DATE: 07/10/2020

TITLE:

Phase I Trial of MK-3475 and Concurrent Chemo/Radiation for the Elimination of Small Cell Lung Cancer

NCT NUMBER: 02402920

SPONSOR: MDACC

TITLE:

Phase I Trial of MK-3475 and Concurrent Chemo/Radiation for the Elimination of Small Cell Lung Cancer

IND NUMBER:

EudraCT NUMBER:

Table of Contents

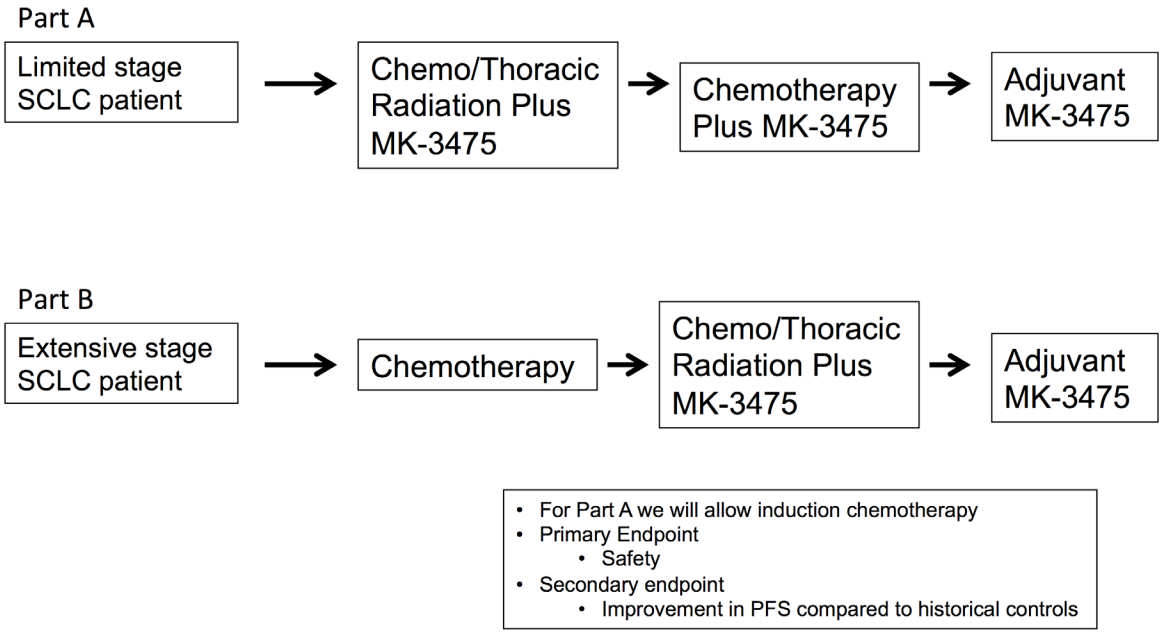
1.0 TRIAL SUMMARY

Abbreviated Title	**Phase I Trial of MK-3475 and Concurrent Chemo/Radiation for the Elimination of Small cell lung cancer**
Trial Phase	I
Clinical Indication	SCLC
Trial Type	Investigator initiated
Type of control	None
Route of administration	IV
Trial Blinding	NO
Treatment Groups	
Number of trial subjects	
Estimated duration of trial	
Duration of Participation	

2.0 TRIAL DESIGN

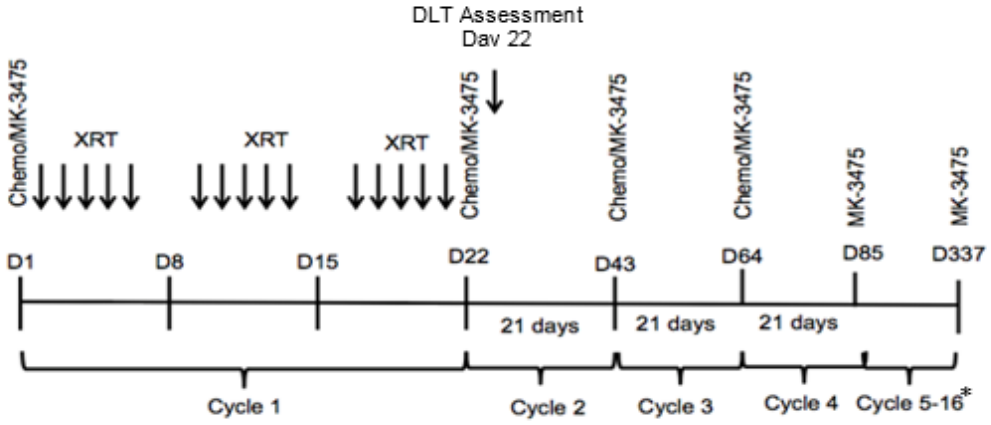
2.1 Trial Design: 3x3 dose escalation

2.2 Trial Diagram


Part A
Limited stage SCLC patient
Chemo/Thoracic Radiation Plus MK-3475
Chemotherapy Plus MK-3475
Adjuvant MK-3475
Part B
Extensive stage SCLC patient
Chemotherapy
Chemo/Thoracic Radiation Plus MK-3475
Adjuvant MK-3475
• For Part A we will allow induction chemotherapy
• Primary Endpoint
• Safety
• Secondary endpoint
• Improvement in PFS compared to historical controls

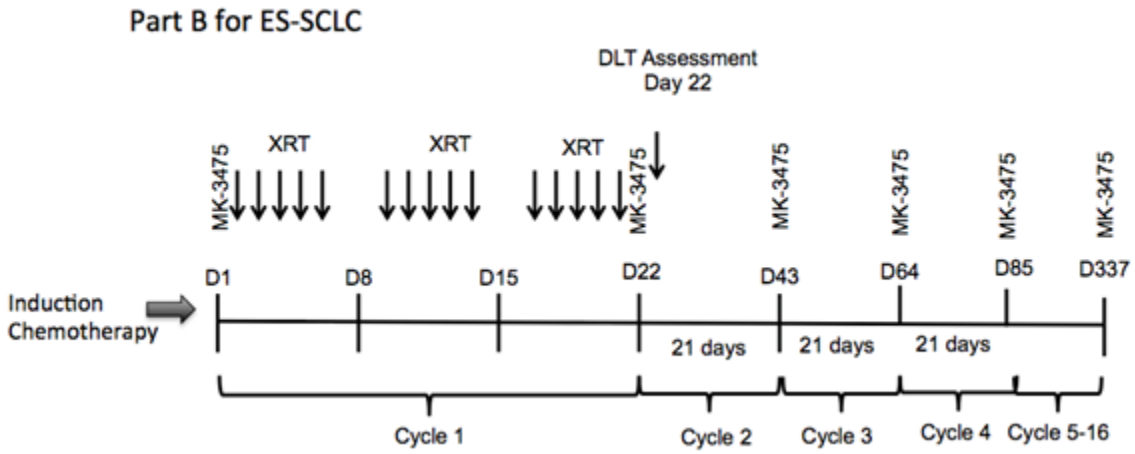
Part A: Is only for patients with Limited Stage SCLC, we will allow induction chemotherapy. The total cycles of chemotherapy recommended will be 4, as such if a patient had two cycles of induction chemotherapy they would only get an additional two with MK-3475. PCI will be allowed based on the treating physician discretion and will be done after chemotherapy has been completed. PCI will delay the next dose of MK-3475 by one cycle and PCI should start approximately three weeks after MK-3475. MK-3475 can be resumed following the completion of PCI. LS-SCLC patients, who achieve systemic disease control during/after completion of 16 cycles of MK-3475, will be eligible to get additional 16 cycles of MK-3475, provided they did not exhibit severe (grade >3) MK-3475 related toxicity during therapy. Systemic disease control is defined as stable disease or partial response or complete response, based on irRC criteria.

Part A for LS-SCLC



* Eligible patients may receive additional 16 cycles.

Part B: Is only for patients with Extensive Stage SCLC who are receiving consolidation XRT after 1-6 cycles of chemotherapy. Patients needing PCI are encouraged to have it completed prior to enrollment in this trial. If PCI needs to be given on study, after thoracic XRT, then it should be done in a manner consistent with part A. PCI will delay the next dose of MK-3475 by one cycle and PCI should start approximately three weeks after MK-3475. MK-3475 can be resumed following the completion of PCI.) Patients needing XRT treatment to other sites outside the thorax will be allowed, but is encouraged to be done prior to starting the trial.



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** Safety of MK 3475 plus chemo/radiation for LS-SCLC and safety of MK 3475 plus radiation for ES-SCLC

Hypothesis: MK-3475 with chemoradiation for LS-SCLC and with radiation for ES-SCLC will demonstrate an acceptable toxicity profile comparable to previous trials

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: MK-3475 will improve PFS compared to historical controls for LS-SCLC and ES-SCLC.

Hypothesis: The addition of MK3475 will provide T cell activation that will help improve both local and distant disease progression in SCLC.

3.3 Exploratory Objective

(1) **Objective:**

MK-3475 will increase T cells and CD8 positive cells in non-irradiated tumors, compare before and after MK-3475.

Radiation will turn the tumor into a vaccine produce new antigens and stimulate T cells which can then circulate and increase T cell responses in the non-irradiated tumors

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [2; 3; 4; 5; 6]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [7; 8]. The structure of murine PD-1 has been resolved [9]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade [7; 10; 11; 12]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [13; 14]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells [15; 16]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [17]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [18; 19; 20; 13]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [13]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL) [21]. This suggests that the PD-1/PD-L1 pathway plays a

critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

MK-3475 (previously known as SCH 900475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

4.1.2 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Radiation has been demonstrated to provide clear survival advantages to patients with both limited stage and extensive stage SCLC[1,2]. Radiations historical use has been to provide local control, by sterilizing tumor that is non-surgically resectable. Radiations ability to sterilize not only the primary tumor but lymph nodes and draining lymphatic channels have made it an integral part of the treatment of many solid tumors include SCLC which have a proclivity for metastatic spread.

Moreover, despite the known benefit of ionizing radiation in terms of local tumor control, it also enhances the release of cytokines such as TGF-β, a known inducer of tumor invasion and the epithelial-mesenchymal transition.[3-5] On the other hand, radiation can also promote the immune response through the induction of neoantigens and the stimulation of factors such as interferon-gamma that can actually enhance T cell infiltration.[6] This dual ability to control local tumor progression yet also influence metastatic spread and immune response constitute a compelling argument for including radiation in tests of the current arsenal of immune checkpoint inhibitors now entering the clinic.

