Product: MK-3475
Protocol/Amendment No.:

2014-1020
Version 16

INDUSTRY SUPPORT: Merck

TITLE: Phase I/II Trial of MK-3475 and Hypofractionated Stereotactic Radiation Therapy in Patients with NSCLC

IND NUMBER:

EudraCT NUMBER:

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1.0 TRIAL SUMMARY

Abbreviated Title	MK-3475 and radiation
Trial Phase	I/II
Clinical Indication	Stage IV non-small cell lung cancer
Trial Type	Treatment
Type of control	NA
Route of administration	IV and external beam
Trial Blinding	NA
Treatment Groups (Phase I)	Group 1: SBRT concurrent MK-3475, Group 2: WFRT concurrent MK-3475
Treatment Groups (Phase II)	Group 1: SBRT concurrent MK-3475, Group 2: MK-3475 with salvage SBRT, Group 3: WFRT concurrent MK-3475, Group 4: MK-3475 with salvage WFRT, Group 5: SBRT or WFRT + MK3475 + low dose XRT
Number of trial subjects	Phase I 24 pts Phase II 80, Phase II group 5 40 pts Total 144 pts
Estimated duration of trial	4 years
Duration of Participation	2.5 years

2.0 TRIAL DESIGN

2.1 Trial Design

This study will consist of a phase I component to establish a maximum tolerable dose (MTD) for the combination of radiation therapy (either stereotactic body radiation therapy [SBRT] or non-stereotactic wide-field radiation therapy [WFRT]) for local treatment of thoracic or liver lesions concurrent with systemic administration of MK-3475 (pembrolizumab). The choice of radiation treatment (for either SBRT or WFRT) will be at the discretion of the treating radiation oncologist. There will be a subsequent stage II component to determine preliminary evidence of efficacy. The phase I component will initiate in all treatment groups with 100 mg MK-3475 every 21 days for a total of 16 cycles (12 months). To be eligible, all patients must have metastatic NSCLC with at least one thoracic or liver lesion amenable to radiation therapy (either WFRT or SBRT) and at least one additional non-contiguous lesion amenable to radiographic monitoring. For all phases of the study the first dose of MK-3475 will optimally be administered on a Monday. Radiation can be ideally started that same day or the day after, but can also be initiated anytime during the week when MK-3475 was administered. All dates proposed in this study are given an allowance of +/- 3 days from the scheduled date.

Phase I Component:

The phase I component will consist of two parallel treatment groups. Patients will be considered for the first treatment group if they exhibit a thoracic or liver lesion of size and location amenable to SBRT. In the first treatment group, patients will receive SBRT to a total dose of 50 Gy in 12.5 Gy fractions (4 fractions total) concurrent with MK-3475 administration.

The phase I component will consist of a 3+3 dose escalation design with anticipated escalation from 100 mg to 200 mg IV MK-3475.

Patients will be considered for the second treatment group if they exhibit a thoracic or liver lesion of size or location not amenable to SBRT, but amenable to WFRT. In this treatment group, WFRT will be administered to a total dose of 45 Gy in 3 Gy fractions to the PTV (15 fractions total), a simultaneous integrated boost will be allowed to increase the GTV dose up to 60Gy, via the radiation modality judged most appropriate by the treating radiation oncologist: either 3 dimensional conformation radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT), or proton beam therapy (PBT). MK-3475 will be subject to the same dose modification scheme as in the first treatment group.

Phase II Component:

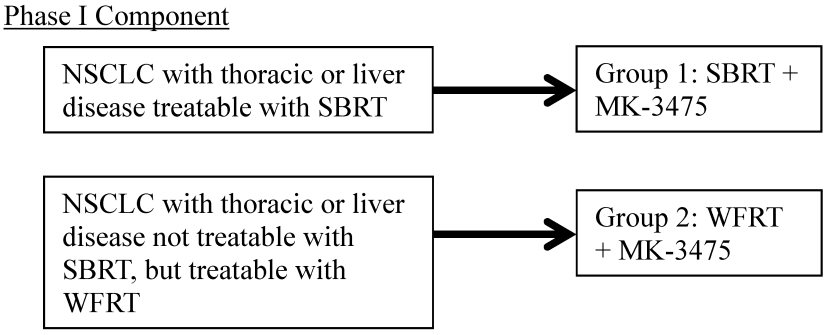
The phase II component will consist of five parallel treatment groups utilizing the MK-3475 dose determined in the previous phase I component.

Patients will be randomized between the first and second treatment groups if they exhibit a thoracic or liver lesion with size and location amenable to SBRT. In the first treatment group, patients will be treated with upfront concurrent SBRT and MK-3475. In the second treatment group, patients will be treated with MK-3475 without radiation. At the first planned efficacy evaluation (5 weeks) and any imaging timepoint after this while on study, patients exhibiting progressive disease (PD) will be treated with SBRT concurrent with the remaining cycles of MK-3475. To allow adequate time for treatment planning, radiation can be delayed up to 2 weeks in patients receiving salvage radiation therapy. In the event that lesion size has progressed to the point where the attending physician no longer considers SBRT safe, then the patient will be treated with WFRT and analyzed as part of the fourth treatment group (see below).

