ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

UPDATE TO ALLIANCE A091605

A RANDOMIZED PHASE II STUDY OF ANTI-PD1 ANTIBODY [MK-3475 (PEMBROLIZUMAB)] ALONE VERSUS ANTI-PD1 ANTIBODY PLUS STEREOTACTIC BODY RADIATION THERAPY IN ADVANCED MERKEL CELL CARCINOMA

[X] **Update:**	[ ] **Status Change:**
[ ] Eligibility changes	[ ] Pre-Activation
[ ] Therapy / Dose Modifications / Study Calendar changes	[ ] Activation
[X] Informed Consent changes	[ ] Closure
[ ] Scientific / Statistical Considerations changes	[ ] Suspension / temporary closure
[ ] Data Submission / Forms changes	[ ] Reactivation
[X] Editorial / Administrative changes	
[X] Other:MK-3475 (Pembrolizumab) CAEPR update	

The changes included in this update to A091605 have been made in response to an action letter from Dr. Elad Sharon (sharone@mail.nih.gov). This Action Letter is posted on the A091605 Study Page on the Alliance and CTSU web sites. A revised CAEPR with the new risks has been added to the protocol. Therefore, the model consent form has been revised to incorporate these new risks consistent with the new NCI Model Template Instructions. There are no changes to the risk/benefit ratio.

If your site utilizes the CIRB as your IRB of record:
No recommended IRB level of review is provided by the Alliance since the CIRB is the IRB of record for this trial. The site has 30 days after the posting of this amendment to implement it at their site. Please refer to the amendment application and CIRB guidelines for further instructions.

***If your site utilizes a local IRB as your IRB of record**:*
Expedited IRB is allowed. IRB approval (or disapproval) is required within 90 days. Please follow your local IRB guidelines. The proposed changes in this amendment are minor and do not affect the overall risk/benefit ratio.

UPDATES TO THE PROTOCOL:

Section 9.4.1 (CAEPR for MK-3475)

The CAEPR for MK-3475 (pembrolizumab) has been updated with the most recent version, Version 2.6, July 15, 2021. Changes from version 2.5 to 2.6 include the following:

- Added New Risk:
  - Rare but Serious: Hepatobiliary disorders - Other (sclerosing cholangitis)
- Decrease in Risk Attribution:

    - Changed to Rare but Serious from Less Likely: Blood and lymphatic system disorders - Other (immune thrombocytopenic purpura)
- Provided Further Clarification:
    - Thrombotic thrombocytopenic purpura is now reported as Blood and lymphatic system disorders - Other (immune thrombocytopenic purpura).

UPDATES TO THE MODEL CONSENT:

What possible risks can I expect from taking part in this study?

Based on the revisions to the MK-3475 (pembrolizumab) CAEPR that were previously described, the NCI had made the following changes to the NCI condensed risk profile for MK-3475 (pembrolizumab):

- Added New Risk:
    - Rare: Swelling of the gallbladder

A replacement protocol document and model consent form have been issued.

This study remains permanently closed to new patient accrual.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A091605

A RANDOMIZED PHASE II STUDY OF ANTI-PD1 ANTIBODY [PEMBROLIZUMAB (MK-3475)] ALONE VERSUS ANTI-PD1 ANTIBODY PLUS STEREOTACTIC BODY RADIATION THERAPY IN ADVANCED MERKEL CELL CARCINOMA

NCI-supplied agents: Pembrolizumab (MK-3475) (NSC # 776864)

ClinicalTrials.gov Identifier: NCT#03304639

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

Protocol Contacts:

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Drug Supply Questions
Pharmaceutical Management Branch,
CTEP/DCTD/NCI
(240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email
PMBAfterHours@mail.nih.gov

Alliance Biorepository at Ohio State
The Ohio State University
Innovation Centre
2001 Polaris Parkway
Columbus, OH 43240
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path.calgb@osumc.edu

IROC Rhode Island
640 George Washington Highway
Building B, Suite 201
Lincoln, RI 02865
Tel: 401-753-7600 Fax: 401-753-7601
www.irocri.qarc.org

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:	appropriate Alliance Biorepository
Questions regarding drug supply	PMB
Questions regarding drug administration	Pharmacy Contact

The specimen collection of this study is supported by the Ludwig Center for Metastasis Research at the University of Chicago.

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 CTSU via the Regulatory Submission Portal. (Sign in at 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 at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 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). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password.		
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.		

A RANDOMIZED PHASE II STUDY OF ANTI-PD1 ANTIBODY [PEMBROLIZUMAB (MK-3475)] ALONE VERSUS ANTI-PD1 ANTIBODY PLUS STEREOTACTIC BODY RADIATION THERAPY IN ADVANCED MERKEL CELL CARCINOMA

Registration Eligibility Criteria (See Section 3.2)

Pathologically (histologically or cytologically) proven diagnosis of MCC by local pathology review.

Have measurable disease based on RECIST 1.1 with at least two cancerous deposits. At least one deposit must be RECIST measurable while at least ***one deposit*** must meet criteria for SBRT (See Section 7.1)

Advanced or metastatic MCC defined as evidence of distant metastasis(es) on imaging.

No prior immunotherapy for advanced/metastatic MCC (prior palliative RT is allowed as long as there are two unirradiated measurable cancerous deposits

No History of the following:

- Autoimmunity requiring systemic immunosuppression within 2 years
- Patients known to be HIV positive are eligible if they meet the following criteria within 30 days prior to registration: stable and adequate CD4 counts (≥ 350 mm^3), and serum HIV viral load of < 25,000 IU/ml. Patients may be on or off antiviral therapy so long as they meet the CD4 count criteria.

Required Initial Laboratory Values	
Absolute neutrophil count (ANC)	≥ 1500/mm^3
Platelet Count	≥ 100,000/mm^3
Hemoglobin	≥ 9.0g/dl
Total Bilirubin	≤ 2.0 mg/dl
AST / ALT	≤ 3.0 x ULN WNL*
Systolic BP	≤150 mg HG
Diastolic BP	≤ 90 mg HG
Albumin	>3mg/dl
BUN	≤30 mg/dl
Creatinine	≤1.7 mg/dl
* Supplementation acceptable	

No other active malignancy that the investigator determines would interfere with treatment and safety analysis.

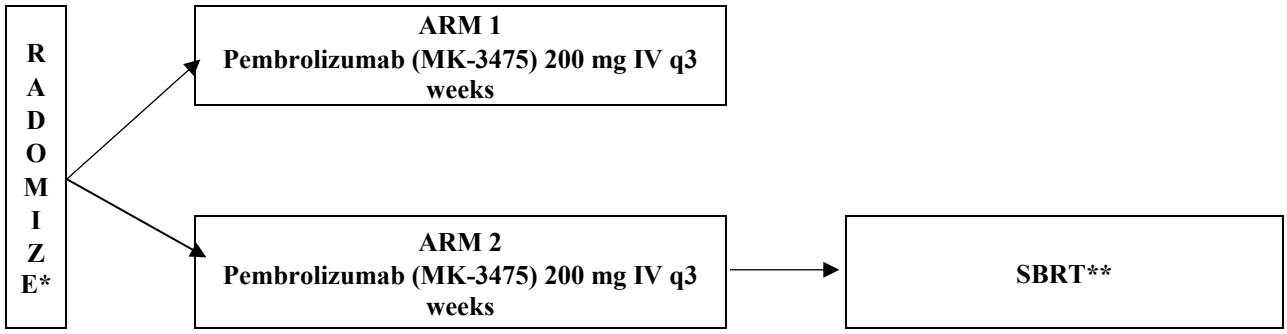
Not pregnant and not nursing (See Section 3.2)

Age ≥ 18

ECOG performance status 0 - 2

Schema

1 Cycle = 21 Days



* All sites have identified the metastasis to be irradiated in the event their patient is randomized to arm 2.

** Radiation therapy will be administered to 1 cancer deposit concurrent with the first dose or started within the first cycle of pembrolizumab (MK-3475) administration. This cancer deposit to be irradiated will be defined prior to randomization and treatment per the guidelines in Section 7.1.

Treatment is to continue until disease progression or unacceptable adverse event for a maximum period of two years. Patients will be followed for 5 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.

Table of Contents

1.0 BACKGROUND

1.1 Merkel cell carcinoma background and role of PD1 blockade

Merkel cell carcinoma (MCC) is a rare but extremely aggressive cutaneous malignancy. Risk factors for the development of MCC include chronic ultraviolet light exposure as well as immunosuppression. [1, 2]Approximately 80-90% of MCC are associated with infection by the Merkel cell polyomomavirus which leads to oncogenic expression of viral proteins including the large and small T antigens [3-5]. Approximately 40% of MCC patients develop metastatic disease with a median overall survival of approximately 9.5 months [6]. Similar to other neuroendocrine cancers, standard treatment for metastatic MCC has historically included platinum based chemotherapy with radiation therapy reserved for palliation in appropriate symptomatic patients.[7]

However, given poor survival in metastatic MCC, novel treatment strategies are needed. One such strategy is using immune based therapies to treat metastatic MCC. These approaches are based on the viral etiology for a large fraction of MCC. Blockade of the PD1/L1 axis particularly has been an attractive target given the known association of PD-L1 expression in virally infected cells. Given that MCPyV-specific T cells are detected in up to 67% of MCC tumors [8], and approximately 55% of MCC tumor cells express PD-L1[9] there is a strong rationale for anti-PD-L1 therapy in MCC. Furthermore, MCPyV-negative tumors have higher mutation and neoantigen burden[3], which may be associated with higher response to PD-L1.

The activity of anti-PD1/L1 antibodies has been recently described in MCC suggesting that this approach is likely to become firstline standard of care therapy for metastatic MCC. In a phase II study of the anti-PD1 antibody pembrolizumab (MK-3475) in previously untreated metastatic MCC patients a response rate of 56% was observed[10]. Similar to what has been observed in other tumors, the median duration of response was not reached with 86% of responses on-going at the time of datalock. Furthermore, in the second line setting, the anti-PD-L1 antibody avelumab has been associated with substantial clinical benefit. Presented at ASCO 2016 an objective response rate of 32% was seen with a 6-mo durable response rate of 29.1% (95% CI: 19.5, 38.8). These responses lead to this agent being awarded Breakthrough Designation for MCC treatment by the FDA[11][11][11]. Despite the ability to get good responses with anti-PD1/L1 therapy the median progression free survival is only nine months indicating that while an important step forward, this treatment paradigm needs to be augmented to improve response rates and survival of metastatic MCC patients.

