECIST guidelines help define progression in the context of immune therapy. New lesions should be assessed and subcategorized as target lesions (new lesion, target) and measured for further follow up, or non-target lesions (new lesion, non-target). At the time of initial iUPD, patients must be clinically stable by investigator assessment (see definition below) in order to continue immunotherapy-based treatments. iRECIST guidelines also recommend that confirmation of progression be obtained between 4 to 8 weeks of the initial iUPD scan date. For purposes of this trial, these scans can be obtained after 4 weeks, and no more than 13 weeks after initial iUPD scans (as standard of care, depending on insurance coverage, as scans will not be billable to this study).

Investigators will need to assess clinical stability to continue treatments at time of iUPD. Clinical stability to continue treatment in light of iUPD is defined as follows. Absence of any of the following:

worsening of performance status, clinically relevant increase in disease-related symptoms such as pain or dyspnea that are associated with disease progression, and increased management/treatments of disease-related symptoms (including increased analgesic agents, radiation, or other palliative treatments). Imaging findings and recommendation to continue with treatment should be discussed with the patient before the decision to continue.

Patients with iUPD and who are clinically unstable should be designated as clinically unstable in the database. Patients with iUPD and clinically unstable will stop study treatments and continue with standard of care treatments. These patients will continue to be followed for other outcomes.

Please refer to full iRECIST guidelines for further guidance (31) on assessing response/progression. In particular, Table 2 of the guidelines give specific recommendations of timepoint response assignment and is replicated below. When needed, please contact medical monitor/study chairs to help adjudicate response/progression.

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

Abbreviations:

CR: complete response
iCR: immune complete response
iPR: immune partial response
iUPD: immune unconfirmed progressive disease
iCPD: immune confirmed progressive disease
iSD: immune stable disease
LN: lymph node
PD: progression of disease
PR: partial response
SD: stable disease

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Protocol Treatment

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

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:

- Disease progression per iRECIST guidelines, e.g., discontinuation due to clinical instability or additional new lesions or increase in new lesion size (see Section 11.7)
- 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
- Patient non-compliance
- Pregnancy
- All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
- The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

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: Physical examination and staging scans are required within 12 weeks after the end of treatment, then every 12 weeks until disease progression; thereafter, survival information is required every 3 months until 3 years following registration.

12.3.2 Follow-up for Patients who Stop Study Treatment/Intervention Early

Follow up for patients who receive non-protocol therapy will be for event monitoring

12.3.3 Follow-up for Specimen and QOL Submission

QOL measures are to be completed at baseline, and at 45 days, and at 6, 12, and 24 months following registration. **Measures should continue to be submitted following progression**.

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. No further follow-up will be required for these patients. 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), no follow-up will be required.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design

This is a prospective multicenter, randomized, open-label, phase 2 study evaluating whether the addition of radiation therapy to immunotherapy improves tumor response rate compared to treatment with immunotherapy alone in patients with platinum ineligible/refractory metastatic urothelial cancer. Allocation to the two study arms will be performed using stratified randomization as described in Section 4.6. Patients will be randomized 1:1 to immunotherapy (Arm A) or to immunotherapy plus radiation (Arm B). This trial is a superiority trial with the primary endpoint of tumor response. One formal interim analysis will be conducted for futility after 50% of the patients have been followed for 6 months after randomization; accrual will not be suspended for the interim analysis.

13.2 Study Endpoints

13.2.1 Primary Endpoint

The primary endpoint is tumor response within 6 months of randomization. Tumor response is defined as a complete response (CR) or partial response (PR) as assessed by the treating physician using RECIST v1.1 criteria.

13.2.2 Secondary Endpoints

Tumor response using iRECIST: A patient will be determined to have a tumor response if they have a CR or PR as assessed using iRECIST by central review.

Progression-free survival (PFS): This will be the time from randomization until disease progression as assessed by the treating physician using RECIST 1.1 or death due to any cause. Patients who are alive and without documented progression will be censored at the time of last disease evaluation.

Overall survival (OS): This will be the time from randomization until death due to any cause. Patients who are not known to be dead at time of analysis will be censored at the time of their last follow-up.