Patients will be randomized between the third and fourth treatment groups if they exhibit a thoracic or liver lesion with size and location not amenable to SBRT, but amenable to WFRT. In the third treatment group, patients will be treated with upfront concurrent WFRT and MK-3475. In the fourth treatment group, patients will be treated with MK-3475 without radiation. The decision on when to start XRT will be assessed first at week 5 (after the second dose of MK-3475). If a patient has PD based on irRC (section 7.1.2.6.2) then XRT will be delivered after the third dose of MK-3475. While pts with SD or PR will not start XRT and will continue to be followed. These patients will then have follow up CT scans every 6 weeks. However, patients enrolled in Phase II Groups 1, 3 and 5 will have imaging done prior to cycle 3 then repeat imaging will be done every 12 weeks +/- 7 days or at the discretion of the treating physician for the remainder of the trial; any patient at this point with PD will then have XRT delivered with the sixth dose of MK-3475.

Phase I, Treatment Group 1: Patients with 1-4 liver or thoracic lesion(s) amenable to SBRT will be treated with concurrent MK-3475 and SBRT: 50 Gy in 4 fractions.

Phase I, Treatment Group 2: Patients with 1-4 liver or thoracic lesion(s) not amenable to SBRT, but amenable to WFRT, will be treated with concurrent MK-3475 and WFRT: 45 Gy in 15 fractions.



Dose Modification: Phase I

Dose Level	**Phase I MK-3475 Doses**
2	MK-3475 200mg IV
1	MK-3475 100mg IV

Phase II, Treatment Group 1: Patients with 1-4 liver or thoracic lesion(s) amenable to SBRT will be randomized between this group and **Phase II, Treatment Group 2**. Treatment will consist of concurrent MK-3475 and SBRT: 50 Gy in 4 fractions.

Phase II, Treatment Group 2: Patients with 1-4 liver or thoracic lesion(s) amenable to SBRT will be randomized between this group and **Phase II, Treatment Group 1**. Treatment will consist of MK-3475 alone. If progressive disease (PD) is noted at 5 weeks (first planned efficacy evaluation) patients will be treated with SBRT concurrent with their remaining cycles of MK-3475. In the event that lesion size has progressed to the point where the attending physician no longer considers SBRT safe, then the patient will be salvaged with WFRT and analyzed as part of the fourth treatment group (see below).

Patients who are receiving a PD-1 inhibitor (Pembrolizumab, Nivolumab, etc.) not on this study and are exhibiting progressive disease can be enrolled directly into Phase II, Treatment Group 2 if they exhibit a liver or thoracic lesion amenable to SBRT and meet all other study inclusion and exclusion requirements. Patients who access the study in this manner will initiate SBRT and concurrent MK-3475 at this study MTD for a total of 32 cycles (counting prior cycles of PD-1 inhibitor).

Phase II, Treatment Group 3: Patients with 1-4 liver or thoracic lesion(s) not amenable to SBRT, but amenable to WFRT, will be randomized between this group and **Phase II, Treatment Group 4**. Patients will be treated with MK-3475 and WFRT: 45 Gy in 15 fractions.

Phase II, Treatment Group 4: Patients with 1-4 liver or thoracic lesion(s) not amenable to SBRT, but amenable to WFRT, will be randomized between this group and **Phase II, Treatment Group 3**. Treatment will consist of MK-3475 alone. If PD is noted at 6 weeks (first planned efficacy evaluation) patients will be treated with WFRT concurrent with their remaining cycles of MK-3475.

Patients who are receiving a PD-1 inhibitor (Pembrolizumab, Nivolumab, etc.) not on this study and are exhibiting progressive disease can be enrolled directly into Phase II, Group 4 if they exhibit a liver or thoracic lesion amenable to WFRT and meet all other study inclusion and exclusion requirements. Patients who access the study in this manner will initiate WFRT and concurrent MK-3475 at this study MTD for a total of 32 cycles (counting prior cycles of PD-1 inhibitor).