<u>Rationale for radiation with immunotherapy and in Merkel Cell Carcinoma</u>

Radiation therapy has long been used to treat MCC either definitively, adjuvantly or palliatively. In the palliative setting for MCC, a single 8 Gy dose of radiation therapy for metastatic MCC has been associated with high response rates, and prolonged treated metastasis control, and minimal toxicity [12]. This approach is associated with a robust initial response rate however modest progression-free survival (~3 months) and no known overall survival benefit[13]. More recently, data has emerged indicating that 24 Gy delivered in three, 8 Gy doses is associated with improved treated tumor control, compared to a single 8 Gy fraction.[14].

Newer radiation techniques, commonly termed stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR), but perhaps most accurately described as hypofractionated image-guided radiotherapy (HIGRT), precisely deliver single or few radiation treatments at doses 2-10 times that of conventional radiation treatments[15]. Derived from intracranial stereotactic radiosurgery, these treatments deliver radiation doses wrapped tightly around targeted metastases, while sparing surrounding normal tissues. Stereotactic

Body Radiotherapy (SBRT) reduces the overall time of radiation treatment and offers a greater potential for cell kill compared to standard fractionation schemas of 1.8-3.0 Gy/day. SBRT Treatments have been shown to have high rates of treated tumor control and is standard of care for inoperable early stage NSCLC, prostate cancer, pancreatic cancer, and hepatocellular cancer. Furthermore, SBRT has been shown to have high rates of treated tumor control for patients with limited metastases in the lung, liver, adrenal gland, spine, and other locations [15] with limited toxicity.

Implanted tumor models show that concomitant administration of radiation and anti-PD-L1 antibody results in significantly greater tumor reduction, as compared with radiation or anti-PD-L1 antibody treatment alone, in a murine system.[16] This effect was observed in both tumors within the radiation field as well as distant tumors, suggesting the beneficial effects of radiation on the immune response have systemic impact. Case reports of patients having responses in distant sites from radiation, while undergoing immunotherapy, also support this [17]. SBRT to metastatic sites may improve the efficacy of immune modulating agents. Described mechanisms for this improvement include but are not limited to increased tumor antigen exposure, improved antigen presentation and T cell function as well as modulation of immunosuppressive cell populations such as T regulatory cells and myeloid derived suppressor cells.[18-20] Preclinical modeling also supports a benefit when combining radiation with anti-PD1 axis blockade. Beyond synergistic mechanisms of modulating the immune response, direct tumor debulking by radiation may also be particularly well suited as an adjunct to immunotherapy. Additionally, higher dose per fraction of radiation has been associated with more robust adaptive immune responses in multiple tumors. Radiation to sites of bulk tumor would be presumed to improve the overall response rate of combination therapy. Additionally, reports of SBRT combinations with systemic therapies have suggested that time to progression is improved.[21, 22] Therefore, the combination of SBRT and anti-PD-1/PD-L1 treatment may not only have improved treated tumor control, but may also have improved overall progression free survival if SBRT enhances the effect of systemic therapy

1.2 Rationale

Here we propose a clinical trial testing the hypothesis that the addition of SBRT radiation to pembrolizumab will improve progression-free survival and clinical benefit compared to pembrolizumab alone in MCC.

2.0 OBJECTIVES

2.1 Primary objective

To describe the PFS of SBRT + pembrolizumab (MK-3475) compared to pembrolizumab (MK-3475) alone in advanced/metastatic MCC patients.

2.2 Secondary objective(s)

2.2.1 To describe the PFS of SBRT + pembrolizumab (MK-3475) compared to pembrolizumab (MK-3475) alone across RECIST measurable (including both radiated and non-radiated) cancer deposits.

2.2.2 To describe the overall response rate of SBRT + pembrolizumab (MK-3475) compared to pembrolizumab (MK-3475) alone in both radiated and in non-radiated deposit(s).

2.2.3 To determine the PFS at 6 months of SBRT + pembrolizumab (MK-3475) compared to pembrolizumab (MK-3475) alone across all cancerous deposits by RECIST.

2.2.4 To determine the rate of grade >3-4 adverse events, by organ system, by CTCAEv5.0.

2.2.5 To determine the local control of SBRT treated tumors.

2.2.6 To calculate delivered radiation dose using cone-beam CT images collected on the radiation treatment table in the final treatment position.

2.3 Correlative science objective(s)

2.3.1 To test the utility of CT-based radiomics to predict radiation-induced pneumonitis and true delivered dose of SBRT based on cone beam collected imaging and diagnostic scans.

2.3.2 Biobanking for future correlative science projects

3.0 PATIENT SELECTION

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

3.1 On-Study Guidelines

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

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

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers 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 due to the teratogenic potential of the therapy utilized in this trial. Include as applicable: Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.2 Eligibility Criteria

___ **3.2.1 Documentation of Disease:**

Patients must have pathologically (histologically or cytologically) proven diagnosis of MCC by local pathology review.

___ **3.2.2 Measurable disease and/or non-measurable disease as defined in Section 11.0.**

Have measurable disease based on RECIST 1.1 including at least two cancerous deposits. At least one deposit must be RECIST measurable while at least ***one deposit*** must meet criteria for SBRT (See Section 7.1). Non-radiated tumor will be identified prior to randomization on the protocol.

___ **3.2.3 Patients must have advanced or metastatic MCC defined as evidence of distant metastasis(es) on imaging.**

- Patients with locoregionally confined disease are not eligible.

___ **3.2.4 Prior Treatment**

- No prior immunotherapy for advanced/metastatic MCC
- Patients with known or suspected CNS metastases, untreated CNS metastases, or with the CNS as the only site of disease are excluded. However, subjects with controlled brain metastases will be allowed to enroll. Controlled brain metastases are defined as no radiographic progression for at least 4 weeks following radiation and/or surgical treatment (or 4 weeks of observation if no intervention is clinically indicated), and off of steroids for at least 2 weeks, and no new or progressive neurological signs and symptoms
- Patients having received palliative radiotherapy for extracranial metastasis(es) are eligible as long as there are 2 cancerous deposits that have not received prior RT and they meet the following criteria.
    - No prior radiation therapy (>5 Gy) to the metastasis intended to be treated with SBRT

___ **3.2.5 No History of the following:**

- Autoimmunity requiring systemic immunosuppression within 2 years
- Patients known to be HIV positive are eligible if they meet the following:
    - CD4 counts ≥ 350 mm^3
    - Serum HIV viral load of <25,000 IU/ml.

___ **3.2.6 No other active malignancy that the investigator determines would interfere with the treatment and safety analysis.**

___ **3.2.7 Not pregnant and not nursing,** because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown.

Therefore, for women of childbearing potential only, a negative (if your test schedule specifically indicates a urine or serum pregnancy test, add that information at this point) pregnancy test done ≤ 28 days prior to registration is required.

___ **3.2.8 Age ≥ 18 years**

___ **3.2.9 ECOG Performance Status 0-2**

___ **3.2.10 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC)	≥ 1,500/mm^3
Platelet Count	≥ 100,000/mm^3
Hemoglobin	≥ 9.0g/dl
Total Bilirubin	≤ 2.0 mg/dl
AST / ALT	≤ 3.0 x ULN
Systolic BP	≤150 mg HG
Diastolic BP	≤ 90 mg HG
Albumin	>3mg/dl
BUN	≤30 mg/dl
Creatinine	≤1.7 mg/dl

___ **3.2.11 Required pre-treatment diagnostic imaging:**

The following imaging workup to document metastases within 45 days prior to study registration are required: CT scans of the chest, abdomen and pelvis with radionuclide bone scan OR whole body (at least skullbase to midthigh) PET/CT.

4.0 PATIENT REGISTRATION

4.1 CTEP Investigator Registration Procedures

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

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

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

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

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

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

4.2 CTSU Site Registration Procedures

This study is supported by the NCI CTSU.

IRB Approval

For 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 after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

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

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

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

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;

- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 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 based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- 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 A091605.
- Click on Documents, select Site Registration, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.2 Checking Site's 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 sites 5-character CTEP Institution Code and click on Go.
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

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

4.2.3 Submitting Regulatory Documents

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

To access the Regulatory Submission Portal log 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 at 1-866-651-2878 in order to receive further instruction and support.

4.2.4 Credentialing

See Section 15.0 for credentialing requirements.

4.3 Patient Registration Requirements

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.

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

4.4 Patient Registration/Randomization Procedures

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

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

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

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

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

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. 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 Stratification Factors and Treatment Assignments

Number of metastases (2-4 vs. >4)

Age <70 vs. ≥ 70 years old

ECOG 0-1 vs 2

5.0 STUDY CALENDAR

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.

- To be completed ≤ 28 DAYS before registration: All laboratory studies, history and physical.
- To be completed ≤ 28 DAYS before registration: Any X-ray, scan of any type or ultrasound which is utilized for tumor measurement per protocol.
- To be completed ≤ 28 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*	**Arm 2 only:** Radiation***	**Arms 1&2** (MK3475): Day 1 of each cycle	Post treatment follow-up**
Tests & Observations				
History and physical, weight, PS	X	X	X	X
Height	X			
Adverse Event Assessment		X	X	X
Registration Fatigue/Uniscale Assessment	X(1)			
Laboratory Studies				
Complete Blood Count, Differential, Platelets	X		X	X
Serum Creatinine,	X		X	X
Albumin, glucose	X		X	X
AST, ALT, Alk. Phos., Bili	X		X	X
TSH (with reflexive TFTs if abnormal)	X		X	X
Serum or Urine HCG	X(2)			
Staging				
Brain Imaging (MRI or CT with contrast)†	X			
Tumor Measurement	X		A	X
CT/MRI chest/abd/pelvis #	X(3)		A	X
Correlative studies: For patients who consent to participate				
Blood samples	*Collected at baseline, after RT (prior to pembrolizumab (MK-3475)(Arm 2 patients only), day 1 of cycle 3, and at the time of first restaging imaging (i.e. 3 months after cycle 1), see Section 6.2.*			
Tissue	*Collected at baseline prior to any treatment*			

* Labs completed prior to registration may be used for day 1 of cycle 1 tests if obtained ≤ 7 days prior to treatment. For subsequent cycles, labs, scans, tests and observations may be obtained ≤ 72 hours prior to day of treatment.

** Physical examination, adverse event assessments, labs and scans are required ≤ 12 weeks after the end of treatment; thereafter, every 6 months until disease progression for a maximum of 5 years following registration or more frequently as clinically indicated. See also Section 12.0. At time of progression, withdrawal or removal, only survival information should be collected every 6 months for 5 years after registration.

*** Radiation therapy will be administered to 1 cancer deposit concurrent with the first dose or started within the first cycle of pembrolizumab (MK-3475) administration. Eligibility must have been documented prior to administration of radiation.

† Only required if there is evidence or suspected brain mets

All sites of known disease as clinically indicated.

1 To be completed after registration and prior to treatment (See Appendix I). This questionnaire is included on all Alliance trials in order to further study the relationship between these assessments and overall survival in a meta-analysis setting.