Rate of treatment discontinuation at 1 year: The proportion of patients who discontinue their protocol directed treatment prior to one year from date of study registration will be determined. Patients who stop their protocol directed treatment for any reason prior to one year from study registration will be considered to have discontinued their treatment.

Adverse events: These will be assessed using CTCAE v5.0.

13.3 Subgroup Analysis

Subgroup analysis may be conducted in the following groups for efficacy endpoints including tumor response, PFS, and OS.

1) Platinum status: platinum ineligible versus platinum refractory
2) Visceral metastasis: present versus absent

13.4 Sample Size Calculation

The sample size was determined with nQuery (v8.6.1.0) under the following assumptions:

1) one-sided alpha = 0.10
2) power = 90%
3) arm A (control arm) tumor response rate = 20%
4) minimum detectable increase in response rate = 20% (absolute)
5) one interim analysis for futility after 50% of patients followed for response

This requires a total sample size = 136 evaluable patients (68 in each arm). The sample size will be inflated by 5% to account for ineligible or non-evaluable patients, so the target accrual is 144 patients.

13.5 Accrual time and study duration

The anticipated accrual rate is approximately 5 patients per month. The maximum expected accrual period is approximately 30 months (if trial is not stopped early for futility). Patients will be followed for tumor response for 6 months following randomization; therefore the maximum total study duration for the primary endpoint (including OS follow-up) approximately 36 months. Patients will be followed for PFS and OS for 3 years.

13.6 Primary Analysis Plan

Interim analysis for futility: There will be one interim analyses for futility. The interim analysis will occur after 50% of the patients (i.e. 68) have been followed for six months. If at this time the tumor response for Arm A (immunotherapy alone) is greater than the tumor response rate for Arm B (immunotherapy plus radiation), which would correspond to an OR > 1, the recommendation will be to stop the trial due to futility.

Final Analysis: The final analysis will occur after 136 evaluable patients have completed 6 months of follow-up. The tumor response rate will be analyzed with a Mantel-Haenszel test (that accounts for the randomization stratification factors) comparing the response rates between the two treatment arms. The analysis will be a modified intent-to-treat analysis where patients are ineligible or not evaluable will be excluded. An additional analysis will be conducted using logistic regression analysis that includes treatment arm and any baseline variables that are imbalanced between the arms as explanatory variable.

13.7 Secondary Analysis Plans

A key secondary analysis will be to repeat the primary analysis that defines a tumor response by central review using iRECIST criteria.

For the secondary time-to-event endpoints, stratified Cox models will be used to compare the outcomes between the two treatment groups. This includes PFS and OS. The subgroup analyses will be done using a stratified Cox model that includes the treatment arm assignment as an explanatory variable and a separate model will be generated for each level for the subgroup of interest. The results will be summarized with a forest plot displaying the estimate of the hazard ratio and corresponding 95% confidence interval.

The rates of treatment discontinuation at one year will be summarized with a binomial point estimate and corresponding 95% confidence interval by arm. The denominator will be all patients randomized to the treatment arm and who are still alive and progression-free at one year and the numerator will be the number of patients who are alive and progression-free at one year and discontinued the protocol

treatment prior to one year. A comparison between the rates will be performed with a chi-square test or a Fisher's exact test if the assumptions of the chi-square test are violated.

Adverse events will be summarized with frequencies and relative frequencies. The maximum grade for an AE will be recorded for each patient by treatment arm. The number (percent) of patients that experience each observed adverse event will be summarized by treatment arm. In addition, the proportion of patients that experience a grade 3+, grade 4+, and grade 5 adverse event will be summarized as the number and percent of patients by treatment arm. The primary summary will be regardless of attribution. We will also do an analogous summary of the adverse events that were deemed at least possibly related to treatment.