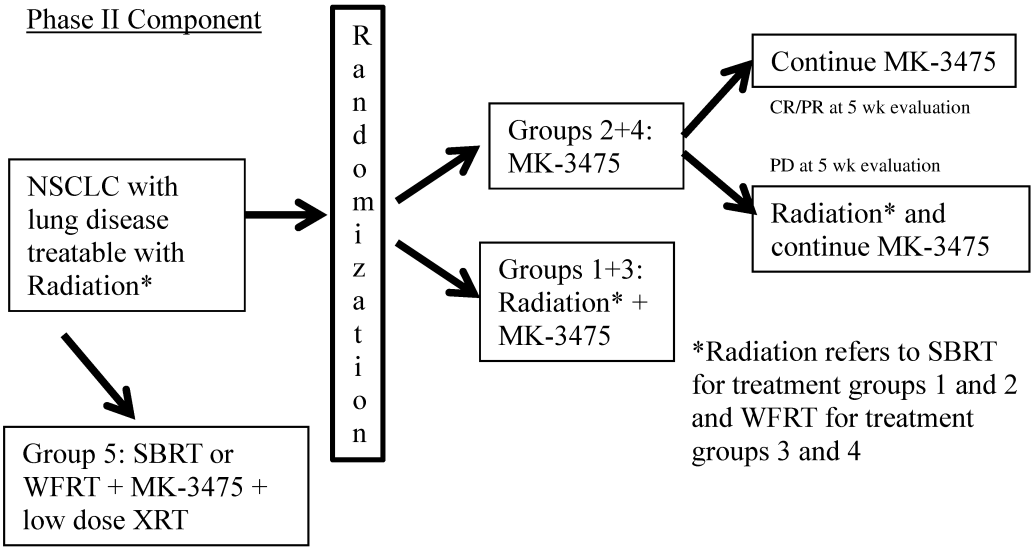
A formal toxicity monitoring mechanism will carry over to the phase II aspect of this trial. Using the simple rule that for each cohort that we will stop accrual if the aggregated DLT rate at any time exceeds 33%, for toxicity attributed to the combination of MK-3475 + radiation.

Phase II, Treatment Group 5: Patients with lesion(s) amenable to SBRT or WFRT, will be assigned to this group (n=40). Treatment will consist of up to 32 cycles MK-3475 and WFRT: 45 Gy in 15 fractions to the primary lesions and low dose radiation (500-1000cGy) radiation to other lesions or SBRT: 50 Gy in 4 fractions to the primary lesions and low dose radiation (500-1000cGy) to the other lesions. Low dose XRT will be defined as a total dose between 500-1000cGy, it will be delivered at the same time as the high dose radiation over the same number of fractions, so if we are using 50Gy in 4 fractions low dose will be delivered over 4 fractions, while for pts receiving 15 fractions of high dose then the low dose will be delivered over 15 fractions.

Phase II Treatment Groups

Patient Lung Lesion Size and Location

		Lesion treatable with SBRT (n=80)	**Lesion treatable with WFRT (n=40)**
Randomization	**MK-3475 and concurrent radiation**	Treatment Group 1 (n=20): SBRT+MK-3475	Treatment Group 3 (n=20): WFRT+MK-3475
	MK-3475 alone (radiation if PD at 3 mo. evaluation)	Treatment Group 2 (n=20): MK-3475 alone (if PD then SBRT+MK-3475)	Treatment Group 4 (n=20): MK-3475 alone (if PD then WFRT+MK-3475)
	MK-3475 and concurrent high and low dose radiation	Treatment Group 5 (**n=40**): SBRT or WFRT + MK-3475 + low dose XRT	



2.2 Trial Diagrams

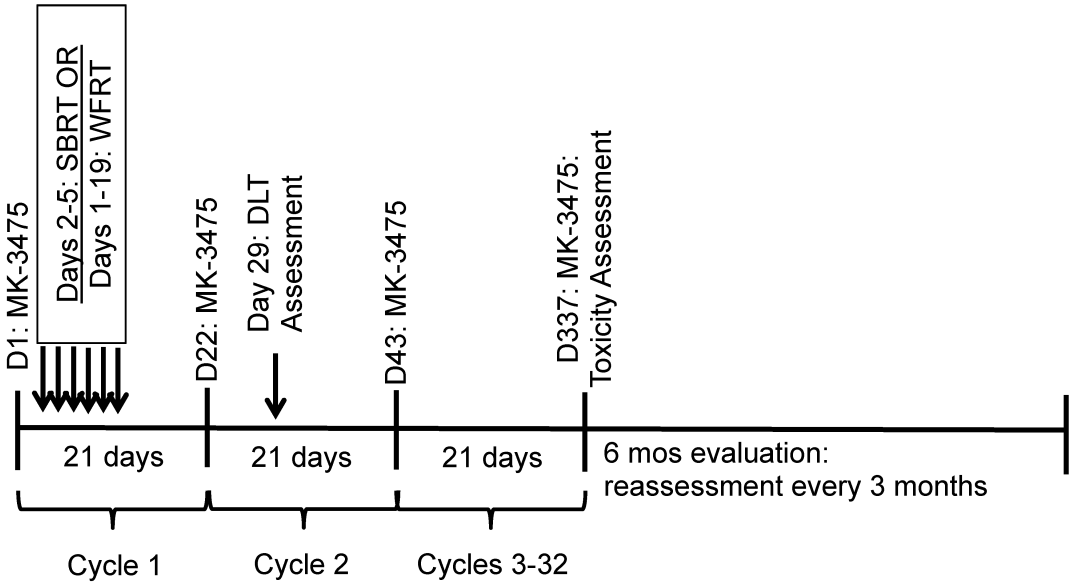


Diagram of treatment schedule for concurrent treatment groups: Phase I Treatment Groups 1 and 2 and Phase II Treatment Groups 1, 3 and 5. (Indicated DLT assessment window applicable for Phase I dose escalation consideration).