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

3 Baseline scans can include either: 1) a CT, spiral CT, or MRI or 2) an FDG-PET scan and diagnostic CT performed with both IV and oral contrast, and the CT acquired with 5 mm or less slice thickness. Supporting documentation is to be submitted, per Section 6.1. Response assessment should include assessment of all sites of disease and use the same imaging method as was used at baseline.

A After Cycle 3 (prior to cycle 4) then every 9 weeks, (prior to the start of cycles 4, 7,10, 13, 15, etc.).

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

Requirements to access Rave via iMedidata:

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

Rave role requirements:

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

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

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

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password and click on the accept link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

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

> Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com**.**

ePRO:

The data from the patients' responses are submitted directly from the device into the Rave database. There are no documents to audit. The electronic responses are the source documentation.

6.1.3 Supporting documentation

This study requires supporting documentation for diagnosis and progression. Supporting documentation will include a pathology report and radiology report. These must be de-identified and uploaded into iMedidata Rave at registration and progression.

6.2 Data Quality Portal

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

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

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

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

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

6.3 Specimen collection and submission

6.3.1 Overview of specimen collection and submission

For patients who consent to participate, tissue, blood, and fecal samples will be collected at the following time points for these studies:

	Before first dose of pembrolizumab (MK-3475) (Arm 1 & 2)	**After RT (Arm 2 Only)**	**Day 1 of Cycle 3 (Arm 1 & 2)**	**First Restaging (i.e 3 Months after Cycle 1) (Arm 1 & 2)**	**Storage/ Shipping conditions**	**Submit to:**
For patients consented to A091605 biobanking, submit the following:						
Paraffin block OR unstained	X(1)				Ambient/ shipping overnight	ABOSU

slides of tumor tissue						
Peripheral whole blood (EDTA)(2)	1 x 10 mL				Cool pack/ship overnight	ABOSU
Peripheral whole Blood (green top heparin) (3)	5 x 10 mL	5 x 10 mL			Ambient/ shipping overnight	ABOSU
Peripheral whole blood for serum (red top) (3)	1 x 10 mL		1 x 10 mL	1 x 10 mL	Cool pack/ship overnight	ABOSU
Stool for microbiome (kit provided) (4)	X				Dry ice/ship overnight	ABOSU

1 Blocks are preferred. Paraffin blocks of primary and, when available, metastatic tissue obtained from archival tumor specimens should be sent. If not please submit 20 unstained slides (5 micron thickness) charged (or as many as possible) but up to 20. For patient who consented to model consent question "I agree to have my blood and tissue collected and I agree that my tissue and blood and related information may be kept in a Biobank for use in future health research." Tissue will be used as described in Section 14.1

2 For patient who consented to model consent question "I agree to have my blood and tissue collected and I agree that my tissue and blood and related information may be kept in a Biobank for use in future health research." Whole blood in EDTA tubes will be used as described in Section 14.1. This whole blood can be collected at any time while patient is on study, but the preferred time is before the first dose of pembrolizumab (MK-3475).

3 For patient who consented to model consent question "I agree to have my blood and tissue collected and I agree that my tissue and blood and related information may be kept in a Biobank for use in future health research." Blood samples will be used as described in Section 14.1.

4 For patient who consented to model consent question "I agree to have my stool collected and I agree that my stool and related information may be kept in a Biobank for use in future health research." Stool samples will be used as described in Section 14.1.

6.3.2 Specimen Submission Using the Alliance Biospecimen Management System

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: http://bioms.allianceforclinicaltrialsinoncology.org using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS webpage to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: 1-855-55-BIOMS or Bioms@alliancenctn.org. For assistance in using the

application or questions or problems related to specific specimen logging, please contact: 1-855-55-BIOMS or Bioms@alliancenctn.org.

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the protocol number (A091605), Alliance patient number, patient's initials, date and type of specimen collected (e.g., serum, whole blood).

Note to study authors: When specimens are time-sensitive, and/or are required for communication of test results back to institutions and patients, they should be labeled with patient initials and date of procurement, in addition to protocol number, Alliance patient number and specimen type. Specimens that are not time-sensitive, and/or are not submitted for the purpose of performing an integral test that will be reported back to patients, should not include patient initials or date of procurement.

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

Ship specimens on Monday through Thursday only. Shipping by overnight service to assure receipt is encouraged. Do not ship specimens on Fridays or Saturdays, or the day before a holiday.

All specimens should be sent to the following address:

Alliance Biorepository at Ohio State

The Ohio State University

Innovation Centre

2001 Polaris Parkway

Columbus, OH 43240

Tel: 614-293-7073 Fax: 614-293-7967

6.3.3 Collection of paraffin tumor tissue

For patients who consent to participate in A091605 biobanking (model consent question, "I agree to have my blood and tissue collected and I agree that my tissue and blood and related information may be kept in a Biobank for use in future health research"), tumor blocks/slides will be used as described in Section 14.1.

Paraffin blocks of primary and, when available, metastatic tissue obtained from archival tumor specimens should be sent to the Alliance biorepository at Ohio State University (ABOSU). Please specify the source of the tumor block (primary or metastatic site).

Label the blocks with the following information:

1) Alliance Patient ID Number
2) Patient Initials
3) Alliance Study Number (i.e. A091605)

4) Institutional Surgical Pathology Number/Block ID

Please DO NOT use sticky labels, and DO NOT put labels/tape on top of the actual tissue.

The goal of the Alliance Biorepository is to provide investigators with quality histology sections for their research while maintaining the integrity of the tissue. For these reasons it is preferred that the Alliance Biorepository bank the block until the study investigator requests thin sections. Please contact the Alliance Biorepository if additional assurances with your hospital pathology department are required.

The Alliance has instituted special considerations for the small percentage of hospitals whose policy prohibits long-term storage of blocks, and the smaller percentage of hospitals whose policies prohibit release of any block. If, due to institutional policy, a block cannot be sent, please submit 20 unstained slides at 4-6 micron thickness on plus charged slides. However, blocks are strongly preferred over slides.

Label the slides with the following information:

1) Thickness (e.g. 5 microns)
2) Institutional Surgical Pathology Number/Block ID (either via your institution's standard method for labeling clinical slides or using a permanent marker).

Please DO NOT use sticky labels, and DO NOT put labels/tape on top of the actual tissue.

The slide container should have a label affixed that includes the following information:

1) Date of Collection
2) Alliance Patient ID Number
3) Patient Initials
4) Alliance Study Number (i.e. A091605)

When shipping FFPE tissues (blocks or unstained slides) it is important to avoid extreme heat. If environmental conditions indicate, FFPE tissues should be shipped in containers containing cold packs. It is also important that tissues are shipped in appropriately padded and secure containers to avoid physical damage.

Ship specimens to the Alliance Biorepository at OSU with Priority Overnight on Monday through Thursday for next day delivery. Do not send specimens the day before a holiday.

The goal of the Alliance Biorepository is to provide investigators with quality histology sections for their research while maintaining the integrity of the tissue. For these reasons, it is preferred that the Alliance Biorepository bank the block until the study investigator requests thin sections. Please contact the Alliance Biorepository if additional assurances with your hospital pathology department are required.

A copy of de-identified surgical pathology report should be sent with all tissue submission. Usually, this is generated by obscuring all PHI (names and dates) with white-out or a black magic marker, labeling each page of the report with the Alliance patient ID, and photocopying the report. The surgical pathology case number and block identifier (if applicable) should be maintained on the report so that it can be matched with the physical labeling on the sample.

Specimens may be shipped Priority Overnight to the Alliance biorepository on Monday through Thursday for next day delivery. The biorepository cannot receive specimens on Sundays or holidays. Do not send specimens on Saturday or the day before a holiday. Please refer to the holiday shipping schedule posted in BioMS.

6.3.4 Blood sample submission

For patients who consent to participate in A091605 biobanking (model consent question, "I agree to have my blood and tissue collected and I agree that my tissue and blood and related information may be kept in a Biobank for use in future health research"), blood samples will be used as described in Section 14.1. This sample should be collected prior to 1st dose of pembrolizumab (MK-3475).

Whole Blood in EDTA Lavender Top Tube:

Collect 10 mL of peripheral venous blood in one lavender top tube (K2 or K3 EDTA anti-coagulant) before the 1st dose of pembrolizumab (MK-3475) (baseline). The tubes should be inverted approximately 8-10 times to mix the EDTA. Refrigerate sample until shipping. The blood sample should be placed in a biohazard bag and shipped the same day as the blood is drawn on a cold pack by overnight courier service to the Alliance Biorepository at Ohio State University, where it will then be processed.

Whole Blood in Heparin Green Top Tubes:

Collect 5 x 10 mL of peripheral venous blood into green top (sodium heparin) vacutainer tubes at the following time points: before the 1st dose of pembrolizumab (MK-3475), after radiation (for Arm 2 patients only) and after 4 doses of pembrolizumab (MK-3475)

Specimens should be kept at room temperature until shipping. Invert tubes approximately 8-10 times to mix the additive. Samples should be then placed in a biohazard bag and shipped according to IATA guidelines the same day as the blood is drawn and shipped at **ambient temperature** by overnight courier service to the Alliance Biorepository at OSU for PBMC isolation. **Please do NOT use cold pack during shipping for the whole blood sodium heparin (green top) samples.**

Whole Blood in Red Top Tubes

Collect ~10 mL peripheral venous blood plain red top vacutainer tube(s). Gently invert approximately 5 times to mix clot activator with blood. Let blood clot for 30 minutes. Observe a dense clot. Centrifuge at approximately 1300g (or in accordance with centrifuge manufacturer's instructions) for 10 minutes. The sample should be refrigerated until shipped. Samples should be placed in a biohazard bag and shipped according to IATA guidelines on cool pack by overnight mail to the appropriate Alliance biorepository. The sample should be shipped the same day that the blood is drawn.

All blood samples should be labeled with the following identification:

1) Alliance study number (A091605)
2) Alliance patient ID number
3) Patient's initials
4) Date and time of collection
5) Sample type (eg whole blood).

Specimens may be shipped Priority Overnight to the Alliance biorepository on Monday through Thursday for next day delivery. The biorepository cannot receive specimens on Sundays or holidays. Do not send specimens on Saturday or the day before a holiday.

6.3.5 Stool Specimen Submission

Stool kits should be ordered through BioMS.

For patients who consent to participate in A091605 (model consent question, "I agree to have my stool collected and I agree that my stool and related information may be kept in a Biobank for use in future health research."), fecal samples will be used as described in Section 14.1. This sample should be collected prior to 1st dose of pembrolizumab (MK-3475).