The rational for this trial is based on combing MK-3475 with concurrent radiation in order to use radiation ability to turn a tumor into an in situ-vaccine in order to prime an immune response. MK-3475 will provide T cell activation to allowing for priming and expansion of these activated T cells, which can then enter the systemic circulation and enhance systemic tumor control, and concept often referred to as the abscopal affect. Small Cell lung cancer is a disease with a high failure rate both locally and distantly. As such improvement in both systemic and local therapy are urgently needed. Furthermore Small Cell Lung Cancer has one of the highest endogenous mutation rates of any cancer with up to 7 mutations per 1 million bases[7], all these unique mutations can potentially be used as new antigen for immune stimulation. All this contributes to SCLC being ideal tumor type to evaluate checkpoint inhibitors such as MK-3475.

4.2.2 Rationale for Dose Selection/Regimen/Modification

Radiation for limited stage disease will be administered at the standard doses of 45Gy in twice daily fractions, with concurrent chemotherapy, either cisplatin and etoposide or carboplatin and etoposide. Patients with extensive stage disease will receive thoracic radiation to 45 Gy in daily fractions, without concurrent chemotherapy. While on study, patients are allowed to have further radiation to other clinically appropriate sites as per the discretion of their treating radiation oncologist.

MK-3475: Will be started at 100 mg, 1/2 the MTD of MK-3475 alone (based on MTD dose of 200mg Q 3 weeks). The dose will be changed as per our 3x3 dose escalation rules and either decreased to 70mg, continued at 100m or increased to 150mg and eventually 200mg.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Part A LS-SCLC: The primary endpoint is safety in order to establish the MTD of MK-3475 with concurrent chemo and radiation. The primary acute toxicity for chemo and radiation is esophagitis with a rate of ≥ 32%[8]. While the long term toxicity rate of grade 3 pneumonitis is around 13%[9].

Part B ES-SCLC: The primary endpoint is safety in order to establish the MTD of MK-3475 with concurrent radiation. The primary acute toxicity for chemo and radiation is esophagitis with a rate of ≥ 32%[8]. While the long term toxicity rate of grade 3 pneumonitis is around 13%[9].

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent/assent for the trial.

2. Be ≥ 18 years of age on day of signing informed consent.

3. Modified for clarification as some patient with induction therapy could have no measurable disease. Have a performance status of 0 or 1 or 2 on the ECOG Performance Scale.

4. Demonstrate adequate organ function as defined below; all screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

5. Female subject of childbearing potential should have a negative urine or serum pregnancy within 2 weeks of study entry. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

6. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

7. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

8. Histologic diagnosis of either limited state SCLC (LS-SCLC), or Extensive stage SCLC (ES-SCLC) or neuroendocrine tumor.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is currently participating in or has participated in a study of an investigational agent (except glutamine) or using an investigational device within 2 weeks of the first dose of treatment.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. With the exception of physiologic steroid replacement.

3. Has had a prior monoclonal antibody within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

4. Has had prior chemotherapy, targeted small molecule therapy, within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent. Prior radiation does not require a washout period.

    - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

5. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.

6. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.

7. Has an active automimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.

8. Has evidence of interstitial lung disease or active, non-infectious pneumonitis.

9. Has an active infection requiring systemic therapy.

10. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

11. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

12. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

13. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137.

14. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

15. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

16. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below.

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
MK-3475	70-200 mg	Q 3 weeks	IV infusion	16 cycles	Experimental
The MK-3475 dosing interval may be increased due to toxicity as described in Section 5.2.1.2.					

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

The dose amount required to prepare the MK-3475 infusion solution will be based on the dose level which a patient is being treated on as per table 1.

Radiation will be given as per our institutional standard. For the patient in the LS-SCLC arm we will use 45Gy delivered BID over 15 days (we will allow a GTV boost to 54Gy, as long as the PTV dose remains at 45Gy). For patients with ES-SCLC we will use a dose of 45Gy daily (we will allow at GTV boost dose to 52.5Gy, as long as the PTV dose remains at 45Gy).

5.2.1.2 Dose Modification

MK-3475 will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Table 3 below.

Table 3: Dose modification guidelines for drug-related adverse events.

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Sponsor)
Hematological Toxicity	1, 2, 3	No	N/A	N/A	N/A
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
Non-hematological toxicity Note: Exception to be treated similar to grade 1 toxicity • Grade 2 alopecia • Grade 2 fatigue For additional information regarding Adverse Events with a potential Immune-Etiology reference Section 5.6.1.1.	1	No	N/A	N/A	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0-1 or baseline	*Clinical AE resolves within 4 weeks*: Same dose and schedule (reference Section 5.6.1.2 for recommendations regarding pneumonitis) *Clinical AE does not resolve within 4 weeks:* May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Sponsor)
	3, 4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with the Sponsor. With investigator and Sponsor agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. For information on the management of adverse events, see Section 5.6.1.

Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of MK-3475 should be discontinued from trial treatment.

5.2.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

MK-3475 will be administered as a 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 5.2.1.2). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Procedures Manual contains specific instructions for MK-3475 dose calculation, reconstitution, preparation of the infusion fluid, and administration.

5.2.3 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

5.3 Stratification

There is no stratification for this trial.

5.4 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, the Sponsor, and the subject.

5.4.1 Acceptable Concomitant Medications

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

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.4.2 Prohibited Concomitant Medications

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

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than MK-3475
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.

- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.5 Correlative Studies relating to immunologic response:

The immunotherapy platform will perform immune monitoring, including but not limited to evaluation of CD4 and CD8 T cells in peripheral blood and available tumor samples as previously published, 19,22. All samples will be collected and analyzed as per a separate IRB-approved lab protocol.

5.5.1. Tumor tissues

Tumor tissue collected for diagnostic purposes within 3 months of study entry will be banked under an IRB-approved laboratory protocol and ten to thirty unstained slides or fresh frozen tumor from available tissues will be collected for baseline immune system testing before radiation treatment

Optional biopsy after the completion of radiation therapy:

A biopsy will be done (optional) within 7 days after completion of radiation therapy for immune response monitoring.

5.5.2. Peripheral blood

Up to 150 mL of peripheral blood will be collected under an IRB-approved laboratory protocol (optional) for immune system monitoring described in this clinical protocol at the following time points:

- First collection: At baseline before the start of radiation therapy
- Second collection: within 7 days after completion of radiation therapy.

The treating physician or designee will have the option to cancel the laboratory protocol collection for patient safety without protocol deviation.

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

- Diarrhea: 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). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.

    - In subjects with severe enterocolitis (Grade 3), MK-3475 will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

    - In subjects with moderate enterocolitis (Grade 2), MK-3475 should be withheld and anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Regarding guidelines for continuing treatment with MK-3475, see Section 5.2.

    - All subjects who experience diarrhea 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.

- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

- Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

- Immune-related adverse events: Please see Section 5.6.1.1 below and the separate guidance document in the administrative binder regarding diagnosis and management of adverse experiences of a potential immunologic etiology.

- Management of Infusion Reactions: Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from

allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.

Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of MK-3475.

Table 5 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 treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject 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.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of MK-3475 with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

5.6.1.1 Supportive Care Guidelines for Events of Clinical Interest and Immune-related Adverse Events (irAEs) (Appendix 13.4)

Events of clinical interest of a potential immunologic etiology (irECIs) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. irAEs may be predicted based on the nature of the MK-3475 compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Information on how to identify and evaluate irAEs has been developed and is included in the Event of Clinical Interest and Immune-Related Adverse Event Guidance Document located in the Administrative Binder. Subjects who develop a Grade 2 or higher irAE should be discussed immediately with the Sponsor.

Recommendations to managing irAEs not detailed elsewhere in the protocol are detailed in Table 6.

Table 6 General Approach to Handling irAEs

irAE	Withhold/Discontinue MK-3475?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold MK-3475	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3 and Grade 4	Withhold MK-3475 Discontinue if unable to reduce corticosteroid dose to < 10 mg	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day.

	per day prednisone equivalent within 12 weeks of toxicity	Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

5.6.1.2 Supportive Care Guidelines for Pneumonitis

Subjects with symptomatic pneumonitis should immediately stop receiving MK-3475 and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection. If the subject is determined to have study drug associated pneumonitis, the suggested treatment plan is detailed in Table 7.

Table 7 Recommended Approach to Handling Pneumonitis

Study drug associated pneumonitis	Withhold/Discontinue MK-3475?	Supportive Care
Grade 1 (asymptomatic)	No action	Intervention not indicated
Grade 2	Withhold MK-3475, may return to treatment if improves to Grade 1 or resolves within 12 weeks	Systemic corticosteroids are indicated. Taper if necessary.
Grade 3 and Grade 4	Discontinue MK-3475	Systemic corticosteroids are indicated. The use of infliximab may be indicated as appropriate. Refer to the Event of Clinical Interest and Immune-related Adverse Event Guidance Document for additional recommendations.

For Grade 2 pneumonitis that improves to ≤ Grade 1 within 12 weeks, the following rules should apply:

- First episode of pneumonitis
    - May increase dosing interval by one week in subsequent cycles
- Second episode of pneumonitis – permanently discontinue MK-3475 if upon rechallenge subject develops pneumonitis ≥ Grade 2

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.7.2 Contraception

MK-3475 may have adverse effects on a fetus in utero. Furthermore, it is not known if MK-3475 has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to the Sponsor and to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with MK-3475, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

It is unknown whether MK-3475 is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.3 – Other Procedures.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

  Note: For unconfirmed radiographic disease progression, please see Section 5.2.2

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.1.2.7.1
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of treatment with MK-3475

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop MK-3475 after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.2.1.
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for

disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.9 Subject Replacement Strategy

5.10 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug

In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart (All scheduled tests will be given a window of +/- 3 days)

Treatment Cycle/Title:		Main Study Screening	1	2	3	4	5	6-16 (additional 16 cycles, for eligible patients	Post MK-3475 Follow up	Survival Follow-Up (>2yrs)[a]
Scheduling Window (Days):		-28 to -1		± 3	± 3	± 3	± 3	± 3	Every 12 weeks post discon	Every 12 weeks
Administrative Procedures										
Informed Consent		X								
Medical History		X								
Concomitant Medication Review		X	X	X	X	X	X	X	X[a]	
Trial Treatment Administration			X	X	X	X	X	X		
Survival Status									X[a, f]	X[a, f]
Clinical Procedures/Assessments										
Review Adverse Events			X	X	X	X	X	X		
Directed Physical Examination		X	X	X	X	X	X	X		
Vital Signs and Weight		X	X	X	X	X	X	X		
ECOG Performance Status		X								
Laboratory Procedures/Assessments: Analysis Performed by LOCAL Laboratory										
Pregnancy Test – Urine or Serum β-HCG		X[d]								
PT/INR and aPTT		X								
CBC with Differential		X	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]		
Comprehensive Serum Chemistry Panel (BMP)		X	X	X	X	X	X	X		
T3, FT4 and TSH[b]		X[b]		X[b]		X[b]		X[b]		
PFT's		X							X[c, f]	
Biopsy[c]			X[g]							