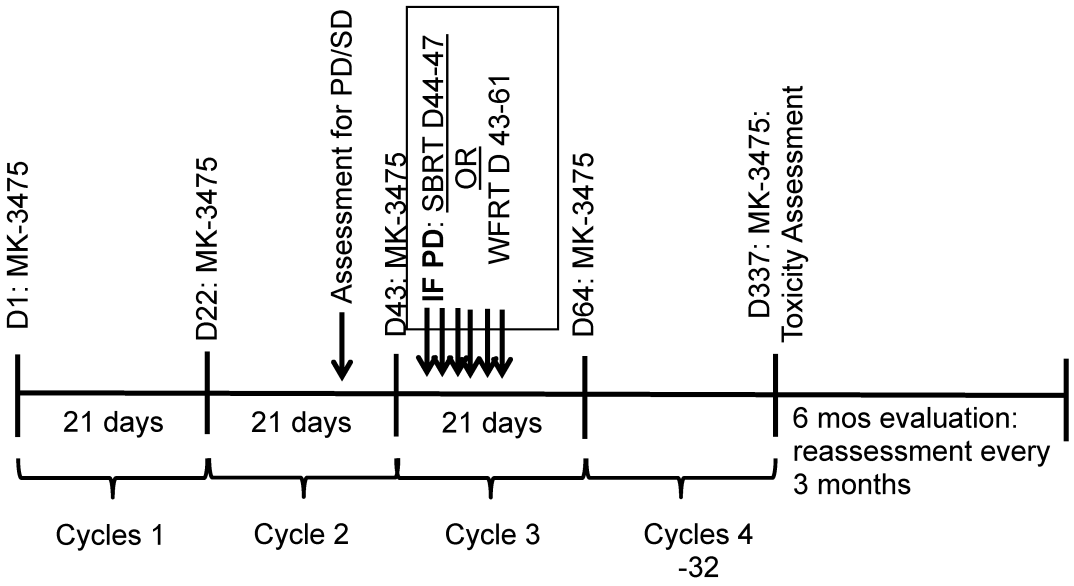


Diagram of treatment schedule for Phase II Groups 2 and 4 (showing progressive disease [PD] assessment and radiation window)

3.0 PHASE I OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To evaluate the safety and toxicity profile of intravenous MK-3475 administered in combination with stereotactic body radiation therapy (SBRT) targeting 1-4 liver or thoracic lesion(s) in patients with metastatic NSCLC

(2) **Objective:** To evaluate the safety and toxicity profile of intravenous MK-3475 administered in combination with non-stereotactic wide-field radiation therapy (WFRT) targeting 1-4 liver or thoracic lesion(s) in patients with metastatic NSCLC.

(3) **Objective:** To determine the maximum tolerated dose (MTD) and dose limiting toxicities (DLTs) of MK-3475 and SBRT combination therapy.

(4) **Objective:** To determine the maximum tolerated dose (MTD) and dose limiting toxicities (DLTs) of MK-3475 and WFRT combination therapy.

Hypothesis: The combination of MK-3475 and radiation (either SBRT or WFRT) is tolerable without a high rate of DLTs.

3.2 Phase II Objective(s) & Hypothesis(es)

(1) **Primary Objective**: The primary objective is to determine the rate of out-of-field objective responses (either CR or PR) of the non-irradiated disease sites, regardless of their location, thoracic or otherwise.

(2) **Secondary Objective:** The secondary objective is to determine the addition of XRT to MK-3475 can improve the PFS rate compared to MK-3475 alone and to determine if low dose radiation therapy to a secondary site can improve the PFS rate compared to the single site XRT with MK-3475 and with MK-3475 alone.

Hypothesis: The combination of MK-3475 and radiation (SBRT, WFRT, or SBRT/WBRT with lose dose XRT) can lead to tumor regression both within the radiation treatment field and outside the field via the abscopal effect and treating a secondary lesion with low dose radiation improves abscopal response.

3.3 Exploratory Biomarkers

The objective of this portion of the study is to correlate systemic serum markers, obtainable by peripheral venous access to patient responses and observed toxicities. Voluntary participation in this portion of the protocol is optional for all study participants.

Systemic lymphocyte counts obtained from routine CBC with differential will be analyzed and associated with clinical outcomes and toxicities from the lab draws obtained throughout this protocol.

Radiomic data from imaging modalities including CT and MRI obtained as standard of care or as part of this study will be evaluated to identify markers that predict treatment response and toxicity.

Tumor-specific antigens that can elicit cellular and humoral immunity, are expressed on cancer cells and can be identified for development of immunotherapy in these patients. Patient serum will be analyzed to assess candidate tumor-associated antigens or genes that elicit cellular and humoral immune responses in patients with solid tumors. This analysis will correlate antigen-expression and immune responses with patient data such as tumor type, treatment response, and clinical outcome of patients who have received ipilimumab and SBRT.