Study subjects will receive a fecal collection kit. that includes a 9x9x9" cardboard box with a Styrofoam container, 2 nitrile gloves, a Ziploc bag with absorbent material containing three 25 ml fecal collection vials with spoons for the stool sample, a disposable "specimen collection toilet adapter with white container" to be placed over the toilet bowl to collect the bowel movement, Wypall absorbent material, parafilm and a sheet of patient instructions. Kits should be ordered through the BioMS website. Study subjects will return the fecal collection kit to the site within 48 hours of collection. Patient does not need to refrigerate the sample.

Once the laboratory at the site receives the stool collection kit, they should perform the following:

- Aliquot the sample into four cryovials* (~100mg per vial). Any extra stool sample should be kept in the original large leak-proof receptacle.
- Label the cryovials with Alliance study number (A091605), Alliance Patient ID, Patient's initials, Date of collection, Sample type (stool).
- Freeze aliquots and the original container at -80°C. Once frozen, samples should not be allowed to thaw.
- Ship samples within 30 days on dry ice by overnight express courier to the Alliance Biorepository at Ohio State University. The biorepository cannot receive specimens on Saturdays, Sundays or holidays. Please keep the stool refrigerated until shipping. Please keep the stool samples frozen until shipping. Sufficient dry ice should be used in the shipping container to ensure that samples remain frozen for at least 72 hours. Keep at least one vial or large receptacle at shipping site.

* Cryovial Choices: Some examples of acceptable 1.8-2.0 mL cryovials are Nalgene (Cat #5012-0020), Fisher (Cat #10-500-26), Corning (Cat #430488), and Nunc (Cat #347627).

6.4 Digital RT Submission Using 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.

6.4.1 TRIAD Access Requirements

Site staff that will be submitting images via TRIAD will need to register with CTEP and have a valid and active CTEP-IAM account.

- Must be registered as an Associate, Associate Plus, Non-Physician Investigator, or Investigator registration type. Refer to the CTEP Registration Procedures section

for instructions on how to request a CTEP-IAM account and complete registration in Registration and Credential Repository (RCR).

To submit images, site staff must hold the TRIAD Site User role on an NCTN or ETCTN roster. Individuals requiring a TRIAD Site User role should contact the person holding a primary role at the site for their affiliated 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.

6.4.2 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 username and password and RCR registration.

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

6.4.3 Procedures for Data Submission via TRIAD

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 as described above. Additional information is available at:

http://triadhelp.acr.org/ClinicalTrials/NCISponsoredTrials.aspx

In the event that a site has not completed all steps required for TRIAD data submission in time to meet the timeline for pre-treatment review, data submitted via SFTP will also be accepted. See the instructions for submission of data via SFTP on the IROC Rhode Island website under Digital Data.

See Section 7.3.7 for items to be submitted for RT QA pre-treatment review

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 21 days of registration.

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

It is acceptable for individual pembrolizumab (MK-3475) to be delivered ≤ a 72-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 Tuesday through the following Monday. In addition, patients are permitted to have a new cycle of pembrolizumab (MK-3475) 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.

Pembrolizumab (MK-3475)) is administered on an outpatient basis. Infusion timing should be as close to 30 minutes as possible; however, a window of -5 minutes and +10 minutes is permitted (*i.e.*, infusion time is 25-40 minutes). Please refer to Section 10.2 for pembrolizumab (MK-3475) compatible infusion set materials, including in-line filter.

Protocol therapy will include pembrolizumab (MK-3475) in both arms (Arms 1 & 2) and radiation (SBRT) in one arm (Arm 2). Radiation will be administered concurrent with the first dose or started

within the first cycle of pembrolizumab (MK-3475). The radiated lesion will be identified prior to randomization and that this lesion will be excluded from the primary endpoint (PFS) calculation. pembrolizumab (MK-3475) treatment will be administered once every 21 days (1 cycle). Treatment will continue until disease progression or unacceptable adverse event for a maximum period of two years.

Agent	Dose	Route	Day	ReRx
pembrolizumab (MK-3475)	200 mg	IV	Day 1	every 3 weeks

7.1 Radiotherapy

Patients in Arm 2 will receive three 8 Gy doses of radiation for a total dose of 24 Gy to a single metastasis (cancer deposit). The radiated lesion will be identified prior to randomization and that this lesion will be excluded from the primary endpoint (PFS) calculation. Each treatment will be separated by a minimum of 40 hours. The expectation is that SBRT will be used for treatment. In cases where the treated tumor is superficial, the use of an electron 3D conformal plan is permitted provided that it provides superior sparing of the organs-at-risk.

Selection of Metastasis to be Irradiated:

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

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

7.1.1. Technical radiotherapy requirements:

To successfully treat using SBRT, centers must satisfy technology requirements for immobilization, simulation, planning, and image-guidance (IGRT) for radiotherapy. These are summarized in the following tables. Questions regarding appropriate technology for this protocol can be directed to the Radiation Oncology PI or medical physics PI.

Table 1.1 Technology Requirements for SBRT

Technology	Requirement	Comments
Beam Modality	MV Photons	ViewRay & Linac are allowed. For superficial tumors, electrons

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

***Note:** Each treatment fraction must be documented with volumetric imaging to enable delivered dose assessment per Section 2.2.6 with the exception of a) robotic systems that do not possess this capability and b) treatments delivered with electrons.

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

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

Table 1.2 Simulation Guidelines

Topic/Parameter	Guideline*
Immobilization	Proper immobilization (e.g., stereotactic body frame, custom-fabricated immobilization) with appropriate clinical devices to ensure reproducibility is required. Patient comfort should be prioritized. Positioning the patient on the treatment couch without any support is discouraged.
Motion Assessment	Ascertain the characteristics of target (and normal tissue) motion with regard to magnitude (amplitude), timing (period), and regularity to determine the need or success of motion control. This is carried out both in simulation and treatment using real time monitoring (e.g., fluoroscopy, 4D CT, beacon tracking, etc.).

Motion Control	Motion control is strongly encouraged when the GTV excursion > 1 cm in any direction. Typical motion control maneuvers include inhibition strategies (e.g., abdominal compression and active breath hold), tracking based on a motion model, and gating to part of the breathing cycle, but others may be applicable. Internal organ management maneuvers must be reliable enough to insure that the GTV does not deviate beyond the confines of the PTV with any significant probability (i.e., < 5%).
CT Slice Thickness	Within 10cm of the PTV, ≤3 mm is recommended. Do not exceed 3 mm. Slices of 1-2 mm are recommended for tumors that are 1 cm or less in the largest dimension.
Use of Contrast	IV contrast is required for treatment of a metastasis in the liver. For targets in other sites, IV contrast is encouraged for better delineation between tumor, pathologic lymph nodes, atelectasis, and vascular structures as well as better definition of normal tissue contours. Oral contrast can be used for OAR delineation at the clinical discretion of the treating physician. Generally, contrast scans are acceptable for dose calculations, although density overrides may be applied in areas of strong contrast (e.g., oral contrast in esophagus). No overrides should be used in the GTV.
CT Scan Range	The CT scan range should include the entirety of the organ that the metastasis to be treated resides in. Additionally, at minimum it should be 10 cm superior and inferior to the treated tumor.

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

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

Treatment Technique	Recommended Method for Motion Assessment During Simulation	Minimum Method for Motion Assessment During Simulation	Scan(s) Recommended for Treatment Planning	Imaging Recommended for Treatment*
Free-breathing using an internal gross target volume (IGTV) approach including abdominal compression	4D CT or fluoroscopy as long as tumor can be directly visualized	Repeated slow acquisition CT scanning through the target (to sample motion) fused to the planning CT dataset	Average intensity projection (AIP) scan from a full field-of-view 4D CT for dose calculations; Maximum intensity projection (MIP) scan to aid IGTV definition; Free-breathing scans are not recommended.	Free-breathing 3D IGRT to ensure visible tumor aligns to IGTV**
Gating with a gating window	4D CT	Exhale CT plus fluoroscopy (free-breathing +	Reconstructed average of gating window scans from	Gated 3D IGRT or fluoroscopy; if

		fluoroscopy strongly discouraged due to baseline shift)	4D CT. Maximum intensity projection (MIP) scan limited to gating window to aid IGTV definition.	not available, then free-breathing CT to ensure visible tumor aligns to MIP contour from 4D CT limited to the gating window
Breath hold (i.e. ABC)	Reproducibility of breath hold confirmed (examples: multiple low dose scans over tumor, repeat fluoroscopy or scout images)	N/A	Scan in breath hold position (inhale recommended since it maximizes lung volume)	Gated 3D IGRT; if not available use manual beam-hold during CBCT acquisition over multiple breath-holds to ensure tumor aligns to IGTV**
Tracking^	4D CT or breath hold CT	N/A	4D CT or breath hold CT	Volumetric imaging or real-time imaging of tumor surrogate required based on treatment machine capabilities.

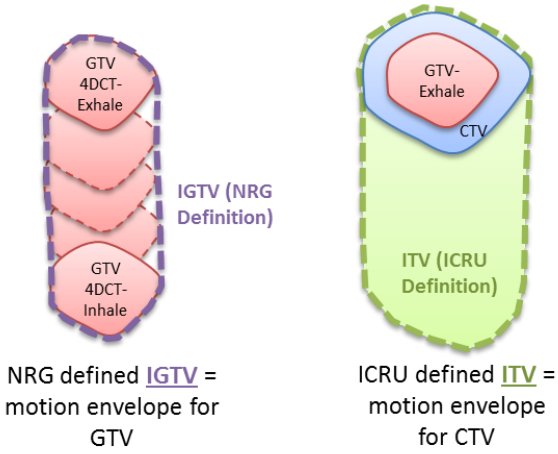
***Note**: Volumetric IGRT for each site must be acquired and submitted for post-treatment assessment of dose per Section 2.2.6 and Table 1.1, except for treatments delivered with electrons or robotic systems without the capability of volumetric IGRT.
****Note:** IGTV is defined in section 7.1.2. In the case when tumor is not visible, please use an appropriate organ surrogate for alignment (i.e., liver as surrogate for a non-visible liver metastasis).
^**Note**: Tracking methods refer to use of robotic or similar systems that provide real-time imaging (i.e., CyberKnife, ViewRay).