To evaluate between-arm differences in patient-reported adverse events as assessed by the PRO-CTCAE from baseline through 24 months, the frequency and proportion of patients with a maximum post-baseline score greater than 0 will be compared across arms using a χ^2 test or Fisher's exact test with a nominal significance level of $\alpha = .10$. Similarly, the frequency and proportion of patients with a maximum post-baseline score greater than or equal to 3 will be compared across arms using a χ^2 test or Fisher's exact test with a nominal significance level of $\alpha = .10$. The same procedure will be applied to patients' maximum baseline-adjusted scores. Patients' maximum baseline-adjusted scores will be calculated using the method described by Dueck et al. If the patient's maximum post-baseline score is greater than his/her baseline score, then the patient's maximum baseline-adjusted score will equal his/her maximum post-baseline score; otherwise, if the patient's maximum post-baseline score is less than or equal to his/her baseline score, then the patient's maximum baseline-adjusted score will equal 0. The aforementioned analyses will be based on all available PRO-CTCAE data. However, the proportion of, and reported reasons for, missing data will be presented by time point and arm. Correlation analysis and logistic regression analysis will be used to examine whether baseline patient characteristics and prognostic factors predict missingness. As a sensitivity analysis, multiple imputation may be performed to assess the robustness of results across different assumptions about the missing data. Since a preferred or optimal statistical methodology for PRO-CTCAE data is yet to be determined, additional analyses of PRO-CTCAE data beyond those specified above may be undertaken based on the current state of the science at time of data maturity for this study.

13.8 Study 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.

The study team and DSMB will monitor the study for safety and whether the trial is meeting its accrual goals in a satisfactory manner. Monthly reports summarizing the adverse events will be generated and reviewed by the study. If at any time after 20 patients are 30% or more of the patients experience a grade 3 or higher AE, accrual will be suspended and the study team will review the adverse event data. In collaboration with CTEP, a decision will be made whether to resume accrual with the original treatment, modify the treatment and resume accrual, or close the study to accrual due to an unacceptable adverse event rate.

Note: Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

13.9 Inclusion of Women and Minorities

Gender or race/ethnicity differences in the intervention effect are not expected. Based on previous data from advanced or metastatic urothelial carcinoma patients enrolled, the accrual targets in individual cells are not large enough to perform subgroup analysis by the two treatment groups. This table is

based on the accrual profile of urothelial carcinoma patients enrolled to 2 Alliance studies (A031501, A031901) the Alliance does not anticipate accrual from some subgroups. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets. However, we plan to perform exploratory analyses within gender, racial, and ethnic groups. Both men and women of all races and ethnic groups are eligible for this study.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	1	1	1	1	4
Asian	1	1	1	1	4
Native Hawaiian or Other Pacific Islander	1	1	1	1	4
Black or African American	1	3	1	1	6
White	23	86	3	9	121
More Than One Race	1	2	1	1	5
Total	28	94	8	14	144

14.0 CORRELATIVE AND COMPANION STUDIES

There will be 1 quality of life substudy and all patients are encouraged to participate. There will also be mandatory specimen related studies and optional biobanking for future research.

14.1 Quality of Life Studies (Alliance A032002-HO1)

14.1.1 Background

Patient-reported quality of life (QOL) for combination radiotherapy and immunotherapy has not been well studied. This trial provides an opportunity to prospectively assess QOL changes for immunotherapy and radiotherapy compared to immunotherapy alone in metastatic bladder cancer. The EORTC QLQ-C30 plus the muscle invasive bladder cancer module QLQ-BLM30 were selected in accordance with robust validation data and prior utilization in clinical trials evaluating immunotherapy in metastatic bladder cancer5, 30-33. The PROMIS-Fatigue 8a was also selected as a well validated, succinct inventory to assess cancer and treatment associated fatigue34.

Even though this is a randomized Phase II (not Phase III) trial, incorporation of QOL is important not only because QOL has not been studied previously for combination radiotherapy and immunotherapy, but also because the QOL data will directly inform clinical care of patients and clinical decision-making after completion of this trial. Specifically, if the primary endpoint (overall response rate) were negative and the QOL were worse for the experimental arm (RT plus immunotherapy) as we hypothesize in Section 14.1.2, then the winning arm of this trial would be immunotherapy alone. On the other hand, if the primary endpoint were positive (i.e. RT plus immunotherapy resulted in a higher overall response rate) but QOL were worse, then the QOL data will provide critically important information for patients and physicians for clinical decision-making and the trade-off between response rate vs QOL. Our assessment of quality-adjusted survival, which combines QOL and survival in a single outcome, further informs patient decisions. Thus, for a trial studying a novel combination therapy (RT and immunotherapy), which may have unexpected impact on patients, collection of QOL is especially important for this trial.