Treatment Cycle/Title:		Main Study Screening	1	2	3	4	5	6-16 (additional 16 cycles, for eligible patients	Post MK-3475 Follow up	Survival Follow-Up (>2yrs)[a]
Scheduling Window (Days):		-28 to -1		± 3	± 3	± 3	± 3	± 3	Every 12 weeks post discon	Every 12 weeks
Blood Biomarker Testing[c]		X	X	X	X	X	X	X	X	
Efficacy Measurements										
Tumor Imaging (CT or PET scan)[e]		X				X		X[f]	X[c, f]	X[c, f]

a. Can be done over the phone.

b. Thyroid functions will be performed with every other MK-3475 cycle, if the first three test are WNL then it can be stopped.

c. Optional biopsy after radiation treatment

d. Within 2 weeks of study entry for women with child bearing potential.

e. Imaging should be performed approximately every 12 weeks (± 4 weeks).

f. standard of care

g. Within 3 months of study entry

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.f

7.1.1.2 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.3 Concomitant Medications Review

7.1.1.3.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.3.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.4 Disease Details and Treatments

7.1.1.4.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.4.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.4.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.1.5 Trial Compliance (Medication/Diet/Activity/Other)

Patients will be monitored for treatment compliance in addition to general compliance with clinic visits, prohibited activities, and concomitant medication. In the event that a patient is unwilling or unable to maintain compliance, then the patient can be removed from the study pending investigator and treating physician discretion.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 13.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with MK-3475 exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE). See Section 5.6.1.1 and the separate guidance document in the administrative binder regarding the identification, evaluation and management of AEs of a potential immunological etiology.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.2.3 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 13.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart. After Cycle 8 assessment of ECOG status will be performed every other cycle in conjunction with the directed or full physical exam.

7.1.2.5 Tumor Imaging and Assessment of Disease

Response and progression will be evaluated in this study using guidelines proposed by the Immune Related Response Criteria (irRC). Patients with measurable disease will also be assessed using standard RECIST v 1.1 and World Health Organization (WHO) treatment response criteria.

7.1.2.5.1 irRC: Measurable Disease Prior to Therapy

Index lesions: Up to 15 index lesions per patient (5 per organ, up to 10 visceral and 5 cutaneous) with minimum size 5 x 5 mm will be accurately measured in two dimensions (two largest perpendicular diameters) on CT or MRI scan (slice thickness no greater than 5 mm) prior to therapy initiation. Lesions measured with calipers by clinical exam may be conducted on lesions no smaller than 10 mm in the smallest dimension. Lesions that cannot be accurately measured with calipers should be recorded as non-measurable.

XRT-treated index lesions: Defined as all index lesions treated by XRT as part of this protocol.

Non-XRT-treated index lesions: Defined as all index lesions not treated by XRT as part of this protocol.

irRC: Index and non-Index Lesions:

For the irRC, index and measurable new lesions are taken into account (in contrast to conventional WHO treatment response criteria, which do not require the measurement of new lesions, nor are new lesion measurements included in the assessment of evolving tumor

burden). At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥5 x 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 new visceral lesions) are added together to provide the total tumor burden. In addition to a global irRC which will encompass all lesions under the previous definition, the irRC of lesions included within the XRT PTV and outside the XRT PTV will also be assessed as follows:

1. **Global irRC:** irRC that factors all lesions including both index and non-index as outlined in 9.2.4.

2. **In-Field irRC:** irRC in which only index within the XRT PTV will be considered and any non-index lesions arising inside the XRT PTV

3. **Out-Field irRC**: irRC in which only index lesions outside the XRT PTV will be considered and any non-index lesions arising outside the XRT PTV

7.1.2.5.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or physical calipers. All baseline evaluation studies should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

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

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

Multidetector CT, PET/CT. These techniques should be performed with contiguous slices of 5 mm or less in thickness. This applies to tumors of the neck, chest, abdomen and pelvis. Head and neck tumors and those of extremities may require specific imaging protocols or evaluation with ultrasound. When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, Laparoscopy. These will not be used to assess response on this study.

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

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) if clinically indicated.

7.1.2.5.3 Immune Related Response Criteria (irRC).

Evaluation of Target Lesions

Response in new patients will be conducted using the Immune Related Response Criteria (irRC) as described in[10]. "For irRC, only index and measurable new lesions are taken into account. At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥5 x 5mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden:"

For the purposes of this study, 3 separate tumor burdens will be calculated for each patient and used to define 3 separate irRCs as discussed in 9.3. All criteria will be considered separately for all 3 irRCs: global, in-field, and out-field.

Global Tumor Burden = SPD(all index lesions) + SPD(new, measurable lesions)

In-Field Tumor Burden = SPD(all index lesions targeted by XRT in this protocol) + SPD(new, measurable lesions inside the XRT PTV)

Out-Field Tumor Burden = SPD(all index lesions NOT targeted by XRT in this protocol) + SPD(new, measurable lesions outside the XRT PTV)

Complete Response (irCR): irCR, complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented.

Partial Response (irPR): irPR, decrease in tumor burden ≥50% relative to baseline confirmed by a consecutive assessment at least 4 wk after first documentation.

Progressive Disease (irPD): irPD, increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden) confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented.

1. If a patient is classified as having irPD at a post-baseline tumor assessment, then confirmation of irPD by a second scan in the absence of rapid clinical deterioration is required. The definition of confirmation of progression represents an increase in tumor burden ≥25% compared with the nadir at two consecutive time points at least 4 wk apart. It is recommended that this be done at the discretion of the investigator

because follow-up with observation alone may not be appropriate for patients with a rapid decline in performance status.

Stable Disease (irSD): irSD, not meeting criteria for irCR or irPR, in absence of irPD. In contrast to other response criteria, this criteria does not require repeat confirmation.

7.1.2.6 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Procedures Manual.

Laboratory tests for screening should be performed within 28 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3 Other Procedures

7.1.3.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with MK-3475 may discontinue treatment with the option of restarting treatment if they meet the criteria specified. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.4.4).

7.1.4 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.4.1 Screening

The screening assessment will consist of a full history and physical exam, along with listed laboratory screening tests including a pregnancy test in PT/INR.

7.1.4.2 Treatment Period

During treatment patients will have a review of all concurrent medication, vitals and review of adverse events. During radiation delivery patients will see a doctor weekly to review treatments address issues, any potential side effects.

7.1.4.3 Post-Treatment Visits

Following the completion of this study, patients will follow up one month later with new imaging studies to assess response to treatment. At this time we will also perform a physical exam, vitals, medication review, and assess for any prior and or new toxicities and or side effects. Following this the same assessment will be performed every three months for the next 2 years and then every 6 months after that.

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.1.4.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (90 ± 14 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

7.1.4.4.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for MK-3475 by 20% over the prescribed dose. No specific information is available on the treatment of overdose of MK-3475. In the event of overdose, MK-3475 should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event

Refer to Table 10 for additional details regarding each of the above criteria.

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

3. In the event a subject develops any of the following AEs, a detailed narrative of the event should be reported as an ECI to the Sponsor within 24 hours and to Merck Global Safety within 2 working days of the event:

a. Grade ≥ 3 diarrhea
b. Grade ≥ 3 colitis
c. Grade ≥ 2 pneumonitis
d. Grade ≥ 3 hypo- or hyperthyroidism

A separate guidance document has been provided entitled "event of Clinical Interest and Immune-Related Adverse Event Guidance Document." This document provides guidance regarding identification, evaluation and management of ECIs and irAEs. Additional ECIs are identified in this guidance document and also need to be reported to the Sponsor within 24 hours and to Merck Global Safety within 2 working days of the event.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

ECIs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the Merck's product, must be reported within 24 hours to the Sponsor and to Merck Global Safety within 2 working days.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 10 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).**	
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.	
No, there is not a reasonable possibility Merck product relationship	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

8.0 CHEMOTHERAPY

Part A LS-SCLC:

All patients will receive chemotherapy with either cisplatin and etoposide or carboplatin and etoposide. All patients should receive four cycles of chemotherapy, given over 3 weeks each, unless there is evidence of disease progression or patient intolerance. Cisplatin and etoposide is the preferred regimen; for patients unable to tolerate cisplatin in the opinion of the treating clinician, carboplatin/etoposide is an acceptable alternative.

8.1 Drug Supply and Storage

Cisplatin, carboplatin, and etoposide are standard, commercially available drugs. Investigators will use commercially available supplies and will store drug as per the instructions provided in the package insert. This section does no apply to induction chemotherapy given prior to trial enrolment.

8.2 Drug Administration

8.2.1 Etoposide

During cycles 1-4, etoposide 100 mg/m^2 IV will be administered over approximately 4 hours on days 1, 2, and 3 of each 3 week cycle. BSA will be obtained by the Mosteller equation:

$$BSA = ((\ ht(cm) * wt(kg)\ ) / 3600)^{1/2}$$

Etoposide will be given for up to 4 cycles.

8.2.2 Cisplatin

During cycles 1-4 of the induction phase, subjects for whom cisplatin/etoposide has been selected as chemotherapy will receive cisplatin IV at a dose of 80 mg/m^2 on day 1 of each 3 week cycle. The dosage will be administered over approximately 2 hours. BSA will be obtained by the Mosteller equation. Cisplatin will be given for up to four cycles.

Pre-hydration and post-hydration can be administered per institutional standards.

8.2.3 Carboplatin

During cycles 1-4 of the induction phase, subjects for whom carboplatin/etoposide has been selected as chemotherapy will receive carboplatin IV at AUC 5 on day 1 of each 3 week cycle.

The dosage will be administered over approximately 30 minutes. AUC should be calculated using the Calvert formula. Carboplatin will be given for up to four cycles.

Creatinine clearance must be calculated prior to every dose of carboplatin using the Cockroft-Gault formula for estimating creatinine clearance in mL/min based on serum creatinine:

Men: $\frac{[(140\text{-Age (yrs)}) * \text{weight (kg)}]}{[72 * \text{serum creatinine (mg/dL)}]}$

Women: $\frac{[(140\text{-Age (yrs)}) * \text{weight (kg)}]}{[72 * \text{serum creatinine (mg/dL)}]} * 0.85$

If calculated GFR is greater than 125 mL/min, the maximum GFR used to calculate carboplatin dose should be 125 mL/min to avoid potential toxicity due to overdosing.