7.1.2 Target Volumes and Margins

Definitions of GTV, CTV, IGTV, PTV:

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

explicitly avoided to prevent confusion between a motion encompassing CTV and GTV:



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

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

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

Standard Name	***Description***
PTV_2400	PTV to be treated to 2400cGy.
GTV_2400	GTV to be treated to 2400cGy.
IGTV_2400	IGTV to be treated to 2400cGy.
PTV20	PTV with 2cm expansion
E-PTV_2400	External minus PTV
E-PTV20	External minus PTV_20 (PTV with a 2 cm expansion)

7.1.3. Organs-At-Risk (OAR) Naming/Delineation,

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

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

Standard Name	***Description***
BileDuct_Common	Common Bile duct
Bladder	Bladder
BrachialPlex_L	Left Brachial Plexus
BrachialPlex_R	Right Brachial Plexus
BrachialPlexs	Left plus Right Brachial Plexus
Bronchus	Carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus, right and left lower lobe bronchi
Bronchus_NAdj	Non Adjacent Bronchus

Bowel_Large	Large Bowel
CaudaEquina	Cauda equina
Duodenum	Duodenum
Esophagus	Esophagus
Esophagus_NAdj	Non Adjacent Esophagus
External	Body surface
Femur_L	Left whole Femur
Femur_R	Right whole Femur
Femurs	Combined Left and Right Femurs
GreatVes	Great Vessels of the heart (aorta, vena cava S&I, pulmonary A&V)
GreatVes_NAdj	Non Adjacent Great Vessels
Heart	Heart
Jejunum_Ileum	Both ileum and jejunum
Larynx	Larynx
Liver	Liver
Liver-GTV	Liver minus GTV
Lung_L	Left Lung
Lung_R	Right Lung
Lungs	Left plus Right Lungs
Lungs-GTV	Lungs minus GTV
Kidney_Cortex	Renal cortex for both Kidneys
PenileBulb	Penile Bulb
Rectum	Rectum
Rib	Ribs within 10cm of the PTV
SacralPlex	Sacral Plexus
Skin	Outer 0.5cm of the body surface (rind)
SpinalCord	Spinal cord
Stomach	Stomach
Trachea	Trachea
Trachea_NAdj	Trachea non-adjacent wall
Ureter	Ureter

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Jejunum/Ileum(Small bowel)
As a conglomerate of bowel loops within the abdomen distinguished from stomach, duodenum, and colorectum.

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

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

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

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

Liver
The entire liver minus the GTV targets.

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

Femoral Heads
The ball of the head and socket joint.

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

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

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

7.1.4 Treatment Planning Guidelines

Table 1.4 Summary of General Treatment Planning Guidelines

Number of Beams	Typically 7-13 static radiation beams with equal weighting are generally suitable. It is recommended that at least 10 beams be used when possible. Note that dose should be properly distributed between beams due to skin toxicity considerations. Similarly, arcs should cover an appropriate range (≥ 340^{o}) so as to deliver a safe dose to the skin. Single arc plans may be suitable for simple geometries while additional arcs are preferred for more complex geometries.
Beam Arrangement	Coplanar or non-coplanar (non-coplanar are encouraged), non-overlapping, non-opposing beams or arc therapy (non-coplanar arcs encouraged to improve conformity and OAR sparing in complex geometries). Combination of static and arc beams allowed. Gantry clearance verification prior to treatment is recommended.
Minimum Field Size	As planning dictates although only the smallest field size accurately commissioned (e.g. small field output factors are within 5% of published standards or values) at the institution should be used. Because of concerns with small field dosimetry, field sizes above 2 cm x 2 cm are preferable.
Dose Calculation Algorithm*	Modern algorithms that accurately handle tissue heterogeneity and scatter should be used. IROC maintains an updated list of approved algorithms. Density corrections must be applied. Density overrides of the GTV are not recommended for photon treatment.
Dose Grid Resolution	3 mm x 3 mm dose grid resolution or smaller is required. Use of 2 mm x 2 mm is recommended, especially for targets less than 2 cm in diameter.

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

Table 1.5 Dosimetric Guidelines for SBRT Target Coverage

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

***Note**: If target overlaps with OAR please use planning priorities in section 7.1.6 to determine dose coverage.

Table 1.6 Recommendations for Allowable Dose Spillage

PTV Volume (cc)	**R50%** Ratio of 50% Isodose Volume to the PTV Volume		**D2cm**[%] Maximum Dose at 2 cm from PTV in any direction as % of Prescription Dose	
	Per Protocol	Acceptable Variation	Per Protocol	Acceptable Variation
1.8	<5.9	<7.5	<50.0	<57.0
3.8	<5.5	<6.5	<50.0	<57.0
7.4	<5.1	<6.0	<50.0	<58.0
13.2	<4.7	<5.8	<50.0	<58.0
22.0	<4.5	<5.5	<54.0	<63.0
34.0	<4.3	<5.3	<58.0	<68.0
50.0	<4.0	<5.0	<62.0	<77.0
70.0	<3.5	<4.8	<66.0	<86.0
95.0	<3.3	<4.4	<70.0	<89.0
126.0	<3.1	<4.0	<73.0	<91.0
163.0	<2.9	<3.7	<77.0	<94.0

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

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

7.1.6 Treatment Planning Priorities

In general, attempts should be made to successfully satisfy all of the treatment planning criteria without deviation. In some circumstances, improvements can be made to the dosimetry plan beyond simply meeting the specified goals. In other circumstances, it may not be possible to meet the per protocol or variation acceptable criteria for all metrics. In

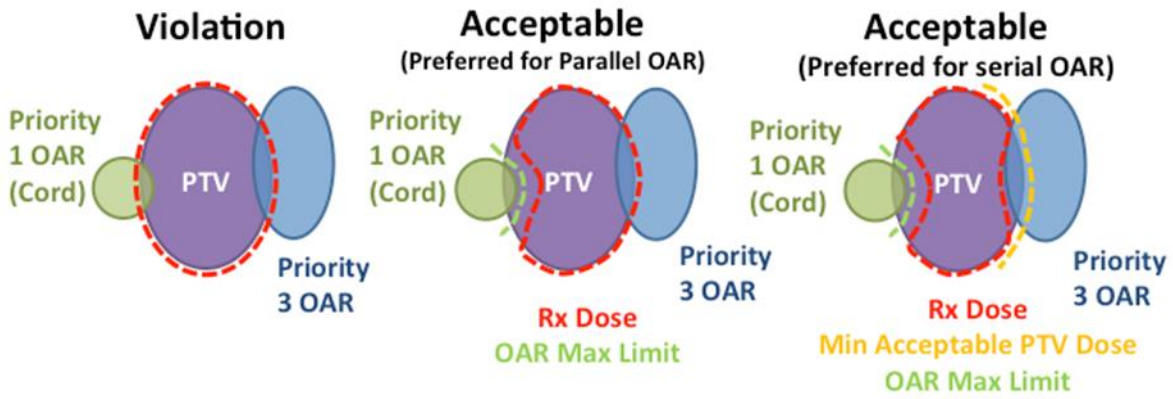
cases where tradeoffs are required, the priorities listed in Table 1.7 should be followed. Figure 1 demonstrates these priorities graphically.

Table 1.7 Treatment Planning Priorities

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

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

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



Section 7.1.7 Dose Constraints

Table 1.8 Dosimetry Compliance for Target

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

Table 1.9 Normal Structure Constraints and Compliance Criteria

Serial Organ	Dosimetric Priority	Volume	Volume Dose (Gy)
Spinal Cord	1	<0.03 cc	22.5

		<1.2 cc	13
Ipsilateral Brachial Plexus	1	< 0.03 cc	26
		<3 cc	22
Cauda Equina	1	<0.03 cc	22.5
		<5 cc	21.9
Sacral Plexus	1	<0.03 cc	24
		<5 cc	22.5
Trachea and Ipsilateral Bronchus (Non-adjacent wall)	3	<0.03 cc	30
		<5cc	25.8
Esophagus (Non-adjacent wall)	1	<0.03 cc	27
		<5cc	17.7
Heart/Pericardium	1	<0.03cc	30
		<15 cc	24
Great vessels (Non-adjacent wall)	3	<0.03cc	45
		<10 cc	39
Skin (non-tumor involved)	1	<0.03cc	33
		<10cc	31
Stomach	1	<0.03cc	30
		<10cc	22.5
Duodenum*	1	<0.03cc	24
		<10cc	15
Jejunum/ileum*	1	<0.03cc	27
		<30cc	17.4

Bowel*	1	<0.03 cc	34.5
		<20cc	24
Rectum*	3	<0.03 cc	49.5
		<3.5 cc	45
		< 20 cc	27.5
Bladder	3	0.03cc	33
		<15 cc	16.8
Ureter	3	<0.03 cc	40
Penile bulb	3	< 3cc	25
Femoral heads	3	<10 cc	24
Bile duct	3	< 0.3 cc	36
Renal hilum/vascular trunk	3	<15 cc	19.5
Rib	3	< 0.03 cc	50
		<5 cc	40
Parallel Organ		**Volume**	**Volume Dose (Gy)**
Lung (total)	3	<15% lung volume	20
		< 37% lung volume	11
		1500 cc	10.5
		1000 cc	11.4
Total Kidney	3	<200cc	15
Liver	3	<700 cc	17.1

***NOTE:** Avoid circumferential irradiation.

NOTE: For all priority-1 OAR, these are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation.

Table 1.10 OAR Compliance Criteria

Structure	Dosimetric Parameter	Per Protocol	Variation Acceptable

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

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

7.1.8 Submission of Digital Radiation Therapy Data

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

http://triadhelp.acr.org/ClinicalTrials/NCISponsoredTrials.aspx

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

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

Treatment Planning System Output

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

Digitally reconstructed radiographs (DRR) for each treatment field, showing the collimator and beam aperture. Submission of DRR's is not required for IMRT/VMT plans.

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

Supportive Data

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

Prescription sheet for entire treatment.

Forms

RT-1 Dosimetry Summary Form

Motion Management Reporting Form

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

IGRT Data -- Volumetric IGRT data in DICOM format from each of the 3 treatment fractions, including the DICOM spatial registration file (REG file) for each fraction if available from your image guidance system.

The RT-2 Radiotherapy Total Dose Record Form

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

Documentation listed above showing any modifications from the original submission.

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

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

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

7.1.9 Compliance Criteria

Definitions of Deviations in Dose to Target Volumes

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

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

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

Definitions of Deviations in Dose to Normal Structures

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

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

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

Definitions of Deviations in Volumes Drawn

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

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

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

8.0 DOSE AND TREATMENT MODIFICATIONS

Adverse events (both non-serious and serious) associated with pembrolizumab (MK-3475) exposure after radiation may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. pembrolizumab (MK-3475) must be withheld for drug-related toxicities and severe or life-threatening AEs as per below. See Section 5.6.1 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

Table 2 Dose Modification Guidelines for Drug-Related Adverse Event

General instructions:
1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. 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. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after 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 - 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 - 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • 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
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

				substituted via IV infusion
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 - 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 - 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
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)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3, 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or	• Monitor for signs and symptoms of thyroid disorders

			liothyronine) per standard of care	
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 – 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	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		

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

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 - 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 - 10.0 x ULN if baseline normal; >3.0 - 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: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

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). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Principal Investigator. The reason for interruption should be documented in the patient's study record.

8.1 Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous 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 (MK-3475) and/or Bifidobacterium dietary supplement.

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.

8.1.1 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.

8.1.2 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.

8.1.3 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.