The European Organization for Research and Treatment of Cancer (EORTC) quality of life instruments consist of a common component (QLQ-C30) which includes questions broadly applicable to all cancer patients, which is meant to be combined with a disease-specific component, in this case QLQ-BLM30. QLQ-C30 assesses 5 functional domains (physical, role, cognitive, emotional, social) and 8 symptoms (fatigue, pain, nausea/vomiting, dyspnea, loss of appetite, insomnia, constipation, diarrhea), together with financial problems and global quality of life. The QLQ-BLM30 bladder-specific module further assesses symptoms in several domains, including urinary function, bowel symptoms, and sexual function (for men and women). Together, the EORTC instrument consists of a total of 60 questions, which takes approximately 10 minutes to complete. The PROMIS-Fatigue 8a consists of eight items that require a response on a scale from "not at all" to "very much." This questionnaire will take approximately 1 minute to complete34.

Several questions of the EORTC instrument specifically measure potential side effects of immunotherapy, including fatigue, weakness, diarrhea, dyspnea and pain. The PROMIS-Fatigue 8a will interrogate fatigue in greater detail, which is of particular interest for patients receiving both immunotherapy and radiation therapy. QOL data will allow an examination of whether combination immunotherapy-radiotherapy exacerbates urinary and other QOL components compared to immunotherapy alone – which has not been previously studied.

The EQ-5D-5L is a short, 6-question, instrument which assesses a patient's overall quality of life or health state35. The addition of the EQ-5D-5L will allow for computation and comparison between arms of health utilities and quality adjusted survival.

The quality of life questionnaire is expected to take about 15 minutes total to complete, and will be assessed at baseline and 4 follow-up time points over 2 years.

14.1.2 Objectives

Primary Objective

To compare patient-reported fatigue as assessed by the PROMIS-Fatigue 8a from baseline through 24 months between patients treated with immunotherapy alone and immunotherapy plus radiotherapy to a single site. Hypothesis: Fatigue from baseline through 24 months will be worse in patients randomized to immunotherapy plus radiotherapy to a single site compared to immunotherapy alone.

Secondary Objectives

To compare health-related quality of life (HRQOL) as assessed by the EORTC QLQ-C30 from baseline through 24 months between patients treated with immunotherapy alone and immunotherapy plus radiotherapy to a single site. Hypothesis: HRQOL from baseline through 24 months will be worse in patients randomized to immunotherapy plus radiotherapy to a single site compared to immunotherapy alone.

To compare urinary symptoms as assessed by the EORTC QLQ-BLM30 from baseline through 24 months between patients treated with immunotherapy alone and immunotherapy plus radiotherapy to a single site. Hypothesis: Urinary symptoms from baseline through 24 months will be worse in patients randomized to immunotherapy plus radiotherapy to a single site compared to immunotherapy alone.

To compare patient-reported diarrhea, shortness of breath and pain as assessed by the EORTC QLQ-C30 from baseline through 24 months between patients treated with immunotherapy alone and immunotherapy plus radiotherapy to a single site. Hypothesis: Diarrhea, shortness of breath and pain from baseline through 24 months will be worse in patients randomized to immunotherapy plus radiotherapy to a single site compared to immunotherapy alone.

To compare health utilities and quality-adjusted survival between patients treated with immunotherapy alone and immunotherapy plus radiotherapy to a single site. Hypothesis: Health utilities (based on the EQ-5D-5L index score at 45 days, and at 6, 12, and 24 months) will be worse in patients randomized to immunotherapy plus radiotherapy to a single site compared to

immunotherapy alone; however, quality-adjusted survival (which combines health utilities at baseline, at 45 days, and at 6, 12, and 24 months with overall survival) will continue to favor immunotherapy plus radiotherapy to a single site over immunotherapy alone.