8.2.4 Cisplatin Versus Carboplatin

Cisplatin is the preferred platinum agent. For patients unable to tolerate cisplatin in the opinion of the treating clinician, carboplatin is an acceptable alternative. Subjects are allowed to switch from cisplatin to carboplatin during therapy, if the subject becomes ineligible for further cisplatin therapy in the opinion of the treating clinician, and the clinician feels that switching to carboplatin is in the best interest of the subject

8.3 Dose Delays and Dose Modifications for Cytotoxic Chemotherapy

8.3.1 Dose Delays

Drug related toxicities must be resolved to baseline or ≤ grade 1 (with the exception of alopecia and grade 2 fatigue) prior to administering the next dose. Subjects should not receive the next cycle of chemotherapy if any of the following apply:

- Absolute neutrophil count (ANC) <1500/mm^3
- Platelet count <100,000/mm^3
- Hemoglobin <9 g/dL
- Total bilirubin >2.5 times the upper limit of normal (ULN)
- AST and ALT >2.5 times ULN, or >5 times ULN if liver metastases are present
- Inadequate renal function defined as creatinine clearance < 45 mL/min by the standard Cockroft and Gault formula
- Additionally, treatment may be delayed due to any other reasons as per the treating physician's discretion.

Chemotherapy treatment may be delayed up to 21 days.

8.3.2 Dose Modifications

Dose modifications for carboplatin, cisplatin, and etoposide will follow local guidelines. Suggestions for dose reductions are provided below.

	Etoposide Dose	Cisplatin Dose	Carboplatin Dose
Starting Dose	100 mg/m^2	80 mg/m^2	AUC 5
Dose Level -1	75 mg/m^2	60 mg/m^2	AUC 4
Dose Level -2	50 mg/m^2	40 mg/m^2	AUC 3

8.3.2.1 Suggested Dose Modifications for Hematologic Toxicity

Drug Related Toxicity	Etoposide	Cisplatin	Carboplatin
Febrile Neutropenia (temperature ≥38.5˚C and ANC <1000/m^3)	Decrease 1 dose level	Decrease 1 dose level	Decrease 1 dose level
Platelets <25,000/m^3	Decrease 1 dose level	Decrease 1 dose level	Decrease 1 dose level
Grade 4 anemia (Hgb<6.5 g/dL)	Decrease 1 dose level	Decrease 1 dose level	Decrease 1 dose level

8.3.2.3 Suggested Dose Modifications for Non-Hematologic Toxicity

For all toxicity ≤ grade 2 (except neuropathy), the dose level for all drugs should be maintained. All dose modifications should be made based on the worst grade toxicity seen.

Drug Related Toxicity	Etoposide	Cisplatin	Carboplatin
Nausea/Vomiting ≥ Grade 3 despite optimal medical treatment	Decrease 1 dose level	Decrease 1 dose level	Decrease 1 dose level

Diarrhea ≥ Grade 3 despite optimal medical treatment	Decrease 1 dose level	Decrease 1 dose level	Decrease 1 dose level
Neuropathy, grade 2 lasting > 7 days or grade 3	No modification	Decrease 2 dose levels	No modification
Neuropathy grade 4	No modification	Discontinue	No modification
Total bilirubin >2 x ULN	50% of previous dose	No modification	No modification
Total bilirubin >5 x ULN	Discontinue	No modification	No modification
Other grade ≥ 3 toxicities (except fatigue and arthralgia/myalgia)	Decrease 1 dose level	Decrease 1 dose level	Decrease 1 dose level

9.0 STATISTICAL ANALYSIS PLAN

Data Protection and Confidentiality

We will have two independent phase I 3x3 escalations going on simultaneously, one for LS-SCLC patient in part A (with chemotherapy) and those for ES-SCLC (without chemotherapy) for part B.

All patients who meet eligibility criteria and are enrolled in this trial will be registered in Clinical Oncology Research Database (CORe) at the University of Texas M D Anderson Cancer Center at Houston. All protocol participants must be registered in the CORE. The date in the current informed consent document is displayed to ensure only the most current IRB approved version is used. Consent date, registration date, off study date, and evaluability data are required for all registrants.

The principal investigator agrees to keep all information and results concerning the study confidential. The confidentiality obligation applies to all personnel involved with this clinical trial. The Investigator must ensure that each participant's anonymity will be maintained in accordance with applicable laws. The principal investigator should keep a separate log of ID numbers, names and addresses. Documents that contain the names associated with these ID numbers (e.g., written consent/assent forms), should be maintained by the Investigator in strict confidence except to the extent necessary to allow auditing by regulatory authorities, auditing or monitoring by the IRB.

The Principal Investigator shall obtain all such permissions and authorizations as may be necessary or desirable to allow the collection and use of information protected under federal privacy laws and state privacy laws, including permission/authorization for monitoring and analysis (including

re-analysis in combination with results of other studies), for regulatory submission purposes and for applicable reporting (if any).

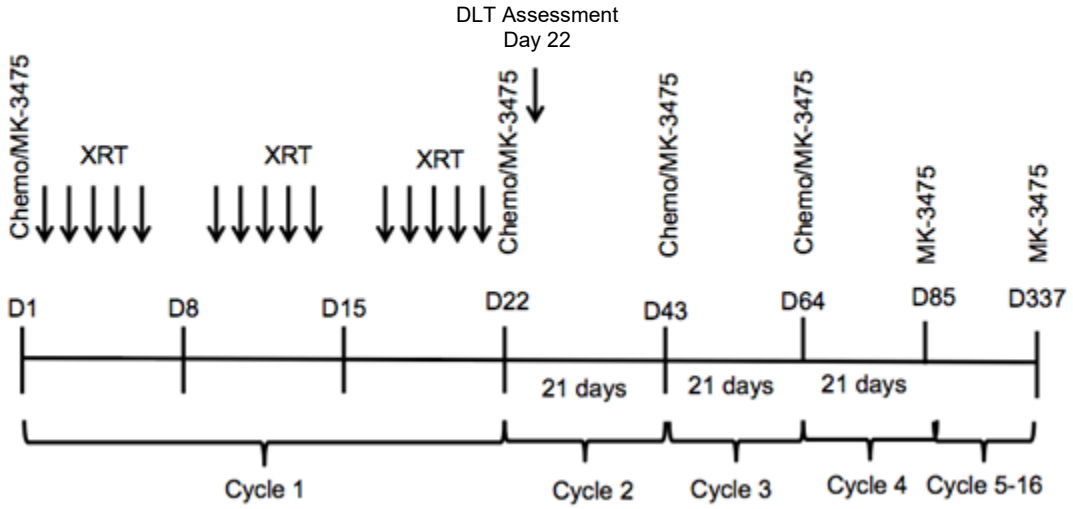
Under this protocol, we will collaborator with Dr. Vivek Verma at the University of Nebraska. All data sent to Dr. Verma will be de-identified with no names, dates, or medical record numbers. The de-identified data will be sent in an Excel spreadsheet via MDACC encrypted email and will be used to perform analysis. Patient identification information will be removed from all documents. The data will be coded by anonymous study numbers using a key kept separate from the database that only the principal investigator will have access to. Data will be stored on a password and firewall protected computer.

9.1 Data Set Descriptions

This study will utilize a standard 3+3 design and dose de-escalation will proceed according to the following scheme. Three doses of MK-3475 (100 mg, 150 mg, 200 mg) will be given to 3 different groups of 3 patients. If the toxicity is greater than 1/3 in one group then the next lower dose will be used. This will establish the MTD, if present. If more than 1/3 of patients experience DLTs at the lowest dose (70 mg), it will be concluded that MK-3475 cannot be given safely with chemo/radiation. If one of three patients at any dose level experiences grade 3 or greater toxicity then another 3 patient will be accrued at the same dose level. If 1/6 patients has grade 3 or higher toxicity then escalation will proceed, if 2/6 has grade 3 or greater toxicity then this is declared the MTD. If 3/6 has grade 3 or greater then we will reduce the dose level.

Part A: Is only for patients with Limited stage SCLC, we will allow induction chemotherapy.

Part A for LS-SCLC



Part B: Is only for patients with Extensive stage SCLC who are receiving consolidation XRT after 1-6 cycles of chemotherapy.

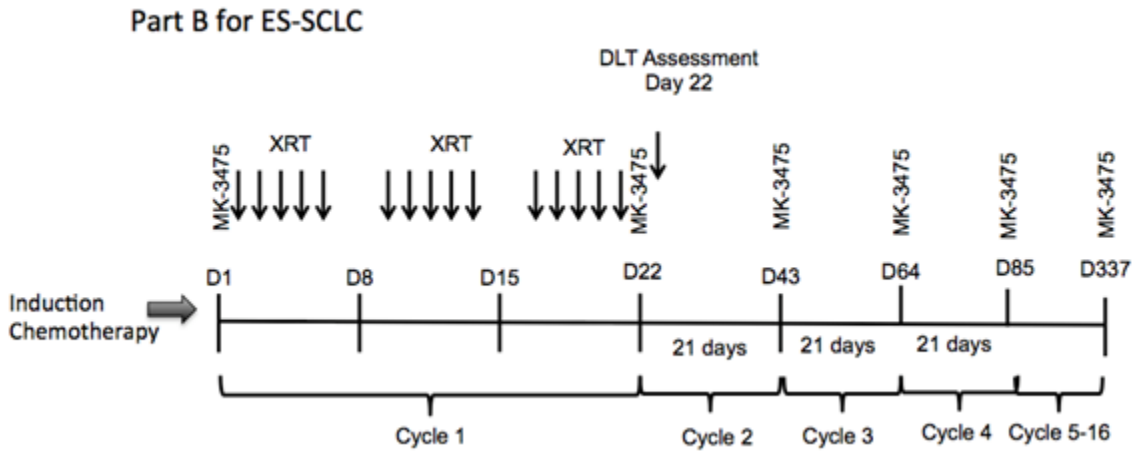


Table 1: Dose De-escalation, For Part A and B

Dose Level	MK-3475 (dose during XRT)	Toxicity Assessment	New MK 3475 dose
+2	200mg Q 3 weeks	If over 1/3 grade 3 toxicity is seen	150mg Q 3 weeks
+1	150mg Q 3 weeks	If over 1/3 grade 3 toxicity is seen If 0/3 grade 3 toxicity is seen	100mg Q 3 weeks 200mg Q 3 weeks
0 (starting dose)	100mg Q 3 weeks	If over 1/3 grade 3 toxicity is seen If 0/3 grade 3 toxicity is seen	70mg Q 3 weeks 150mg Q3 weeks
-1	70mg Q 3 weeks	If over 1/3 grade 3 toxicity is seen	We will conclude MK-3475 cannot be safely given after Chemo/radiation

Once the MTD is determined for each study part we will accrue at this MTD until we reach a total of 40 patients for each study part. Should DLTs occur in more than 1/3 of patients enrolled into this expanded cohort, dosing at that level will be stopped. A review of all DLTs observed will be conducted, and the need to lower the dose will be based on the discussion and agreement between

the IRB and the Investigator. Once at dose level +2, if 0/3 toxicity is seen we will not close the study for new patient enrollment until the third patient has passed the DLT assessment period, because even if this third patient has a DLT was seen it would no change the dose for future patients as another 3 patients at the same dose level would be needed.