8.1.4 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.

8.1.5 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.
- 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.

8.1.6 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.

8.1.7 Renal Failure or Nephritis:

- 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.

8.1.8 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.

Table 3 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 3 Infusion Reaction Treatment Guidelines

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	**Stop Infusion and monitor symptoms.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	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 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.**	of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
<u>Grades 3 or 4</u> 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.	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	Subject is permanently discontinued from further trial treatment administration.	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

8.1.9 Management of Stevens-Johnson syndrome and Toxic Epidermal Necrolysis:

To date, approximately 11,000 patients in clinical trials and 27,000 patients in the post-marketing setting have been treated with pembrolizumab (MK-3475). One fatal case of SJS in a clinical trial and one fatal case of TEN in the post-marketing setting have been reported in patients treated with pembrolizumab (MK-3475). Including these cases, there have been 8 cases of SJS (6 in clinical trials, and 2 post-marketing) and 2 cases of TEN (both post-marketing) all of which were serious.

- For signs or symptoms of SJS or TEN, withhold pembrolizumab (MK-3475) and refer the patient for specialized care for assessment and treatment.
- If SJS or TEN is confirmed, permanently discontinue pembrolizumab (MK-3475).

8.1.10 Management of Immune-mediated myocarditis:

A total of 6 cases of myocarditis have been reported in patients treated with pembrolizumab (MK-3475) in clinical trials or in an expanded access program. There was 1 fatal case reported in a clinical trial.

- For suspected immune-mediated myocarditis, ensure adequate evaluation to exclude other etiologies, and administer corticosteroids as appropriate.

8.2 Dose Modifications

The dose of pembrolizumab (MK-3475) is not modified. Doses may be delayed or held as above.

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.

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. For this trial, the form "Adverse Events" is used for routine AE reporting in Rave.

This trial will be utilizing the Rave-CTEP-AERS integration. All routine, post-baseline adverse events reported in Rave will be evaluated for expedited reporting using protocol-specific rules. If an expedited report is recommended, a deep-link within Rave can be used to automatically launch and log-in to CTEP-AERS to complete the expedited report. Adverse event data in Rave that is required for expedited reporting will be pushed to CTEP-AERS.

Note: Modifications to AE data must begin in Rave since it is the data source. Any adverse event data modified in Rave must be re-submitted for rule evaluation and will then be pushed to CTEP-AERS.

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 by CTCAE.

CTCAE v5.0 Term	**CTCAE v5.0 System Organ Class (SOC)**
Hyperthyroidism	Endocrine disorders
Hypothyroidism	Endocrine disorders
Headache	Nervous system disorders
Blurred Vision	Eye disorders
Agitation	Psychiatric disorders
Libido decreased	Psychiatric disorders
Personality change	Psychiatric disorders
Diarrhea	Gastrointestinal disorders
Colitis	Gastrointestinal disorders
Abdominal Pain	Gastrointestinal disorders
Pruritus	Skin and subcutaneous tissue disorders
Rash maculo-papular	Skin and subcutaneous tissue disorders
Bullous dermatitis	Skin and subcutaneous tissue disorders
Mucositis oral	Gastrointestinal disorders
Bruising	Injury, poisoning and procedural complications
Generalized muscle weakness	Musculoskeletal and connective tissue disorders
Peripheral sensory neuropathy	Nervous system disorders
Dyspnea	Respiratory, thoracic and mediastinal disorders

9.2 CTCAE Routine Reporting Requirements

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

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

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

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

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

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Alliance Central Protocol Operations Program, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. 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 appropriate treatment areas should have access to a copy of the CTCAE. All reactions must first be reported in Rave on the "Adverse Events" Form and sent for rule evaluation at the time the event is known. Adverse event data should not be entered in CTEP-AERS prior to entry in Rave for rules evaluation. Additional information about Rave-CTEP-AERS is available on the CTSU website (https://www.ctsu.org) under the "Resources" tab.

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

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/Intervention1, 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="2">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 a CTEP IND.

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

9.3.3 Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- Alliance A091605 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.
- 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.
- 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. In CTCAE version 5.0, the events may be reported as either: (1) Leukemia secondary to oncology chemotherapy, (2) Myelodysplastic syndrome, or (3) Treatment-related secondary malignancy. 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.

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

Second Malignancy:

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.
- Treatment expected adverse events include those listed in Section 10.0 and in the package insert.
- CTEP-AERS reports should be submitted electronically.
- 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.

9.4 CAEPRs

9.4.1 CAEPR for MK-3475

Comprehensive Adverse Events and Potential Risks list (CAEPR) **for MK-3475 (pembrolizumab, 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 3793 patients. Below is the CAEPR for MK-3475 (pembrolizumab).

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

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
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 (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]		***Diarrhea[2] (Gr 2)***
	Mucositis oral[2]		
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[2]		
	Small intestinal mucositis[2]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills[2]		
Fatigue			***Fatigue (Gr 2)***
	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]	

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Immune system disorders - Other (pseudoprogression/tumor inflammation)[2]		
	Immune system disorders - Other (sarcoidosis)[2]		
		Serum sickness[2]	
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased		
	CPK 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]		***Arthralgia[2] (Gr 2)***
	Arthritis[2]		
	Avascular necrosis[2]		
	Back pain		
	Joint effusion[2]		
	Joint range of motion decreased		
	Musculoskeletal and connective tissue disorder - Other (tenosynovitis)[2]		
	Myalgia[2]		
	Myositis[2]		
NERVOUS SYSTEM DISORDERS			
		Guillain-Barre syndrome[2]	
		Nervous system disorders - Other (myasthenic syndrome)[2]	
		Nervous system disorders - Other (neuromyopathy)[2]	

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		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 (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		
	Pleuritic pain[2]		
	Pneumonitis[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Bullous dermatitis[2]		
		Erythema multiforme[2]	
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus[2]		***Pruritus[2] (Gr 2)***
	Rash acneiform[2]		
	Rash maculo-papular[2]		***Rash maculo-papular[2] (Gr 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]	

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

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

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

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

Adverse events reported on MK-3475 (pembrolizumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MK-3475 (pembrolizumab) 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 - 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; 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; 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: MK-3475 (pembrolizumab) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.0 DRUG INFORMATION

10.1 General Considerations:

The total administered dose of pembrolizumab (MK-3475) is 200mg in all infusions.

Pembrolizumab (MK-3475) may be administered at a non-registering institution.

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

10.2 Pembrolizumab (MK-3475) (NSC 776864, IND Holder: CTEP)

Investigator Brochure Availability

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

Procurement and Availability

Pembrolizumab (MK-3475) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. Pembrolizumab (MK-3475) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI.

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

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

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Supply

Pembrolizumab (MK-3475) is supplied by Merck & Co., Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. 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

Pembrolizumab (MK-3475) solution for infusion must be diluted prior to administration. Allow the required number of vials to equilibrate to room temperature. 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 pembrolizumab (MK-3475) to an infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Gently invert the bag 10-15 times to mix the solution. 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.

If a storage temperature excursion is identified, promptly return pembrolizumab (MK-3475) to between 2-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability

Refer to the package label for expiration.

Administer prepared solutions immediately after preparation. If not administered immediately, prepared solutions may be stored refrigerated for up to 24 hours. Pembrolizumab (MK-3475) solutions may be stored at room temperature for a cumulative time of up to 6 hours. This includes room temperature storage of liquid drug product solution in vials, room temperature storage of infusion solution in the IV bag, and the duration of infusion.

Route/Method of Administration

IV infusion only. Do not administer as an IV push or bolus injection.

Infuse over approximately 30 minutes (range: 25 - 40 minutes) using an infusion set containing a low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone or polysulfone. Infusion rate should not exceed 6.7 mL/min. 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.

Compatible infusion set materials: PVC plasticized with DEHP or DEHT, PVC and tri-(2-ethylhexyl) trimellitate, polyethylene lined PVC, polyurethane, or polybutadiene

Drug Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page.

Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Useful Links and Contacts

CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/

NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov

PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm

PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP/

CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/index.jsp

CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov

PMB email: PMBAfterHours@mail.nih.gov

IB Coordinator email: IBCoordinator@mail.nih.gov

PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

Adverse Events

See CAEPR in Section 9.4.1

Nursing Guidelines

- Pembrolizumab (MK-3475) side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids.
- Diarrhea can be 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.
- Rash/pruirits/dermatitis is seen. Patients should report any rash to the study team. Treat per section 9.0 and monitor for effectiveness.
- Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.
- Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.
- Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysistis, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and "not feeling well" . Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.
- Patients who are started on steroid therapy for any side effects of pembrolizimab 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.
- 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.
- Patients should avoid receiving live vaccines within 30 days of study drug administration or per other study guidelines.
- 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 pembrolizumab (MK-3475)
- Myocarditis has been reported and associated with pembrolizumab (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

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1). [23]

Changes in the largest diameter (unidimensional measurement) of the tumors and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations

For the purposes of this study, patients should be reevaluated every 9 weeks.

11.2 Definitions of Measurable and Non-Measurable Disease

11.2.1 Measurable Disease

- A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥ 2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.
- A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- A malignant lymph node is considered measurable if its short axis is >1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).
- Tumor lesions in a previously irradiated area are considered measurable disease under the following conditions:

- If there is a soft tissue component that has grown since completion of radiation.
- Bone metastases with a soft tissue component are considered measureable.

11.2.2 Non-Measurable Disease

- All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥ 1.0 to < 1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.
- Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis < 1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.3.1 Measurement Methods

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up.

For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.

- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.3.2 Acceptable Modalities for Measurable Disease

- 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.
    - 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. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- PET-CT: 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.
- 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 scans are preferable.
- Physical Examination: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A ‘positive’ FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered ‘negative.’ New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
    - Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
    - No FDG-PET at baseline and a positive FDG-PET at follow-up:
        - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
        - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at

that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.

- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance has been described in the protocol and supported by disease-specific medical literature for the indication

However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

11.3.3 Measurement at Follow-up Evaluation:

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.

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

11.4 Measurement of Treatment/Intervention Effect

11.4.1 Target Lesions & Target Lymph Nodes

- The protocol defined irradiated tumor will not be considered for response in the primary endpoint.
- The protocol defined irradiated tumor will be considered for secondary endpoint response.
- Measurable lesions (as defined in Section 11.2.1) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in Section 11.2.1), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.
- Note: If fewer than 5 (for phase III trials replace with "3") target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.
- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.
-

11.4.2 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.2.2) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.4.3.3.