Exploratory Objective

To compare other scale scores of the EORTC QLQ-C30 (global health status and quality of life; physical, role, emotional, cognitive, and social function; symptoms) and EORTC QLQ-BLM30 (urostomy problems, catheter problems, future perspectives, abdominal bloating and flatulence, body image, sexual function) at 45 days, and at 6, 12, and 24 months between patients treated with immunotherapy alone and immunotherapy plus radiotherapy to a single site.

14.1.3 Methods

For Schedule of Assessments for this quality of life study, see Section 6.5. All participating institutions must ask patients for their consent to participate in this quality of life study (A032002-HO1), although patient participation is optional. Paper booklets will be used for this study. For information regarding ordering the booklets, see Section 4.5. For all patients who consent to participate in this quality of life study (A032002-HO1), a booklet will be given to the patient to complete at the specified planned clinic visits before any procedures/tests are initiated at the site visit and prior to any discussion of their status with healthcare personnel at the site. Booklets will be collected at the following time points: during screening and approximately at 45 days, and at 6, 12, and 24 months post-randomization. The booklet contains 66 questions and it is anticipated that the booklet will take approximately 10-15 minutes for the patient to complete at each administration time point. We anticipate having booklets available in a range of languages. Patients who consent to participate in this quality of life study (A0320021-HO1) may decline to complete a booklet at any time. The primary reason for each missed booklet will be collected on a case report form.

14.1.4 Statistical Considerations

All questionnaires will be scored according to published scoring algorithms, including recommendations for addressing missing items within a scale. An intent-to-treat approach will be used for all analyses. To evaluate between-arm differences in patient-reported fatigue from baseline through 24 months, the area under the curve will be calculated as a summary statistic for each arm based on estimates from a mixed model for patient-reported fatigue as assessed by the PROMIS-Fatigue 8a at baseline, at 45 days, and at 6, 12, and 24 months. This approach of estimating each arm's area under the curve as a summary statistic (rather than each patient's area under the curve as a summary measure) is recommended for addressing missing data over time[27]. The mixed model will include a fixed intercept; fixed effect for time, arm, and arm by time interaction; and residual covariance matrix based on the observed covariances. An unstructured residual covariance matrix will initially be used, though alternative structures will be investigated with final selection based on convergence of the mixed model and minimization of the Akaike information criterion. Stratification factors used in the randomization as well as baseline patient characteristics and prognostic factors may be included in the mixed model as covariates. Estimates from the mixed model will be used to construct a 90% confidence interval for the difference in area under the curve between arms. The contrast estimated via the mixed model will involve a two-sided *t*-test with a nominal significance level of $\alpha = .10$.

To evaluate between-arm differences in HRQOL from baseline through 24 months, the area under the curve will be calculated as a summary statistic for each arm based on estimates from a mixed model for HRQOL as assessed by the EORTC QLQ-C30 at baseline, at 45 days, and at 6, 12, and 24 months. Estimates from the mixed model will be used to construct a 90% confidence interval for the difference in area under the curve between arms. The contrast estimated via the mixed model will involve a two-sided *t*-test with a nominal significance level of $\alpha = .10$.

To evaluate between-arm differences in urinary symptoms from baseline through 24 months for patients with a urostomy, the area under the curve will be calculated as a summary statistic for each arm based on estimates from a mixed model for urinary symptoms as assessed by the

EORTC QLQ-BLM30 at baseline, at 45 days, and at 6, 12, and 24 months. Estimates from the mixed model will be used to construct a 90% confidence interval for the difference in area under the curve between arms. The contrast estimated via the mixed model will involve a two-sided *t*-test with a nominal significance level of $\alpha = .10$. If the sample size permits, the same procedure will be used to evaluate between-arm differences in urinary symptoms from baseline through 24 months for patients with a urostomy.