All patients who receive any MK-3475 will be considered evaluable for response and will be included in the efficacy data set.

DLT is defined as any:

- DLTs are defined as any adverse event(s) considered related to the combination of MK-3475 plus radiation as described below:
    - Any ≥ Grade 3 bronchospasm or other hypersensitivity reaction;
    - Any other ≥ Grade 3 non-skin related adverse event with the exception of laboratory abnormalities;
    - Any Grade 4 laboratory abnormalities, except AST, ALT, or total bilirubin;
        - AST or ALT > 8 x ULN,
        - Total bilirubin > 5 x ULN;
    - Any other Grade 4 adverse event;

1. Any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued study drug dosing;
2. Subject experiences an allergic/infusion reaction while receiving study drug at a slower infusion rate due to a prior allergic/infusion reaction;
3. Any motor neurologic toxicity ≥ Grade 3 regardless of causality;
4. Any ≥ Grade 3 treatment-related sensory neurologic toxicity.
5. Drug related toxicity that prevents administration of MK-3475 for > 21 days from the scheduled dose

- The time frame for DLT assessment will be within 22 days of therapy initiation.
- Any grade 4 neutropenia (with or without fever and/or sepsis) or thrombocytopenia (with or without bleeding) lasting at least 1 week or longer (as defined by the NCI-CTC v4.0).
- Any other grade 3 non-hematologic toxicity including symptoms/signs of vascular leak or cytokine release syndrome; or any severe or life-threatening complication or abnormality not defined in the NCI-CTCAE v4.0 that is attributable to the therapy.

9.2.1. *Statistical Analysis*

Descriptive statistics will be computed for all relevant outcomes, including toxicity, tumor response, PFS, OS, and biomarker response. Descriptive analysis will include a global assessment of patient outcomes for parts A and B separately. All patients receiving at least 1 treatment with MK-3475 will be included in the analysis.

9.2.2. *Demographics and Baseline Characteristics*

Frequency distributions of gender and race will be tabulated by dose/cohort. Summary statistics for age, body weight, height, and Body Mass Index (BMI) will be tabulated by dose/cohort.

9.2.3. *Safety Analyses*

All recorded adverse events will be recorded per MDACC guidelines using CTCAE Version 4.0. Frequency of adverse events will be tabulated by grade, type, and dose/cohort. Relative frequencies and confidence intervals will also be constructed.

9.2.4. *Efficacy Analyses*

Efficacy data from part A and part B will be performed using the criteria below**.**

1. **Global irRC:** irRC that factors all lesions both index and non-index.

2. **In-Field irRC:** irRC in which only XRT-treated lesions will be considered and non-index lesions arising inside the XRT PTV

3. **Out-Field irRC**: irRC in which only non XRT-treated lesions will be considered and non-index lesions arising outside the XRT PTV

Time-to-event distributions for PFS and OS will be estimated via Kaplan-Meier analysis. Summary statistics will be computed along with confidence intervals. The limited sample size precludes formal statistical comparison with historical controls.

9.2.5. *Sample Size/Accrual Rate*

The maximum planned number of patients will be 80, with 40 patients being treated with LS-SCLC and 40 patients with ES-SCLC. It is estimated that approximately 1.5 patients per month (for both LS-SCLC and ES-SCLC) will be accrued over 26 months. With 40 patients, the probability of seeing at least one patient with toxicity if the true toxicity rate is 0.1 is 88%. The 95% binomial confidence interval for 6/20 (30%) extends from 15% to 52%.

10.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

10.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck as summarized in Table 11.

Table 11 Product Descriptions

Product Name & Potency	Dosage Form
MK-3475 100 mg/ 4mL	Solution for Injection

10.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

10.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

10.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

10.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal

have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

11.0 ADMINISTRATIVE AND REGULATORY DETAILS

11.1 Confidentiality

Confidentiality will be maintained throughout this study in accordance with the Health Insurance Portability and Accountability Act. This study will be presented and approved by the Internal Review Board at MD Anderson Cancer Center.

11.2 Compliance with Financial Disclosure Requirements

N/A

11.3 Compliance with Law, Audit and Debarment

N/A

11.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

12.0 LIST OF REFERENCES

1. Disis ML. Immune regulation of cancer. J Clin Oncol 2010; 28(29):4531-8.

2. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002;8(8):793-800.

3. Sharpe AH, Freeman GJ. The B7-CD28 superfamily. Nature 2002;2:116-26.

4. Brown JA, Dorfman DM, Ma F-R, Sullivan EL, Munoz O, Wood CR, et al. Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. J Immunol 2003;170:1257-66.

5. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.

6. Thompson RH, Dong H, Lohse CM, Leibovich BC, Blute ML, Cheville JC, et al. PD-1 expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. Clin Caner Res 2007;13(6):1757-61.

7. Talmadge JE, Donkor M, Scholar E. Inflammatory cell infiltration of tumors: Jekyll or Hyde. Cancer Metastasis Rev 2007;26:373-400.

8. Usubütün A, Ayhan A, Uygur MC, zen H, klu C, acan S. Prognostic factors in renal cell carcinoma. J Exp Clin Cancer Res 1998;17(1):77-81.

9. Al-Shibli KI, Donnem T, Al-Saad S, Persson M, Bremnes RM, Busund L-T. Prognostic effect of epithelial and stromal symphocyte infiltration in non-small cell lung cancer. Clin Cancer Res 2008;14(16):5220-7.

10. Deschoolmeester V, Baay M, Van Marck E, Weyler J, Vermeulen p, Lardon F, et al. Tumor infiltrating lymphocytes: an intriguing player in the survival of colorectal cancer patients. BMC Immunol 2010;11:19.

11. Diez M, Pollán M, Enriquez JM, Dominguez P, Santana A, Tobaruela E, et al. Histopathologic prognostic score in colorectal adenocarcinomas. Anticancer Res 1998;18:689-94.

12. Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pagès C, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 2006;313:1960-4.

13. Hiraoka N. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: molecular biology. Int J Clin Oncol 2010;15:544-51.

14. Nobili C, Degrate L, Caprotti R, Franciosi C, Leone BE, Trezzi R, et al. Prolonged survival of a patient affected by pancreatic adenocarcinoma with massive lymphocyte and dendritic cell infiltration after interleukin-2 immunotherapy. Report of a case. Tumori 2008;94:426-30.

15. Hodi FS, Dranoff G. The biologic importance of tumor-infiltrating lymphocytes. J Cutan Pathol 2010;37(Suppl 1):48-53.

16. Kloor M. Lymphocyte infiltration and prognosis in colorectal cancer. Lancet 2009;10(840):841.

17. Hillen F, Baeten CIM, van de Winkel A, Creytens D, van der Schaft DWJ, Winnepenninckx V, et al. Leukocyte infiltration and tumor cell plasticity are parameters of aggressiveness in primary cutaneous melanoma. Cancer Immunol Immunother 2008;57:97-106.

18. Lee HE, Chae SW, Lee YJ, Kim MA, Lee HS, Lee BL, et al. Prognostic implications of type and density of tumour-infiltrating lymphocytes in gastric cancer. Br J Cancer 2008;99(10):1704-11.

19. Leffers N, Gooden MJM, de Jong RA, Hoogeboom B-N, ten Hoor KA, Hollema H, et al. Prognostic significance of tumor-infiltrating T-lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer. Cancer Immunol Immunother 2009;58:449-59.

20. Nishimura H, Honjo T, Minato N. Facilitation of β selection and modification of positive selection in the thymus of PD-1-deficient mice. J Exp Med 2000;191(5):891-7.

21. Liotta F, Gacci M, Frosali F, Querci V, Vittori G, Lapini A, et al. Frequency of regulatory T cells in peripheral blood and in tumour-infiltrating lymphocytes correlates with poor prognosis in renal cell carcinoma. BJU Intern 2010;107:1500-6.

22. Ropponen KM, Eskelinen MJ, Lipponen PK, Alhava E, Kosma V-M. Prognostic value of tumour-infiltrating lynmphocytes (TILs) in colorectal cancer. J Pathol 1997;182:318-24.

23. Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.

24. Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.

25. Ölcher M, Braun M, Friedrichs N, Rudlowski C, Bercht E, Fimmers R, et al. Foxp3+ cell infiltration and granzyme B+/Foxp3+ cell ratio are associated with outcome in neoadjuvant chemotherapy-treated ovarian carcinoma. Cancer Immunol Immunother 2010;59:909-19.

26. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. PNAS 2001;98(24):13866-71.

27. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisted. Annu Rev Immunol 2005;23:515-48.

28. Homsi J, Kashani-Sabet M, Messina JL, Daud A. Cutaneous melanoma: prognostic factors. Cancer Control 2005;12(4):223-9.

29. Iannone R, Gergich K, Cong C, Kang P, Daud A, Dronca R, et al. Efficacy and safety of MK-3475 in patients with advanced melanoma. Pigment Cell Melanoma Res 2012;25:836-903.

30. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of Anti-PD-1 antibody in cancer. N Engl J Med 2012:doi: 10.1056/NEJMoa1200690.

31. Lyford-Pike S, Peng S, Young GD, et al. Evidence for a role of the PD-1:PD-L1 pathway in immune resistance of HPV-associated head and neck squamous cell carcinoma. Cancer Res 2013;73(2): Published online January 3.

32. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent R, Ford R, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

33. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.

34. Blum JL, Jones SE, Buzdar AU, LoRusso PM, et al. Multicenter Phase II Study of Capecitabine in Paclitaxel-Refractory Metastatic Breast Cancer. J Clin Oncol 17: 485-493, 1999

35. Martin M, Ruiz A, Munoz M, Balil A, Garcia-Mata J, Calvo L, et al. Gemcitabine plus vinorelbine monotherapy in patients with metastatic breast cancer previously treated with anthracyclines and taxanes: final results of the phase III Spanish Breast Cancer Research Group (GEICAM) trial. Lancet Oncol. 2007;8(3):219.

36. Sledge GW, Neuberg D, Bernardo P, Ingle JN, Martino S, et al. Phase III Trial of Doxorubicin, Paclitaxel, and the Combination of Doxorubicin and Paclitaxel as Front-Line Chemotherapy for Metastatic Breast Cancer: An Intergroup Trial (E1193). J Clin Oncol. 2003;21(4):588.

37. Stewart JSW, Ezra E.W. Cohen EEW, Licitra L, Van Herpen CML, et al. Phase III Study of Gefitinib Compared With Intravenous Methotrexate for Recurrent Squamous Cell Carcinoma of the Head and Neck. J Clin Oncol. 2009;27(11):1864.