11.4.3 Response Criteria

All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

- Evaluation of Target Lesions
    - Complete Response (CR): All of the following must be true:
        - Disappearance of all target lesions.
        - Each target lymph node must have reduction in short axis to < 1.0 cm.
    - Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (see Section 11.4.1).
    - Progression (PD): At least one of the following must be true:
        - At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
        - At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.4.1). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

        - See Section 11.3.2 for details in regards to the requirements for PD via FDG-PET imaging.
    - Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.
- Evaluation of Non-Target Lesions & Non-target Lymph Nodes
    - Complete Response (CR): All of the following must be true:
        - Disappearance of all non-target lesions.
        - Each non-target lymph node must have a reduction in short axis to <1.0 cm.
    - Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.
    - Progression (PD): At least one of the following must be true:
        - At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
        - Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)
        - See Section 11.3.2 for details in regards to the requirements for PD via FDG-PET imaging.
- Evaluation of Elevated Hormone Levels (when present)
    - This evaluation will be done for each patient for descriptive purposes only and will not be used to evaluate the primary endpoint of objective response. Biochemical progression without the demonstration of objective progression of target or nontarget lesion will not be sufficient indication to remove the patient from the study (refer to Section 13.1).
    - Biochemical response (B-RESP): Reduction in elevated hormone level by at least 50% of normalization of an elevated value, confirmed with 2 successive measures.
    - Biochemical progression (B-PROG): Increase in elevated hormone level by 50%, confirmed with 2 successive measures. If patient has had biochemical response as defined above, then subsequent biochemical progression is defined as >50% increase from the lowest recorded level while on study.
    - Biochemical stability (B-STAB): Elevated hormone level does not change enough to qualify as response or progression.

11.4.4 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

* See Section 11.4.3.1

11.4.5 Symptomatic Deterioration

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration.

11.5 Immune-Related Response Assessment (iRECIST)

All study endpoints requiring measurement data will be assessed per RECIST criteria (defined above). Patients will not be required to end study participation at the first evidence of progression since Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size of malignant lesions, or undetectable lesions becoming detectable. For this reason, iRECIST [24] will be utilized in order to help to make the decision to remove a patient from the study after first evidence of progression. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression. Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix.

11.5.1 Confirming Progression

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but not longer than 9 weeks after iUPD.

For patients that had an iUPD in the previous assessment, iCPD is confirmed in two ways:

1) Existing iUPD gets worse in any lesion type (target, non-target, or new lesions) which contributed to the current iUPD status (a patient can have more than one of the following sources of iUPD).

If iUPD was at least partially based on…	Then iCPD is confirmed if…
Target lesions	A cumulative increase (can occur over multiple assessments) of at least 5 mm in the absolute value of the sum from the first occurrence of the current iUPD
Non-target lesions	Any increase in the non-target lesion burden from the first occurrence of the current iUPD
New lesions	A cumulative increase (can occur over multiple assessments) of at least 5 mm in the absolute value of the sum of those considered to be target new lesions or any new lesions (from the first occurrence of the current iUPD)

2) RECIST 1.1 criteria are met in lesion types (target, non-target, or new lesions) which did not contribute to current iUPD status, including the appearance of new lesions.

If a patient meets either (or both) of these criteria, they are considered to have confirmed progression (iCPD). See Appendix III for examples of confirming progression.

11.5.2 New Lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria, and recorded as New Lesion-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of NLT should NOT be included in the sum of measures of original target lesions identified at baseline.

Progression is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 9 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR and increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of new lesions.

The following table summarizes how to use iRECIST in a number of different scenarios.

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	Prior iUPD**; ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR

iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on: - further increase in SOM of at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: - previously identified T lesion iUPD SOM ≥5 mm and / or - NT lesion iUPD (prior assessment - need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: - previously identified T lesion iUPD ≥5 mm and / or - previously identified NT lesion iUPD (need not be unequivocal) and /or - size or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on - increase in size or number of new lesions previously identified

* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same.
** In any lesion category.
*** Previously identified in assessment immediately prior to this TP.

11.6 Definitions of Analysis Variables

Formal definitions of variables used in analyses can be found in the Statistical Considerations section of the protocol.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Treatment

12.1.1 CR, PR, or SD

Patients who are in CR, PR or SD will continue on therapy for a total of two years of treatment. After treatment is discontinued, patients will be followed per the study calendar in section 5.0.

12.1.2 Disease Progression

Remove from protocol therapy any patient with confirmed disease progression. Document details, including tumor measurements, on data forms. Patients who are clinically well may

continue on therapy following RECIST progression with new lesions or increase in target lesions if the increase in disease burden does not meet the definition of iCPD by immune response criteria [24] outlined in section 11.5.

After removal for disease progression, patients should be followed for survival per the study calendar (Section 5.0).

12.1.3 Discontinuation of Study Agent

If the patient discontinues pembrolizumab (MK-3475), patients should be followed for survival per the study calendar (Section 5.0).

12.2 Follow-up for patients who stop protocol therapy

12.2.1 Withdrawal of consent

Patients who withdraw consent should not be followed anymore and should not be contacted for any study related inquiries.

12.2.2 Stopping study treatment due to toxicity

If the patient discontinues study treatment due to toxicity they will be followed for survival per the study calendar (Section 5.0).

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

Definition of ineligible patient

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

Follow-up for ineligible patients who continue with protocol treatment

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

Follow-up for ineligible patients who discontinue protocol treatment

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

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

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

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

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.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design

The study population in this randomized phase II trial are patients with advanced Merkel cell carcinoma. The trial is designed to compare Progression Free Survival (PFS) in patients that receive SBRT + pembrolizumab (MK-3475) compared to pembrolizumab (MK-3475) alone in non-radiated lesion(s). This trial implements a group sequential design with one interim analysis for futility. East v6 was utilized to create the statistical design described below.

13.2 Statistical Design and Analysis for the Primary Endpoint

13.2.1 Primary Endpoint:

We are comparing the Progression Free Survival (PFS) in non-radiated lesion(s) of patients receiving either (a) SBRT + pembrolizumab (MK-3475) compared to (b) pembrolizumab (MK-3475) alone in patients with advanced Merkel cell carcinoma. For each patient, during screening, one lesion will be identified as the one to be potentially radiated (if randomized to the arm with SBRT). Then up to 5 additional lesions will be identified that are followed for PFS. For patients in both arms, the lesion identified to be radiated (pre-randomization) will be followed separately (i.e. it will not be a target lesion). If this lesion changes in a way that leads to a change in the patient's treatment (e.g. adding a non-protocol treatment or removal of the patient from the study), then the patient's PFS data would be considered censored at the time of the change in their treatment.

A patient is considered an event for this endpoint at the time of first evidence of disease progression or death (without evidence of progression) and their PFS time is defined as the time from randomization to either disease progression or death (without progression). For patients that are not considered an event for this endpoint, the PFS time will be censored at their last evaluation for progression. All randomized patients meeting the eligibility criteria who received any quantity of their randomized care and did not have a major treatment violation will be part of the analysis group for the primary endpoint.

13.2.2 Statistical Design:

Based on the patient population in this study it is believed that the median PFS time in patients with pembrolizumab (MK-3475) along will be approximately 9 months.[25] We seek to detect a 50% improvement on this (to 13.5 months) utilizing a design that has an attained type I error rate of 0.20. With 96 evaluable patients (48 randomized to each arm), a one-sided alpha=0.20 log rank test will have 80% power to detect a 33% decrease in the hazard of progression with SBRT + pembrolizumab (MK-3475) compared to pembrolizumab (MK-3475) alone, which corresponds to a 50% increase in the median PFS time. If after 75 events have been observed, the hazard ratio is greater than 0.837, the study will be declared unpromising.

Interim Analysis Decision Rules: The chosen design has one interim look for futility that will occur after the 38th event is observed. If, at this time, the hazard ratio is greater than 1.013 accrual will be suspended due to futility and the study will be declared unpromising.

13.2.3 Analysis Plan:

The main analysis with regards to the primary endpoint is described above, in section 13.2.2. In addition to this Kaplan- Meier curves will be constructed and median PFS times will be calculated for each arm.

13.3 Sample Size, Accrual time, and Study Duration

13.3.1 Sample Size

The chosen design requires 75 events (progressions plus deaths without progressions) and will accrue 96 evaluable patients (48 to each arm) to attain these events. In order to account for patients that: (a) do not have any non-radiated lesions, (b) are deemed ineligible, (c) cancel study participation prior to receiving any randomized treatment, or (d) have a major protocol violation, we will plan to accrue an additional 4 patients making the maximum overall accrual N=100 patients.

13.3.2 Accrual Rate and Study Duration:

The disease sites applicable to this study have not yet been studied extensively within the Alliance. As such an accrual rate of 3 evaluable patients per month was estimated based on experience in the clinic. The study team believes that this rate will be on the low end of what is possible.

At this rate, the accrual phase of the trial will require ~32 months. Under the alternative hypothesis (i.e. that there is a PFS benefit for SBRT + pembrolizumab (MK-3475) compared to pembrolizumab (MK-3475) alone) the 75th event will occur at ~41 months. To account for data entry and cleaning, this means the primary endpoint analysis can occur approximately 45 months after the beginning of the trial, depending on the actual rate of observed events.

13.3.3 Primary Endpoint Completion Date for ClinicalTrials.gov Reporting:

For purpose of ClinicalTrail.gov reporting, the Primary Endpoint Completion Date (PECD) for this study is the time that the 75th event is observed on an evaluable patient. This will be approximately 45 months after the study has begun enrollment under the alternative hypothesis.

13.4 Supplementary Analysis Plans

13.4.1 Secondary Endpoints

Progression Free Survival among all RECIST lesions: This endpoint is the same as the primary endpoint, but includes both irradiated and non-radiated lesions. It is a time to event endpoint and will be evaluated using the Kaplan- Meier method. PFS time is defined as the number of days from randomization to either evidence of disease progression or death (without evidence of progression). Median PFS times will be calculated for each arm and a cox proportional hazards model will be constructed to determine if there is a PFS benefit for patients receiving SBRT + pembrolizumab (MK-3475) compared to pembrolizumab (MK-3475) alone.

Overall Response Rate (OS): A patient will be declared to have responded to therapy if they have at least a PR on 2 consecutive evaluations (i.e. the response is confirmed). Response rates will be calculated and compared across treatment arms utilizing a chi-square test.

Progression Free Survival at 6 months (PFS6): A patient will be declared a success for this endpoint if they remain on study and progression free at 6 months. The rates of success will be calculated and compared across treatment arms utilizing a chi-square test.

Safety/Toxicity: Maximum grade adverse events will be summarized by treatment arm in a tabular setting. This will be done overall and for the 3 month time period from date of registration.

Local control of SBRT treated lesion: The protocol irradiated tumors are considered to be controlled if they have no evidence of progression. No evidence of progression is defined as CR, PR, or SD. If the protocol irradiated tumor progresses the date of progression will be recorded. Local control of the protocol-irradiated tumor will be described using the Kaplan-Meier technique.