To evaluate between-arm differences in patient-reported diarrhea from baseline through 24 months, the area under the curve will be calculated as a summary statistic for each arm based on estimates from a mixed model for patient-reported diarrhea as assessed by the EORTC QLQ-C30 at baseline, at 45 days, and at 6, 12, and 24 months. Estimates from the mixed model will be used to construct a 90% confidence interval for the difference in area under the curve between arms. The contrast estimated via the mixed model will involve a two-sided *t*-test with a nominal significance level of $\alpha = .10$. The same procedure will be used to evaluate between-arm differences in patient-reported shortness of breath and pain from baseline through 24 months.

To evaluate between-arm differences in quality-adjusted survival, each patient's quality-adjusted survival will be calculated using the area under the curve approach (with and without discounting) based on health utilities derived from the EQ-5D-5L. All data through the follow-up of the earliest censored patient will be used. A population-based approach will also be used such that the area under the curve of a quality-adjusted survival curve (i.e., mean health utility multiplied by the proportion of patients surviving based on Kaplan-Meier estimates) is the mean quality-adjusted survival for the population. Mean quality-adjusted survival will be compared between arms using a bootstrap approach.

To evaluate between-arm differences in all other scale scores of the EORTC QLQ-C30(global health status and quality of life; physical, role, emotional, cognitive, and social function; symptoms) and, EORTC QLQ-BLM30, **(**urostomy problems, catheter problems, future perspectives, abdominal bloating and flatulence, body image, sexual function**)** at 45 days, and at 6, 12, and 24 months, a mixed model will be estimated for each scale score. Estimates from the mixed model will be used to construct a 90% confidence interval for the mean difference in each scale score between arms at each time point. The contrast estimated via the mixed model will involve a two-sided *t*-test with a nominal significance level of $\alpha = .10$.

The proportion of, and reported reasons for, missing data will be presented by time point and arm. Correlation analysis and logistic regression analysis will be used to examine whether baseline patient characteristics and prognostic factors predict missingness. The mixed models will provide unbiased parameter estimates under a missing completely at random or missing at random mechanism. However, a sensitivity analysis will be conducted to assess the robustness of the results across various assumptions about the missing data.

Power: To evaluate between-arm differences in patient-reported fatigue from baseline through 24 months, 120 evaluable patients from among the 143 randomized patients on the parent protocol (i.e., allowing 15% of patients to decline consent or miss booklets for any reason) provide 80% power to detect a mean difference in patient-reported fatigue between arms based on a two-sided *t*-test estimated via a mixed model with 5 assessments per patient, nominal significance level of $\alpha = .10$, intraclass correlation of 0.50, and population standardized mean difference of 0.35 (i.e., between a small and moderate effect size based on Cohen's conventions)[36]. The same power calculation applies when evaluating between-arm differences in HRQOL, urinary symptoms, diarrhea, shortness of breath, and pain from baseline through 24 months.

Analyses will be coordinated by the Alliance SDC A032002 Statistician using the dataset used for the analysis of the clinical endpoints to ensure consistent data is reported for the primary and secondary endpoints (e.g., data associated with censoring, proper inclusion of crossover data, and data to be excluded in cases of consent withdrawals for follow-up and correlative studies).

14.2 Correlative Science

14.2.1 Central Pathology Review and Specimen Biobanking

Tissue, urine and blood samples described in Section 6.2 for mandatory central pathology review and optional biobanking. Biospecimens will be submitted and stored at the Alliance Biorepository. Testing of banked samples will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved by NCI in accordance with National Clinical Trials Network (NCTN) policies.

15.0 General Regulatory Considerations and Credentialing

15.1 Institutional Credentialing

15.1.1 IROC Institutional Requirements

Institutions using IMRT or SBRT must be credentialed prior to delivery of radiation therapy on any protocol patient. Institutions previously credentialed for use of IMRT in clinical trials need not repeat IMRT credentialing for this trial.