38. Vermorken JB, Trigo J, Hitt R, Koralewski P, Diaz-Rubio E, et al. Open-Label, Uncontrolled, Multicenter Phase II Study to Evaluate the Efficacy and Toxicity of Cetuximab As a Single Agent in Patients With Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck Who Failed to Respond to Platinum-Based Therapy. J Clin Oncol. 2007;25(16):2171.

39. Bellmunt J, Théodore C, Demkov T, Komyakov B, Sengelov L, et al. Phase III Trial of Vinflunine Plus Best Supportive Care Compared With Best Supportive Care Alone After a Platinum-Containing Regimen in Patients With Advanced Transitional Cell Carcinoma of the Urothelial Tract. J Clin Oncol. 2009;27(27):4454

40. Sweeney CJ, Roth BJ, Kabbinavar FF, Vaughn DJ, Arning M, et al. Phase II Study of Pemetrexed for Second-Line Treatment of Transitional Cell Cancer of the Urothelium. J Clin Oncol. 2006;24(21):3451

41. Clopper C and Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404-413.

Additional references

1 Slotman, B. *et al.* Prophylactic cranial irradiation in extensive small-cell lung cancer. *The New England journal of medicine* **357**, 664-672, doi:10.1056/NEJMoa071780 (2007).

2 Murray, N. & Turrisi, A. T., 3rd. A review of first-line treatment for small-cell lung cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* **1**, 270-278 (2006).

3 Morrison, C. D., Parvani, J. G. & Schiemann, W. P. The relevance of the TGF-beta Paradox to EMT-MET programs. *Cancer Lett*, doi:S0304-3835(13)00211-5

4 Andarawewa, K. L. *et al.* Ionizing radiation predisposes nonmalignant human mammary epithelial cells to undergo transforming growth factor beta induced epithelial to mesenchymal transition. *Cancer Res* **67**, 8662-8670, doi:67/18/8662

5 Jung, J. W. *et al.* Ionising radiation induces changes associated with epithelial-mesenchymal transdifferentiation and increased cell motility of A549 lung epithelial cells. *Eur J Cancer* **43**, 1214-1224, doi:S0959-8049(07)00121-9

6 Baschnagel, A. M. *et al.* c-Met Expression Is a Marker of Poor Prognosis in Patients With Locally Advanced Head and Neck Squamous Cell Carcinoma Treated With Chemoradiation. *International journal of radiation oncology, biology, physics* **88**, 701-707, doi:10.1016/j.ijrobp.2013.11.013 (2014).

7 Peifer, M. *et al.* Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. *Nat Genet* **44**, 1104-1110, doi:10.1038/ng.2396 (2012).

8 Turrisi, A. T., 3rd *et al.* Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *The New England journal of medicine* **340**, 265-271, doi:10.1056/NEJM199901283400403 (1999).

9 Roach, M., 3rd *et al.* Radiation pneumonitis following combined modality therapy for lung cancer: analysis of prognostic factors. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **13**, 2606-2612 (1995).

10 Wolchok, J. D. *et al.* Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clinical cancer research : an official journal of the American Association for Cancer Research* **15**, 7412-7420, doi:10.1158/1078-0432.CCR-09-1624 (2009).

13.0 APPENDICES

13.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

13.2 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

13.3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe,

J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

In addition, volumetric analysis will be explored by central review for response assessment.

13.4

MK-3475

PEMBROLIZUMAB PROGRAM

(MK-3475)

EVENT OF CLINICAL INTEREST

GUIDANCE DOCUMENT

Version 3.0

REVISION HISTORY LOG

Version	Effective Date*	Revision Author	Action
1	08-Aug-2012	Kevin Gergich	Initial Release of guidance document for MK-3475
2	07-June-2013	Marty Huber, Kevin Gergich, Holly Brown	Revised title, formerly was "MK-3475 Immune-Related Adverse Event Identification, Evaluation and Management Guidance Document for Investigators" Revised the format of irAE Guidance document, including layout, font, sectioning, etc. for consistency with Sponsor Events of Clinical Interest guidance documents. Modified Categories for irAEs: – Replaced GI with Colitis category. – Removed Neurologic category. – Added Renal category. Removed detail in the irAE Guidance document that can be located in the Investigator's Brochure for MK-3475. Removed details regarding non-MK-3475 compounds. Added ECI reporting guidelines. Included a Table Events of Clinical Interest: Immune-Related Adverse Events that includes the key terms. – Also placed a pull-out quick-review sheet in the Appendix.

			Updated background, diagnosis and course of treatment details for irAEs.
3		Marty Huber, Kevin Gergich, Holly Brown	Renamed the document: "Pembrolizumab Program (MK-3475) - Events of Clinical Interest Guidance Document". Introduced generic name: pembrolizumab (MK-3475) and inserted throughout the document. Updated Overview – Section 1 - Clarified the scope of the document and the reporting window for ECIs - Updated Table 1 with medDRA Preferred Terms for adverse events to correspond with reporting of terms to clinical database, rearranged the order, and updated the reporting criteria. - Updated the dose modification/discontinuation section to clarify discontinuation and hold terminology. Updated Section 2 – ECI Reporting Guidelines – Clarified that ECIs must be reported to Merck **within 24 hours** regardless of attribution to study treatment or etiology. Updated Section 3 – For All Sections, removed the Course of Action for Grade 1 events. - Section 3.1 Pneumonitis – Moved Pneumonitis to beginning of ECI Section – Updated management guidelines for Grade 2 and Grade 3-4 events - Section 3.2 Colitis:

			- Updated AE terms and ECI criteria, updated course of action language for clarity - Section 3.3 Endocrine: - Updated ECI criteria and updated course of action language for clarity. - Added subsections for hypophysitis, hyperthyroidism and hypothyroidism to clarify management guidelines. - Section 3.4 Hematologic: - New section added. - Section 3.5: Hepatic: - Updated terms and added additional guidance for reporting of DILI ECI; updated course of action for clarity - Section 3.6 Neurologic: - New section added. - Section 3.7 Ocular: - Changed the name of this section from Eye to Ocular - Added the term “iritis”, updated ECI guidance, and updated course of action language for clarity - Section 3.8 Renal: - Updated section for clarity. - Section 3.9 Skin: - Updated list of terms and added terms for reporting of other skin ECIs; added section 3.9.1: Immediate Evaluation for Potential Skin ECIs - Section 3.10 Other:

			- Updated list of terms for clarity; revised course of action for clarity. - Section 3.11 Infusion Reactions: - New section added. - Section 3.12: Follow-up to Resolution: - New section added. - Section 4: - References updated. - Section 5: - ECI table updated for consistency with Table 1. - Section 6: Appendix 2 – Past Medical History Related to Dermatologic Event: New section added. - Section 7: Appendix 3 – Presentation of the Dermatologic Event: New section added. - Section 8: Appendix 4 – Focused Skin Examination: New section added.

*Ensure that you are using the most current version of this document.

TABLE OF CONTENTS

1. OVERVIEW

The purpose of this document is to provide study sites with guidance on the identification and management of Events of Clinical Interest for the MK-3475 (also known as pembrolizumab) program.

Based on the literature review [1-11], and consideration of mechanism of action of pembrolizumab, potential immune-related adverse events (irAEs) are the primary Event of Clinical Interest (ECI). Immune-related AEs are adverse events associated with the treatment of patients with immunotherapy treatments that appear to be associated with the immune therapy's mechanism of action. Based on these potential irAEs, the sponsor has defined a list of specific adverse event terms (ECIs) that are selected adverse experiences that **must be reported to Merck within 24 hours** from the time the Investigator/physician is aware of such an occurrence, regardless of whether or not the investigator/physician considers the event to be related to study drug(s). In addition, these ECIs require additional detailed information to be collected and entered in the study database. ECIs may be identified through spontaneous patient report and / or upon review of subject data. **Table 1** provides the list of terms and reporting requirements for AEs that must be reported as ECIs for MK-3475 protocols. Of note, the requirement for reporting of ECIs applies to all arms, including comparators, of MK-3475 clinical trials

Given that our current list of events of clinical interest is not comprehensive for all potential immune-related events, it is possible that AEs other than those listed in this document may be observed in patients receiving pembrolizumab. Therefore any Grade 3 or higher event that the investigator/physician considers to be immune-related should be reported as an ECI regardless of whether the specific event term is in Table 1 **and reported to Merck within 24 hours** from the time the Investigator/physician is aware of such an occurrence. Adverse events that are both an SAE and an ECI should be reported one time as an SAE only, however the event must be appropriately identified as an ECI as well in in the database.

Table 3: Events of Clinical Interest

Pneumonitis (reported as ECI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis

Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis		
Hematologic (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Haemolytic Uraemic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as ECI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE**)**		
Hepatitis	Autoimmune hepatitis	Transaminase elevations
Infusion Reactions (reported as ECI for any grade)		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic (reported as ECI for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as ECI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as ECI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as ECI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		

Skin (reported as ECI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		
Other (reported as ECI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

Each of the events above is described within this guidance document, along with site requirements for reporting these events to the Sponsor. The information collected should be entered into the narrative field(s) of the Adverse Event module in the database (please note, if narrative entry into the database is not available, please use the narrative text box on the 1727/AER Form). If additional Medical History or Concomitant Medications are reported, the Medical History and Concomitant Medication modules in the database must be updated.

In addition, the guidelines include recommendations on the management of these ECIs. These guidelines are intended to be applied when the physician determines the events to be related to pembrolizumab. Note: if after the evaluation the event is determined not to be related, the physician is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (below). Therefore, these recommendations should be seen as guidelines and the treating physician should exercise individual clinical judgment based on the patient. For any question of dose modification or other treatment options, the specific language in the protocol should be followed. Any questions pertaining to the collection of this information or management of ECIs should be directed to your local Sponsor contact.

Dose Modification/Discontinuation

The treatment guidance provides specific direction when to hold and/or discontinue pembrolizumab for each immune related adverse event. Of note, when the guidance states to "discontinue" pembrolizumab this is the permanent discontinuation of treatment with pembrolizumab. "Hold" means to stop treating with pembrolizumab but resumption of treatment may be considered assuming the patient meets the criteria for resumption of treatment.

2. ECI REPORTING GUIDELINES

ECIs are selected non-serious and serious adverse experiences that must be reported to Merck **within 24 hours** regardless of attribution to study treatment. The AEs listed in this document and any event that meets the ECI criteria (as noted) in Table 1 or in the respective protocol (event term and Grade) must be reported regardless of physician-determined causality with study medication and whether or not considered immune-related by the physician (unless otherwise specified). Physicians/study coordinators/designated site personnel are required to record these experiences as ECIs on the Adverse Experience electronic Case Report Forms (eCRFs) (or on paper) and to provide supplemental information (such as medical history, concomitant medications, investigations, etc.) about the event.