This study will be done in collaboration with Dr. Padmanee Sharma, MD/PhD, and Dr. James Allison, PhD and covered by the immunotherapy platform supported by an MD Anderson IRB approved laboratory protocol. All samples will be collected using procedures characterized in this protocol and all patients will be consented for procedures done under this optional protocol separately. Specifically, this study will allow for the collection of up to 8 cc of blood, to be drawn at the time of routine blood-draw, to be used for biomarker analysis. Serum samples will be collected in 10 cc green top, heparin tubes for biomarker analysis. Optional biopsies will be collected twice before drug initiation after radiation.

Tumor Tissue Samples for Exploratory Research
From all consented patients enrolled on this study, if the archival tissue is available, a portion of the submitted archival tumor tissue (up to 10 slides from the tissue submitted) will be used to assess exploratory biomarkers. Assessments may include but not limited to testing for molecular alterations (NGS), IHC of PDL1, protein expression (RPPA), methylation status. Samples will be collected and stored in Dr. James Welsh's and Dr. John Heymach's laboratories until analysis. We will utilize Tissue Station for sample de-identification and record management.

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[2-6]. 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[7,10-12]. 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[13,18-20]. 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

PN001 is the Phase I first in human (FIH) study of MK-3475 and represents the most mature dose escalation study to date. This study examined 3 dose levels (1, 3, and 10 mg/kg) in patients with solid tumors. As of 26-Jul-2013, there have been 789 patients, with preliminary safety data available from 479 patients. Within this study, MK-3475 has been generally well-tolerated at doses up to 10 mg/kg every other week without DLTs (IB ver. 6).

Regarding efficacy, Hamid et al. reported on 135 advanced melanoma patients treated with MK-3475 10 mg/kg every 2-3 weeks or 2 mg/kg every 3 weeks. At the 12 week assessment, the response rate via Response Evaluation Criteria in Solid Tumors (RECIST) was 38%[22]. Of the patients who exhibited a response, 82% maintained responses at a median follow-up of 11 months. Of note, the response rate was not modified by prior ipilimumab (anti-CTLA4 antibody) immunotherapy. Toxicity was manageable with 79% drug-related adverse events and 13% grade 3 or 4 toxicities. Categorically, the most frequent toxicities were fatigue, rash/pruritus, and diarrhea. Treatment related pneumonitis was reported in 4% of patients, none of which were grade 3 or higher. Most toxicities improved after discontinuation of MK-3475 and glucocorticoid administration[22].

Reports with other PD-1 inhibitors have been similarly promising. Topalian et al. reported on 296 patients with advanced solid malignancies treated with 0.1 to 10 mg of the anti-PD-1 antibody BMS-936558 (nivolumab) every 2 weeks. Once again the rate of grade 3-4 toxicities was manageable at 14%. Substantial response rates were observed in patients with non-small cell lung cancer (NSCLC) (18%), melanoma (28%), and renal cell carcinoma (RCC) (27%)[23]. Of 31 patients with at least 1 year follow up, 20 patients had durable responses lasting at least 1 year. Combination immunotherapies have shown even greater rates of efficacy compared to monotherapy. Wolchock et al. reported on combination nivolumab and ipilimumab in 53 patients with advanced melanoma[24]. A high rate of objective response was observed in patients receiving the concurrent regime (40%)[24].

4.1.3 Radiation therapy

The development of precise radiation beam-shaping along with improved algorithms for target tracking, greater computing power for radiation dosimetry, and better techniques to minimize setup variations has facilitated the implementation of stereotactic body radiation therapy (SBRT). This modality allows for highly conformal treatment with markedly increased radiation dose per fraction (>10 Gy per fraction). This process, termed hypofractionation delivers a high biological effective dose (BED) of radiation with high precision to the tumor while sparing normal tissue toxicities, thus achieving high rates of local control[25-27].

In the setting of numerous prospective single arm trials, SBRT has shown efficacy in the control various metastatic disease sites. Herfrath et al reported on a phase I/II clinical trial that achieved local tumor control rates of 81% 18 months following SBRT (14-26 Gy total dose) with no major side effects[25]. More contemporary trials have reported even better rates of local control with higher SBRT doses. Rusthoven et al. reported local control rates of 92% at 2 years following SBRT (36-60 Gy)[26]. Similar results have been reported in the control of pulmonary metastases, with prospective trials reporting 96% local control in 1-3 pulmonary lesions 2 years following SBRT treatment (48-60 Gy)[27].