Web Link for Credentialing Procedures and Instructions: http://irochouston.mdanderson.org

	Treatment Modality	
RT Credentialing Requirements	**Photon**	**Key Information**
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 if your institution has completed the credentialing requirements, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org).
Phantom Irradiation	**X**	An IMRT HN phantom and a lung phantom on appropriate motion platform must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (http://irochouston.mdanderson.org).
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.
Institution	**X**	Institutions will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution and Alliance Headquarters 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

APPENDIX II SUMMARY OF SUGGESTED DOSE CONSTRAINTS

Serial tissue	Max critical volume above threshold	Three fractions: Threshold dose (Gy)	Three fractions: Max point dose (Gy)[a]
Optic pathway	<0.2 cc	15.3 (5.1 Gy/fx)	17.4 (5.8 Gy/fx)
Cochlea			17.1 (5.7 Gy/fx)
Brainstem (not medulla)	<0.5 cc	18 (6 Gy/fx)	23.1 (7.7 Gy/fx)
Spinal cord and medulla	<0.35 cc <1.2 cc	18 (6 Gy/fx) 12.3 (4.1 Gy/fx)	21.9 (7.3 Gy/fx)
Spinal cord subvolume (5–6 mm above and below level treated per Ryu)	<10% of subvolume	18 (6 Gy/fx)	21.9 (7.3 Gy/fx)
Cauda equina	<5 cc	21.9 (7.3 Gy/fx)	24 (8 Gy/fx)
Sacral plexus	<5 cc	22.5 (7.5 Gy/fx)	24 (8 Gy/fx)
Esophagus[b]	<5 cc	17.7 (5.9 Gy/fx)	25.2 (8.4 Gy/fx)
Brachial plexus	<3 cc	20.4 (6.8 Gy/fx)	24 (8 Gy/fx)
Heart/pericardium	<15 cc	24 (8 Gy/fx)	30 (10 Gy/fx)
Great vessels	<10 cc	39 (13 Gy/fx)	45 (15 Gy/fx)
Trachea and large bronchus[b]	<4 cc	15 (5 Gy/fx)	30 (10 Gy/fx)
Bronchus-smaller airways	<0.5 cc	18.9 (6.3 Gy/fx)	23.1 (7.7 Gy/fx)
Rib	<1 cc <30 cc	28.8 (9.6 Gy/fx) 30.0 (10.0 Gy/fx)	36.9 (12.3 Gy/fx)
Skin	<10 cc	30 (10 Gy/fx)	33 (11 Gy/fx)
Stomach	<10 cc	16.5 (5.5 Gy/fx)	22.2 (7.4 Gy/fx)
Duodenum[b]	<5 cc <10 cc	16.5 (5.5 Gy/fx) 11.4 (3.8 Gy/fx)	22.2 (7.4 Gy/fx)
Jejunum/ileum[b]	<5 cc	17.7 (5.9 Gy/fx)	25.2 (8.4 Gy/fx)
Colon[b]	<20 cc	24 (8 Gy/fx)	28.2 (9.4 Gy/fx)
Rectum[b]	<20 cc	24 (8 Gy/fx)	28.2 (9.4 Gy/fx)
Bladder wall	<15 cc	16.8 (5.6 Gy/fx)	28.2 (9.4 Gy/fx)
Penile bulb	<3 cc	21.9 (7.3 Gy/fx)	42 (14 Gy/fx)
Femoral heads (right and left)	<10 cc	21.9 (7.3 Gy/fx)	
Parallel tissue	**Minimum critical volume below threshold**	**Threshold dose(Gy)**	**Max point dose(Gy)[a]**
Lung (right and left)	1500 cc	11.6 (2.9 Gy/fx)	NA-Parallel tissue
Lung (right and left)	1000 cc	12.4 (3.1 Gy/fx)	NA-Parallel tissue
Liver	700 cc	19.2 (4.8 Gy/fx)	NA-Parallel tissue
Renal cortex (right and left)	200 cc	16 (4 Gy/fx)	NA-Parallel tissue

[a]"Point" defined as 0.035 cc or less.
[b]Avoid circumferential irradiation.

APPENDIX III NCI/DCTD COLLABORATIVE AGREEMENT LANGUAGE

NCI/DCTD Collaborative Agreement Language

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

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

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

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

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

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

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm).-Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human

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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.

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