- Please refer to the Data Entry Guidelines (DEGs) for your protocol.
- Please refer to protocol for details on reporting timelines and reporting of Overdose and Drug Induced Liver Injury (DILI).

3. ECI CATEGORIES AND TERMS

This section describes the ECI categories and outlines subject management guidelines when an ECI is reported.

3.1 Pneumonitis

The following AE terms, if considered ≥ Grade 2, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Pneumonitis
- Interstitial lung disease
- Acute interstitial pneumonitis

If symptoms indicate possible new or worsening cardiac abnormalities additional testing and/or a cardiology consultation should be considered.

All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection**. It is important that patients with a suspected diagnosis of pneumonitis be managed as per the guidance below until treatment-related pneumonitis is excluded. Treatment of both a potential infectious etiology and pneumonitis in parallel may be warranted. Management of the treatment of suspected pneumonitis with steroid treatment should not be delayed for a therapeutic trial of antibiotics.** If an alternative diagnosis is established, the patient does not require management as below; however the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:

- Report as ECI
- Hold pembrolizumab.
- Consider pulmonary consultation with bronchoscopy and biopsy/BAL.
- Consider ID consult
- Conduct an in person evaluation approximately twice per week
- Consider frequent Chest X-ray as part of monitoring
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Second episode of pneumonitis – discontinue pembrolizumab if upon re-challenge the patient develops a second episode of Grade 2 or higher pneumonitis.

Grade 3 and 4 events:

- Report as ECI
- Discontinue pembrolizumab.
- Hospitalize patient
- Bronchoscopy with biopsy and/or BAL is recommended.
- Immediately treat with intravenous steroids (methylprednisolone 125 mg IV). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks.
- If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, treat with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures, as needed
- Add prophylactic antibiotics for opportunistic infections.

3.2 Colitis

The following AE terms, if considered ≥ Grade 2 or resulting in dose modification **or use of systemic steroids to treat the AE**, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Colitis
- Colitis microscopic
- Enterocolitis
- Enterocolitis hemorrhagic
- Gastrointestinal perforation
- Intestinal obstruction
- Necrotizing colitis
- Diarrhea

All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, a Clostridium difficile titer and endoscopy. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 Diarrhea/Colitis (4-6 stools/day over baseline, dehydration requiring IV fluids < 24 hours, abdominal pain, mucus or blood in stool):

- Report as ECI
- Hold pembrolizumab.
- Symptomatic Treatment
- For Grade 2 diarrhea that persists >1 week, and for diarrhea with blood and/or mucus,
    - Consider GI consultation and endoscopy to confirm or rule out colitis
    - Administer oral corticosteroids (prednisone 1-2 mg/kg QD or equivalent)
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- If symptoms worsen or persist > 3 days treat as Grade 3

Grade 3 Diarrhea/Colitis (or Grade 2 diarrhea that persist for greater than 3 days):

- Report as ECI
- Hold pembrolizumab.
- Rule out bowel perforation. Imaging with plain films or CT can be useful.
- Recommend consultation with Gastroenterologist and confirmation biopsy with endoscopy.

- Treat with intravenous steroids (methylprednisolone 125 mg) followed by high dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6 to 8 weeks in patients with diffuse and severe ulceration and/or bleeding.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider treatment with additional anti-inflammatory measures as described in the literature [5]. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures as needed.

Grade 4 events:

- Report as ECI
- Permanently discontinue pembrolizumab.
- Manage as per Grade 3.

3.3 Endocrine

The following AE terms, if considered ≥Grade 3 or if ≥Grade 2 and require holding/discontinuation/ modification of pembrolizumab dosing, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Adrenal insufficiency
- Hyperthyroidism
- Hypophysitis
- Hypopituitarism
- Hypothyroidism
- Thyroid disorder
- Thyroiditis

All attempts should be made to rule out other causes such as brain metastases, sepsis and/or infection. However the AE should be reported regardless of etiology.

Hypophysitis or other symptomatic endocrinopathy other than hypo- or hyperthyroidism

Grade 2 events:

- Report as ECI if appropriate
- Hold pembrolizumab
- Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.

- Pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis).
- Treat with prednisone 40 mg p.o. or equivalent per day. 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.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Consultation with an endocrinologist may be considered.

Grade 3 events:

- Report as ECI
- Hold pembrolizumab.
- Endocrine consultation is recommended.
- Rule out infection and sepsis with appropriate cultures and imaging.
- Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. 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.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis.
- Hospitalization and endocrine consultation should be considered.

Grade 4 events:

- Report as ECI
- Discontinue pembrolizumab.
- Manage as per Grade 3

Hyperthyroidism and 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 events (and Grade 3-4 hypothyroidism):

- Report as ECI if appropriate (see Table 1)
- Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
- Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency.
- Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.

- 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.
- Consultation with an endocrinologist may be considered.

Grade 3 hyperthyroidism events:

- Report as ECI
- Hold pembrolizumab.
- Rule out infection and sepsis with appropriate cultures and imaging.
- Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. 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.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Report as ECI
- Discontinue pembrolizumab.
- Manage as per Grade 3

3.4 Hematologic

The following AE term, if considered Grade ≥3 or requiring dose modification or use of systemic steroids to treat the AE, are considered an ECI and should be reported to the Sponsor within 24 hours of the event:

- Autoimmune hemolytic anemia
- Aplastic anemia
- Disseminated Intravascular Coagulation (DIC)
- Haemolytic Uraemic Syndrome (HUS)
- Idiopathic (or immune) Thrombocytopenia Purpura (ITP)
- Thrombotic Thrombocytopenic Purpura (TTP)
- Any Grade 4 anemia regardless of underlying mechanism

All attempts should be made to rule out other causes such as metastases, sepsis and/or infection. Relevant diagnostic studies such as peripheral blood smear, reticulocyte count, LDH, haptoglobin, bone marrow biopsy or Coomb's test, etc., should be considered to confirm the diagnosis. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:

- Report as ECI
- Hold pembrolizumab
- Prednisone 1-2 mg/kg daily may be indicated
- Consider Hematology consultation.
  Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 events:

- Report as ECI
- Hematology consultation.
- Hold pembrolizumab Discontinuation should be considered as per specific protocol guidance.
- Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Report as ECI
- Hematology consultation
- Discontinue pembrolizumab for all solid tumor indications; refer to protocol for hematologic malignancies.
- Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate

3.5 Hepatic

The following AE terms, if considered ≥ Grade 2 or greater (or any grade with dose modification or use of systemic steroids to treat the AE), are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Autoimmune hepatitis
- Hepatitis
- Transaminase elevations

All attempts should be made to rule out other causes such as metastatic disease, infection or other hepatic diseases. However the AE should be reported regardless of etiology.

Drug Induced Liver Injury (DILI)

In addition, the event must be reported as a Drug Induced Liver Injury (DILI) ECI, if the patient meets the laboratory criteria for potential DILI defined as:

- An elevated alanine transaminase (ALT) or aspartate transaminase (AST) lab value that is greater than or equal to three times (3X) the upper limit of normal (ULN) and
- An elevated total bilirubin lab value that is greater than or equal to two times (2X) ULN and
- At the same time, an alkaline phosphatase (ALP) lab value that is less than 2X ULN,
- As a result of within-protocol-specific testing or unscheduled testing.

Note that any hepatic immune ECI meeting DILI criteria should only be reported once as a DILI event.

Course of Action

Grade 2 events:

- Report as ECI
- Hold pembrolizumab when AST or ALT >3.0 to 5.0 times ULN and/or total bilirubin >1.5 to 3.0 times ULN.
- Monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume pembrolizumab per protocol
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Permanently discontinue pembrolizumab for patients with liver metastasis who begin treatment with Grade 2 elevation of AST or ALT, and AST or ALT increases ≥50% relative to baseline and lasts ≥1 week.

Grade 3 events:

- Report as ECI
- Discontinue pembrolizumab when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.
- Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary
- Treat with high-dose intravenous glucocorticosteroids for 24 to 48 hours. When symptoms improve to Grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg should be started and continued over no less than 4 weeks.

- If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.
- Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Report as ECI
- Permanently discontinue pembrolizumab
- Manage patient as per Grade 3 above

3.6 Neurologic

The following AE terms, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Autoimmune neuropathy
- Demyelinating polyneuropathy
- Guillain-Barre syndrome
- Myasthenic syndrome

All attempts should be made to rule out other causes such as metastatic disease, other medications or infectious causes. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:

- Report as ECI
- Moderate (Grade 2) – consider withholding pembrolizumab.
- Consider treatment with prednisone 1-2 mg/kg p.o. daily as appropriate
- Consider Neurology consultation. Consider biopsy for confirmation of diagnosis.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 and 4 events:

- Report as ECI

- Discontinue pembrolizumab
- Obtain neurology consultation. Consider biopsy for confirmation of diagnosis
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. If condition worsens consider IVIG or other immunosuppressive therapies as per local guidelines

When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

3.7 Ocular

The following AE terms, if considered Grade ≥2 or requiring dose modification **or use of systemic steroids to treat the AE**, is considered an ECI and should be reported to the Sponsor within 24 hours of the event:

- Uveitis
- Iritis

All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g. glaucoma or cataracts). However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:

- Evaluation by an ophthalmologist is strongly recommended.
- Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.
- Discontinue pembrolizumab as per protocol if symptoms persist despite treatment with topical immunosuppressive therapy.

Grade 3 events:

- Evaluation by an ophthalmologist is strongly recommended
- Hold pembrolizumab and consider permanent discontinuation as per specific protocol guidance.
- Treat with systemic corticosteroids such as prednisone at a dose of 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Evaluation by an ophthalmologist is strongly recommended
- Permanently discontinue pembrolizumab.
- Treat with corticosteroids as per Grade 3 above

3.8 Renal

The following AEs if ≥ Grade 2 are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Nephritis
- Nephritis autoimmune
- Renal failure
- Renal failure acute

Creatinine elevations ≥ Grade 3 or any grade with dose modification or use of systemic steroids to treat the AE.

All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury due to other chemotherapy agents. A renal consultation is recommended. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:

- Hold pembrolizumab
- Treatment with prednisone 1-2 mg/kg p.o. daily.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3-4 events:

- Discontinue pembrolizumab
- Renal consultation with consideration of ultrasound and/or biopsy as appropriate
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone IV or equivalent once per day.

When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

3.9 Skin

Rash and Pruritus

The following AEs should be considered as ECIs, if ≥ Grade 3 and should be reported to the Sponsor within 24 hours of the event:

- Pruritus
- Rash
- Rash generalized
- Rash maculo-papular
- In addition to CTCAE Grade 3 rash, any rash that is considered clinically significant, in the physician's judgment, should be treated as an ECI. Clinical significance is left to the physician to determine, and could possibly include rashes such as the following:
  - rash with a duration >2 weeks; OR
  - rash that is >10% body surface area; OR
  - rash that causes significant discomfort not relieved by topical medication or temporary cessation of study drug.