Complementary to SBRT are more conventional forms of radiation therapy. Given the high degree of cytotoxicity observed with the hypofractionated schedules utilized in SBRT, limitations exist to its application. Large tumors or centrally located tumors are often untreatable with SBRT given the unacceptably high doses that would be administered to nearby critical structures. For these tumors, conventional radiation therapy utilizing wider fields (for the purpose of this document will be labelled wide field radiation therapy[WFRT]) and lower doses (2-3 Gy per fraction) over more fractions have been employed[28,29]. Various modalities have been utilized to administered WFRT including proton beam therapy (PBT), intensity modulated radiation therapy (IMRT), and 3D conformal radiation therapy (3DCRT). This form of radiation produces a “gentler” treatment, allowing greater time for normal tissues recovery.

In addition to local control, radiation therapy has also been shown to promote a potent immunogenic release of tumor antigen and local cytokines, priming the adaptive immune system towards tumor control[30]. Such immune education has been shown to promote distal disease control (also known as the abscopal effect) both in pre-clinical models, clinical cases, and early clinical trials. Clinical descriptions of this phenomenon have been predominately limited and most often in sporadic case reports where unexpected yet pronounced distal tumor regression are observed outside of radiation fields[31-33]. Furthermore, we have preliminary preclinical and clinical data suggesting that lesions receiving low dose radiation elicit better local control and a more robust immune response, further promoting abscopal response.

4.2 Rationale

A number of early phase I trials have begun to prospectively investigate the pairing of immunotherapies with radiation with the goal of achieving the abscopal effect. Brody et al. reported on a phase I clinical trial on 15 patients with advanced low-grade lymphomas. Objective responses in non-irradiated sites were observed in 6 patients following 4 Gy

radiation coupled with the injection of an immune-stimulating C-G enriched synthetic oligodeoxynucleotide, an established toll-like receptor agonist[34]. Similar results were observed with this treatment for cutaneous lymphomas[35]. Another strategy was employed by Seung et al., who treated 11 metastatic melanoma and renal cell carcinoma patients with 60 Gy SBRT given in 3 fractions followed by adjuvant systemic IL-2 administration in the setting of a prospective trial[36]. Complete metabolic resolution in non-irradiates sites were observed in 6 patients with partial responses in 2 others. Assessment of responders found significantly greater frequencies of proliferating CD4+ T-cells expressing an early activated phenotype, providing evidence of an immune-mediated phenomenon[36]. These trials provide prospective proof-of-concept that immunotherapy in combination with radiation can produce systemic responses. In addition, there is a growing number of case reports documenting the abscopal effect among patients treated with radiation and checkpoint inhibitors for melanoma[37,38] and NSCLC[33].

We therefore hypothesize that host T-cells when primed with the immune potentiating effects of MK-3475 will respond to the antigen release produced by tumor irradiation to promote both local and systemic anti-tumor responses. We further hypothesize that this immunologic anti-tumor response will increase the rates of local control and simultaneously produce systemic regression of non-irradiated tumors.

4.2.1 Rationale for the Trial and Selected Subject Population

NSCLC represents the leading cause of cancer-related deaths in the United States. The majority of patients diagnosed with this disease will die progression including metastases. Within the setting of advanced disease, it is accepted clinical practice to palliate pulmonary disease with radiation therapy as progression in this organ will eventually occlude bronchi, reduce pulmonary capacity, produce pulmonary effusions, and erode adjacent structures including the ribs, heart, diaphragm, major nerves, and vertebrae. As such the use of either SBRT or WBRT is considered within the standard of care for this metastatic population.

NSCLC has been shown to be susceptible to immune therapies, exhibiting a substantial rate of disease response after treatment with the anti PD-1 antibody nivolumab (18%)[23]. Furthermore, a recent report by Golden et al. described the abscopal effect in a patient with metastatic NSCLC. Follow concurrent administration of ipilimumab and fractionated radiation to 30 Gy in 5 fractions (6 Gy per fraction) there was resolution of disease in un-irradiated sites in the lung, liver, and skeleton[33]. Interest in immunotherapy treatments for lung cancer has resulted in the development of several trials utilizing immunotherapy agents including MK-3475 (NCT02039674, NCT01295827), nivolumab (NCT01673867), and ipilimumab (NCT01331525) in addition to others (NCT02000947).

Given the aggressive metastatic nature of NSCLC and indications of susceptibility to immunologic therapies, we believe that this disease represents an ideal candidate to test the combination of MK-3475 and radiation. We believe that development of this therapeutic combination has the potential to produce immediate actionable and efficacious therapies for the large number of patients with this disease.

4.2.2 Rationale for Dose Selection/Regimen/Modification

The initial radiation doses in this protocol represents standard of care at this institution and others for the palliation of NSCLC: 50 Gy in 4 fractions SBRT for generally smaller peripheral lesions and 45 Gy in 15 fractions WFRT for larger central lesions. These two regimes are comprehensive and will cover the spectrum of lung disease for the majority of metastatic NSCLC. By including both forms of radiation, these results may also directly lead into the future study of earlier stage I-III disease. We also will have a group of patients that receive additional low dose radiation to a secondary lesion. The rationale for this is supported by the observation that, within standard radiation treatment plans, secondary lesions that received low dose radiation may be more likely to not only have a local response, but also generate a greater systemic immune response and increase the likelihood of an abscopal response.