Delivered radiation dose using cone-beam CT images: These radiation doses will be summarized descriptively and compared to the planned dose.

13.4.2 Correlative Endpoints

Test utility of CT-based radiomics: To test the utility of CT-based radiomics algorithms to predict radiation-induced and drug induced pneumonitis. Patient imaging will be analyzed based on known radiomic signatures and correlated to incidence of pneumonitis reported as adverse events. The incidence of pneumonitis in total as well as by radiomic signatures will be descriptively summarized.

13.5 Adverse Event Stopping Rule:

The Alliance Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the study statistician. Additionally, in order to ascertain if the study treatments are safe for patients, the following adverse event stopping rules will be employed. The following rules will be applied to each arm separately. If any rule is crossed then accrual will be suspended while the study team evaluates the data, develops a plan, and receives approval for re-opening from the DSMB.

- If at any point during the first 10 patients at least 3 patients experience at least 1 grade 4+ non-hematologic adverse event that is deemed at least possibly related to study treatment, or…
- If at any point after the first 10 patients at least 30% of all patients experience at least 1 grade 4+ non-hematologic adverse event that is deemed at least possibly related to study treatment.

13.6 Study Reporting

13.6.1 Alliance DSMB

This study will be monitored by the Alliance Data Safety Monitoring Board (DSMB), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every six months as per NCI guidelines.

13.6.2 Clinical data Update System (CDUS)

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July

31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site

(http://ctep.cancer.gov/reporting/cdus.html).

Note: If your study has been assigned to CDUS-Complete reporting, all adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS, but expedited adverse events are still required to be submitted via CTEP-AERS.

13.6.3 Result Reporting on ClinicalTrials.Gov

At study activation, this study will have been registered within the "ClincialTrails.gov" web site. The Primary and Secondary Endpoints (i.e., "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov.

13.7 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin. There is no information currently available regarding differential effects of study treatment in subsets defined by race, gender, or ethnicity. Although there is insufficient power to detect small or moderate effects, we will, as always, report the results by gender and ethnicity in exploratory analyses.

There is no reason to believe that there will be a gender difference in this disease and the study team expects there to be approximately 5% racial minorities.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	1	0	0	1
Black or African American	1	1	1	1	4
White	48	47	0	0	95
More Than One Race	0	0	0	0	0
Total	49	49	1	1	100

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

14.0 CORRELATIVE AND COMPANION STUDIES

There is specimen biobanking for this study for future use and all patients are encouraged to participate.

14.1 Biobanking for future Correlative Science

Blood, tissue, and stool specimens will be collected and stored for future translational research for patients who consent to participate. Testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies. Future studies may include the following aims:

Hypotheses/aims for correlative studies*:*

1. Gene expression profiling based on T cell based immune signatures may better predict response or lack of response to monotherapy anti-PD1 and may suggest expression phenotypes where the addition of radiation can facilitate response.*
    a) Gene expression profiling assays have a robust capacity to capture the tumor-immune microenvironment with prior analysis from metastatic melanoma clearly correlating with treatment outcomes to immunotherapy[26-28]. Further in prior studies of pembrolizumab (MK-3475) in head and neck, gastric, urothelial cancers and melanoma, large datasets have supported gene expression as harboring a greater ability to stratify treatment response relative to PD-L1 immunohistochemistry[29-32]. Further, IHC for PD-L1 as well as Merkel-cell polyomavirus did not show statistically significant associations with treatment outcomes in the NEJM report of pembrolizumab (MK-3475), though sample sizes were small[10].

2. The intensity and/or location of staining for CD8 and PD-L1 by immunohistochemistry may differentiate responding vs. non-responding patients to monotherapy anti-PD1 or radiation with immunotherapy.*

    a) Though statistically significant associations have not been observed for PD-L1 and CD8 in MCC to date, the sample sizes investigated were small and such associations have been observed in other tumors[33].

3. Tumor intrinsic mutations or mutational load may predict resistance or response to anti-PD-1 and/or the combination of radiation and immunotherapy.*

    a) Multiple papers have demonstrated associations between mutational load and treatment outcome to anti-PD1 immunotherapy. Further, a hypothesis in the field of MCC has been that non- Merkel-cell polyomavirus associated tumors may have a high response rate due to the presence of increase mutational load (and by extrapolation neoantigen burden).

    b) Recent reports have suggested that de novo or acquired resistance to immunotherapy can be mediated via mutation in JAK/STAT signaling or the antigen processing machinery[34]. Exploratory DNA based genomic analysis will thus be particularly of interest in any patients who have no clinical benefit to this approach of radiation with PD1 Ab.

4. Single nucleotide polymorphisms from the germline DNA may be identified that portend an improved response phenotype to immunotherapy.

    a) The identification of SNPs in immune regulatory genes is an area of increasing interest in the field of immunotherapy. At the University of Chicago, we have identified multiple such targets (data unpublished) and several commercial entities are also moving forward in this space (personal communication Foundation Medicine and Nanostring technologies).

5. The composition of the fecal microbiota may predict the likelihood or response or toxicity to anti-PD1 or radiation with immunotherapy.

    a) We and other groups have previously identified an important role for the gut microbiome in modulating both immunotherapy treatment response outcome as well as toxicity[35-37].

6. Changes in MCPyV specific T lymphocytes and other circulating factors such as MCPyV small T-antigen oncoprotein antibody titers will associated with outcomes to immunotherapy*.

Changes in circulating immune cell populations have been associated with treatment outcome with both CTLA4 and PD1/L1 blocking immunotherapy[38, 39].

* Available tumor tissue will be prioritized for 1 (gene expression) > 2 (IHC) > 3 (exome sequencing)

*Tumor Merkel Cell Polyomavirus (MCPyV) Status

Serology: Baseline serum samples from all patients will be used to measure MCPyV small T-antigen oncoprotein antibody titers at Laboratory Medicine (University of Washington, Seattle, WA) as described[40]. Titers above 74 will be considered positive.

Oncoprotein-specific T cells: All patients will be HLA genotyped to determine eligibility for CD8 T cell specific MCPyV peptide-MHC tetramer screening (Bloodworks Northwest, Seattle, WA). Pretreatment peripheral blood mononuclear cells (PBMCs) will be collected from patients

with HLA-I types that corresponded to available MCPyV-specific tetramers will be tetramer stained to identify MCPyVspecific T cells, and analyzed by flow cytometry. Samples with >0.01% of CD8+ T cells co-staining with tetramers will be considered positive. In addition, PBMCs from patients with available pretreatment and week 12 post-treatment blood collections will be stimulated with pools of MCPyV-specific peptides in a flow cytometry-based intracellular cytokine secretion assay (HIV Vaccine Trials Network, Seattle, WA). PBMCs that secrete interferon-γ and/or IL-2 robustly (≥0.1% of CD8 T cells after background subtraction) will be considered reactive to MCPyV.

15.0 GENERAL REGULATORY CONSIDERATIONS AND CREDENTIALING

15.1 Institutional Credentialing

15.1.1 IROC Ohio Institutional Requirements

15.1.2 Radiation Therapy Requirements

RT Credentialing Requirements	Web Link for Procedures and Instructions: http//irochouston.mdanderson.org			
	Treatment Modality			Key Information
	SBRT	IMRT	3D	
Facility Questionnaire	☐☐	☐☐	☐	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ go to http://irochouston.mdanderson org/questionnaires.
Credentialing Status Inquiry Form	☐☐	☐☐	☐	To determine whether your institution needs to complete any further credentialing requirements, please complete the "Credentialing Status Inquiry Form" found under credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org)
Phantom Irradiation	☐☐	☐☐	☐	Either the lung or liver phantom available from IROC Houston must be successfully irradiated (if the institution has not previously met this credentialing requirement). Credentialing for IMRT allows the institution to also use 3D-CRT SBRT, but credentialing for 3D-CRT SBRT does not allow the institution to use IMRT. Flattening-filter-free (FFF) photon beam delivery, Tomotherapy and Cyberknife treatment delivery modalities must be credentialed individually. Instructions for requesting and irradiating the phantoms are available on the IROC Houston website under credentialing (http//irochouston.mdanderson.org). The phantom must be irradiated with the motion management technique (e.g., tracking, gating) to be used for SBRT protocol treatments.
IGRT Verification Study	☐☐	☐☐	☐	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.
Pre-Treatment Review	☐☐	☐☐	☐	Pre-treatment review of each case will be performed by IROC-Rhode Island
Credentialing Notification				IROC Houston QA Center will notify the a) institution and b) IROC Rhode Island once credentialing requirements have been met.

15.2 Individual Credentialing

15.2.1 Radiological credentialing

Contact IROC for appropriate language.

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APPENDIX I REGISTRATION FATIGUE/UNISCALE ASSESSMENTS

Registration Fatigue/Uniscale Assessments

At patient registration, this form is to be administered by a nurse/CRA, 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 CRADA

Collaborative Agreements Language:

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

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

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

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

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

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

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

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

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

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

Email: ncicteppubs@mail.nih.gov

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

APPENDIX III EXAMPLES OF CONFIRMED PROGRESSION

The following examples show how a patient that is currently an iUPD can become an iCPD (confirmed progression). These examples all use target lesion growth as the source of the first progression (iUPD) and show how additional information in future assessments can lead to iCPD. The examples are not exhaustive, but are meant to be illustrative of how iCPD can occur. Similar examples can be created where non-target lesions and/or new lesions led to the initial iUPD.

1) iUPD due to target lesion growth from baseline followed by iCPD due to continued growth of target lesions (by at least 5 mm).

	Baseline	TP1	TP2
T lesions (sum)	100	125	132
NT lesions	Pres	No change	No change
New lesions		None	None
TP response (R)		PD	PD
TP response (iR)		iUPD	iCPD

2) iUPD due to target lesion growth from baseline followed by iCPD due to gradual continued growth (over 2 assessments) of target lesions (by at least 5 mm from time of first iUPD).

	Baseline	TP1	TP2	TP3
T lesions (sum)	100	125	128	132
NT lesions	Pres	No change	No change	No change
New lesions		None	None	None
TP response (R)		PD	PD	PD
TP response (iR)		iUPD	iUPD	iCPD

3) iUPD due to target lesion growth from baseline followed by iCPD due to new lesion appearing after start of iUPD. This iCPD is based on criteria #2 outlined in section 11.5.1.

	Baseline	TP1	TP2
T lesions (sum)	100	125	125
NT lesions	Pres	No change	No change
New lesions		None	1 new lesion
TP response (R)		PD	PD
TP response (iR)		iUPD	iCPD

4) iUPD due to target lesion growth from baseline followed by iCPD due to additional target lesion growth as well as a new lesion.

	Baseline	TP1	TP2
T lesions (sum)	100	125	132
NT lesions	Pres	No change	No change
New lesions		None	1 new lesion
TP response (R)		PD	PD