Other Skin ECIs

The following AEs should **always** be reported as ECIs, regardless of grade, and should be reported to the Sponsor within 24 hours of the event:

- Dermatitis exfoliative
- Erythema multiforme
- Steven's Johnson syndrome
- Toxic epidermal necrolysis

Please note, the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:

- Symptomatic treatment should be given such as topical glucocorticosteroids (e.g., betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral anti-pruritics (e.g., diphenhydramine HCl or hydroxyzine HCl).
- Treatment with oral steroids is at physician's discretion for Grade 2 events.

Grade 3 events:

- Hold pembrolizumab.
- Consider Dermatology Consultation and biopsy for confirmation of diagnosis.
- Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Permanently discontinue pembrolizumab.
- Dermatology consultation and consideration of biopsy and clinical dermatology photograph.
- Initiate steroids at 1 to 2 mg/kg prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

3.9.1. Immediate Evaluation for Potential Skin ECIs

A. <u>Photographs</u>:

Every attempt should be made to get a photograph of the actual ECI skin lesion or rash as soon as possible**. Obtain appropriate consent for subject photographs if a consent form addendum is required by your IRB/ERC.**

- Take digital photographs of:
  - the head (to assess mucosal or eye involvement),
  - the trunk and extremities, and
  - a close-up of the skin lesion/rash.

- If possible, a ruler should be placed alongside the site of a skin occurrence as a fixed marker of distance.
- The time/date stamp should be set in the 'ON' position for documentation purposes.
- Photographs should be stored with the subject's study records.

- The Sponsor may request copies of photographs. The local study contact (e.g., CRA) will provide guidance to the site, if needed.

B. Past Medical History:

Collect past medical history relevant to the event, using the questions in Appendix 2 (Past Medical History Related to Dermatologic Event) as a guide. Any preexisting conditions not previously reported (e.g., drug allergy) should be entered into the Medical History eCRF.

C. Presentation of the Event:

Collect information on clinical presentation and potential contributing factors using the questions in Appendix 3 (Presentation of the Dermatologic Event) as a guide. This information should be summarized and entered in narrative format in the AE eCRF. Please use the available free-text fields, such as Signs and Symptoms. Note pertinent negatives where applicable to reflect that the information was collected. Any treatments administered should be entered on the Concomitant Medication eCRF.

D. Vitals Signs and Standard Laboratory Tests:

Measure vital signs (pulse, sitting BP, oral temperature, and respiratory rate) and record on the Vital Signs eCRF. Perform standard laboratory tests (CBC with manual differential and serum chemistry panel, including LFTs).

E. Focused Skin Examination:

Perform a focused skin examination using the questions in Appendix 4 (Focused Skin Examination) as a guide. Information should be summarized and entered on the Adverse Experience eCRF as part of the narrative.

F. Dermatology Consult

Refer the subject to a dermatologist as soon as possible.

- For a **"severe rash"**, the subject must be seen within **1-2 days** of reporting the event.
- For **clinically significant rash**, the subject should be seen within **3-5 days**.

The dermatologist should submit a biopsy sample to a certified dermatopathology laboratory or to a pathologist experienced in reviewing skin specimens.

The site should provide the dermatologist with all relevant case history, including copies of clinical photographs and laboratory test results.

3.10 Other

The following AEs, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Myocarditis
- Pericarditis
- Pancreatitis
- Any additional Grade 3 or higher event which the physician considers to be immune related

All attempts should be made to rule out other causes. Therapeutic specialists should be consulted as appropriate. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events or Grade 1 events that do not improve with symptomatic treatment:

- Withhold pembrolizumab.
- Systemic corticosteroids may be indicated.
- Consider biopsy for confirmation of diagnosis.
- If pembrolizumab held and corticosteroid required, manage as per grade 3 below.

Grade 3 events:

- Hold pembrolizumab
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. Otherwise, pembrolizumab treatment may be restarted and the dose modified as specified in the protocol

Grade 4 events:

- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.
- Discontinue pembrolizumab

3.11 Infusion Reactions

The following AE terms, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Allergic reaction
- Anaphylaxis
- Cytokine release syndrome
- Serum sickness
- Infusion reactions
- Infusion-like reactions

Please note, the AE should be reported regardless of etiology.

Course of Action

Refer to infusion reaction table in the protocol and below.

Infusion Reactions

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

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion.** 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.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg p.o. (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg p.o. (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

3.12 Follow-up to Resolution

Subjects should be followed to resolution. The Adverse Experience eCRF should be updated with information regarding duration and clinical course of the event. Information obtained from the consulting specialist, including diagnosis, should be recorded in the appropriate AE fields. Free-text fields should be used to record narrative information:

- Clinical course of the event
- Course of treatment
- Evidence supporting recovery
- Follow-up to the clinical course

Any treatments administered for the event should also be entered in the Concomitant Medication eCRF.

4. REFERENCES

1. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nature Reviews Cancer 2012; 12:252-264.

2. Weber JS Practical Management of Immune-Related Adverse Events from Immune Checkpoint Protein Antibodies for the Oncologist. American Society of Clinical Oncology 2012; 1092-9118/10/1-10.

3. Weber JS, Ka¨hler KC, and Hauschild A. Management of Immune-Related Adverse Events and Kinetics of Response With Ipilimumab. J Clin Oncol 30. 2012. http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2012.41.6750.

4. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, et al. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. N Engl J Med 363:711-723, 2010.

5. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer. N Engl J Med 2012; 366:2443-2454.

6. Brahmer JR, Tykodi SS, Chow LQM, Hwu WJ, et al. Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer. N Engl J Med 2012; 366:2455-2465.

7. Weber J, Thompson JA, Hamid O, et al: A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. Clin Cancer Res 15:5591-5598, 2009.

8. Lemech C and Arkenau HT. Novel Treatments for Metastatic Cutaneous Melanoma and the Management of Emergent Toxicities. Clinical Medicine Insights: Oncology 2012:6 53–66.

9. Phan GQ, Weber JS, and Sondak VK. CTLA-4 Blockade with Monoclonal Antibodies in Patients with Metastatic Cancer: Surgical Issues. Annals of Surgical Oncology 15(11):3014–3021.

10. Bristol-Myers Squibb: YERVOY (ipilimumab): Serious and fatal immune-mediated adverse reactions—YERVOY Risk Evaluation and Mitigation Strategy (REMS). http://www.yervoy.com/hcp/rems.aspx

11. Bristol-Myers Squibb: YERVOY (ipilimumab) prescribing information revised March 2011. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125377s0000lbl.pdf

5. APPENDIX 1 –EVENTS OF CLINICAL INTEREST (ECI) – REFERENCE TABLE

Pneumonitis (reported as ECI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis		
Hematologic (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Haemolytic Uraemic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as ECI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE**)**		
Hepatitis	Autoimmune hepatitis	Transaminase elevations
Infusion Reactions (reported as ECI for any grade)		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions

Neurologic (reported as ECI for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as ECI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as ECI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as ECI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin (reported as ECI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		
Other (reported as ECI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

6. APPENDIX 2 – PAST MEDICAL HISTORY RELATED TO DERMATOLOGIC EVENT

Past Medical History:

Any preexisting conditions not previously reported (e.g., drug allergy) should be entered into the Medical History eCRF.

1. Does the subject have any allergies? □ Yes □ No

If yes, please obtain the following information:

a. Any allergy to drugs (including topical or ophthalmic drugs)? □ Yes □ No

List the drug name(s) and describe the type of allergic response (e.g. rash, anaphylaxis, etc): _____

_____

b. Any allergy to external agents, such as laundry detergents, soaps, poison ivy, nickel, etc.? □ Yes □ No

Describe the agent and type of allergic response: _____

_____

c. Any allergy to food? □ Yes □ No

Describe the food and type of allergic response: _____

_____

d. Any allergy to animals, insects? □ Yes □ No

Describe the allergen and type of allergic response: _____

_____

e. Any other allergy? □ Yes □ No

Describe the allergen and type of allergic response: _____

_____

2. Does the subject have any other history of skin reactions, skin eruptions, or rashes? □ Yes □ No

If so what kind? _____

3. Has the subject ever been treated for a skin condition? □ Yes □ No

If so what kind? _____

4. Is the current finding similar to a past experience? □ Yes □ No

7. APPENDIX 3 – PRESENTATION OF THE DERMATOLOGIC EVENT

Presentation of the event:

Collect information on clinical presentation and potential contributing factors. Key information should be summarized and entered on the Adverse Experience eCRF. Any treatments administered should be entered on the Concomitant Medication eCRF.

1. What is the onset time of the skin reaction, skin eruption, or rash relative to dose of study drug? _____

2. Has the subject contacted any known allergens? □ Yes □ No

If so what kind? _____

3. Has the subject contacted new, special, or unusual substances (e.g., new laundry detergents, soap, personal care product, poison ivy, etc.)? □ Yes □ No

If so what kind? _____

4. Has the subject taken any other medication (over the counter, prescription, vitamins, and supplement)? □ Yes □ No

If so what kind? _____

5. Has the subject consumed unaccustomed, special or unusual foods? □ Yes □ No

If so what kind? _____

6. Does the subject have or had in the last few days any illness? □ Yes □ No

If so what kind? _____

7. Has the subject come into contact with any family or house members who are ill? □ Yes □ No

If so who and what? _____

8. Has the subject recently been near children who have a skin reaction, skin eruption, or rash (e.g. *Molluscum Contagiosum*)? □ Yes □ No

9. Has the subject had recent sun exposure? □ Yes □ No

10. For the current rash, have there been any systemic clinical signs? □ Yes □ No

If so what kind? _____

i. Anaphylaxis? □ Yes □ No
ii. Signs of hypotension? □ Yes □ No
iii. Signs of dyspnea? □ Yes □ No
iv. Fever, night sweats, chills? □ Yes □ No

11. For the current rash, has the subject needed subcutaneous epinephrine or other systemic catecholamine therapy? □ Yes □ No

If so what kind? _____

12. For the current rash, has the subject used any other medication, such as inhaled bronchodilators, antihistaminic medication, topical corticosteroid, and/or systemic corticosteroid? □ Yes □ No

List medication(s) and dose(s): _____

13. Is the rash pruritic (itchy)? □ Yes □ No

8. APPENDIX 4 – FOCUSED SKIN EXAMINATION

Focused Skin Examination:

Key information should be summarized and entered on the Adverse Experience eCRF.

Primary Skin Lesions Description

Color: _____

General description:

_____

_____

Describe the distribution of skin reaction, skin eruption, or rash on the body:

_____

_____

Is skin reaction, skin eruption, or rash resolving or continuing to spread?

_____

_____

Any associated signs on physical examination?

_____