Given that pathologically high levels of PD-L1 is expressed within the tumor microenvironment[39], we hypothesize that blockade of the PD-1/PD-L1 signaling axis will better facilitate radiation-induced immunogenic cell death if administered concurrently with radiation, facilitating the abscopal response.

Regarding the phase I component, as both palliative radiation therapy[25-27] and MK-3475 (IB ver. 6) exhibit low rates of toxicities as monotherapies, we do not predict a high rate of toxicities with their combination at a MK-3475 dose of 200mg. However, given the possibility of rare toxicities with this untested combination, we will initiate the phase I component with MK-3475 at a lower dose (100mg) with a planned dose escalation step.

Regarding the phase II component, we hope to evaluate early indications of treatment efficacy and disease response with this therapy combination. In addition, we hope to test in a preliminary manner the ability radiation therapy to salvage patients who do not respond to MK-3475 alone. Rationale for this approach is provided by prior evidence that MK-3475 is able to achieve disease response in patients refractory to initial ipilimumab treatment[22]. We hypothesize that the immunogenic stimuli provided by radiation can similarly salvage patients who do not respond to MK-3475 monotherapy.

4.2.3 Rationale for Endpoints

Disease response will be assessed via immune-related response criteria (irRC) and toxicity will be assessed with NCI Common Terminology Criteria for Adverse Events v4.0, both of which are considered standard guidelines for a phase I/II immunotherapy trial[40,41]. As we will be treating with salvage radiation treatment, the main efficacy endpoint will be progression free survival.

As immunotherapies exert effects through immune activation, it is not uncommon for novel kinetics where disease response becomes only apparent radiographically following an initial stable disease or disease progression[41,42]. As such early evidence of clinically asymptomatic disease progression or new lesions (less than 3 months) will not be criteria for removal from the study. The main efficacy endpoint evaluations will occur at 3 months and later.

4.2.3.1 Efficacy Endpoints

Disease response will be assessed via immune-related response criteria (irRC)[40] beginning 3 months after initiation of treatment (see study calendar below). The primary efficacy endpoint will be progression free survival from time of enrollment to first evidence of progressive disease evaluated 3 months after treatment initiation.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

All study subjects have pathologically confirmed stage IV non-small cell lung cancer with at least one lesion in the lung (metastatic or primary) amenable radiation therapy (either via SBRT or WFRT) in addition to at least one separate non-contiguous lesion available for monitoring.

5.1.2 Subject Inclusion Criteria

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

1. Pathologically confirmed non-small lung cancer. For patients in group 5, we will allow any solid tumor histology to be included.

2. Stage IV metastatic disease (only during the phase II)

3. At least one thoracic or liver lesion amenable to radiation, for group 5 we need one area that can safely receive SBRT or WFRT, not restricted to lung or liver sites.

4. At least one additional non-contiguous lesion to the irradiated lesion amenable to radiographic evaluation.

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

6. Be □ 18 years of age on day of signing informed consent.

7. Have measurable disease based on immune related response criteria (irRC) criteria (see below).

8. Have a performance status of 0 or 1 on the ECOG Performance Scale.

9. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 28 days prior to study registration up to the first dose of study drug.

10. Patients with brain metastasis will be included as long as they are free of neurologic symptoms related to metastatic brain lesions and who do not require or receive systemic corticosteroid therapy in the 14 days prior to beginning MK-3475 therapy

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.	

11. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

12. 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.

13. 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.

14. We will allow XRT prior to study entry to other sites, with no washout period, prior to study entry as long as at least one measurable sites of disease is kept unirradiated.

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 4 weeks of the first dose of treatment or 5 half-lives, whichever is shorter.

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. Unless the steroid therapy is for physiological replacement.

3. Has a diagnosis of active scleroderma, lupus, or other autoimmune disease which by the opinion of the treating radiation oncologist precludes safe radiation therapy

4. Has had prior radiation therapy to all available thoracic and liver lesions such that additional radiation therapy is unsafe by the opinion of the treating radiation oncologist.

5. Has had a prior monoclonal antibody within 4 weeks or 5 half-lives, whichever is shorter, 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.

6. Has had prior chemotherapy or 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.

    - 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.

7. 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.

8. 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.

9. Has an active autoimmune 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.

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

11. Has an active infection requiring systemic therapy or hospital admission.

12. 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.

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

14. 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.

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

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

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

18. Symptomatic brain metastasis

19. Has experienced a dose limiting toxicity on treatment with either prior radiation or anti PD-1 or PD-L1 inhibitor therapy.

5.2 Trial Treatments

The treatment to be used in this trial is outlined in the below table

Table: Initial Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
MK-3475	100 mg IV[a]	Every 3 weeks[b]	IV infusion	32 treatment cycles	Experimental
SBRT	50 Gy in 4 fractions	Daily	External beam	4 days (not including	Standard of Care

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
				weekends/ holidays)	
	Low dose (0.5-10cGy)	Daily	External beam	4-15 days (not including weekends/holiday)	Experimental
WFRT: IMRT/PBT /3D-CRT	45 Gy in 15 fractions	Daily	External beam	15 days (not including weekends/holidays)	Standard of Care
[a]The MK-3475 dose will be adjusted within the phase I component depending on DLT rates. [b]The MK-3475 dosing interval may be increased due to toxicity as described in Section 5.2.1.2.					

Trial treatment should begin on the day of randomization or as close as possible to the date on which treatment is allocated/assigned.

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.

MK-3475 infusion solution will initiate at 100 mg IV with modification as outlined in section 5.2.3. Details on the dose calculation, preparation and administration are provided in the Procedures Manual.

Radiation will be given as per our institutional standard 50 Gy in 4 fractions SBRT (for tumors close to critical structures we will allow the PTV dose to be reduce to either 40Gy or 30Gy) and 45 Gy in 15 fractions WFRT (we will allow SIB to the GTV of up to 60Gy, as long as PTV dose remains 45Gy). For arm 5 high dose can be either 50Gy in 4 fractions or 45Gy in 15 fractions (with SIB) and the secondary lesions will receive low dose radiation in a similar number of fractions. Low dose XRT will be defined as a total dose between 500-1000cGy, it will be delivered at the same time as the high dose radiation over the same number of fractions, so if we are using 50Gy in 4 fraction low dose will be delivered over 4 fractions, while for pts receiving 15 fractions of high dose then the low dose will be delivered over 15 fractions. We will encourage treatment of all sites to low dose radiation if possible and safe, the ultimate decision so which tumors to treat to low dose will be at the discretion of the treating physician.

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.

Radiation breaks will occur for radiation-related ≥ Grade 3 toxicities uncontrolled by symptom management and medications pending judgment of the treating radiation oncologist. Continual re-evaluation will occur daily while a patient is on a radiation break until which time the treating radiation oncologist re-initiates the patient on radiation or discontinues treatment. Patients will be considered evaluable on the study if at least half of the planned radiation fractions were administered.

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 at the discretion of the principle investigator. 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 DLT Definition

DLT is defined as any adverse event considered related to the combination of MK-3475 and radiation therapy as described below:

- Any ≥ Grade 3 non-hematologic toxicity
- Any ≥ Grade 4 hematologic toxicity lasting for > 5 days
- Drug related toxicity that prevents administration of MK-3475for >21 days from the scheduled dose

The window for DLT assessment for the purposes of dose-finding during the phase I component will be within the 22 days of the first dose of MK-3475. DLT rates will be continually assessed throughout the trial with long-term DLT assessment at the completion of the last cycle of MK-3475.

5.2.3 MK-3475 Dose Escalation

The phase I component will consist of a 3+3 dose escalation design with anticipated escalation to a higher dose. Dose escalation will occur independently and in parallel for both phase I treatment groups:

Dose Modification: Phase I

Dose Level	**Phase I MK-3475 Doses**
2	MK-3475 200mg IV
1	MK-3475 100mg IV

Dose Modification: Phase I Scheme

Number of Patients with DLT* at a Given Dose Level (assessed independent for both phase I cohorts)	**Escalation Decision Rule**
0 out of 3	Enter 3 more patients at next higher dose level
≥2	If at dose level 2: dose de-escalation will occur. Three additional patients will be entered at the lower MK-3475 dose level. (If 2 of 3 patients have DLT at the 100mg level the study will close for that radiation arm.)
1 out of 3	Enter at least 3 more patients at this dose level. If at dose level 2: 0 of these 3 patients experience DLT, then this is the maximum tolerated dose (MTD). If at dose level 2: 1 or more of these 3 patients experience DLT, then dose de-escalation will occur. Three additional patients will be entered at level 1. If at dose level 1: 0 of these 3 patients experience DLT, then dose escalation will occur.
MTD: The highest dose at which no more than 1 of 6 evaluable patients has had a DLT. Six patients should be treated before the dose is declared the MTD.	

5.2.4 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.

Radiation simulation will occur one week prior to radiation administration. Radiation therapy will be administered daily except for weekends or holidays. See section 5.6 for more detail.

5.2.5 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

Patients will be randomized within the phase II component to receive either concurrent radiation (either WFRT or SBRT) concurrent with MK-3475 or MK-3475 alone. This will be conducted using the department of biostatistics at MD Anderson clinical trial conduct website. An adaptive randomization method by Pocock and Simon will be used with a minimization probability parameter of 0.90. The randomization process will be controlled to ensure a balanced stratification by treatment arm.

5.4 Stratification

Patients will be stratified based on the number of metastatic sites (less than or equal to five or >5) and the absolute lymphocyte count as determined via complete blood count with differential conducted as part of the pre-treatment screening evaluation. Two stratification groups will exist based on the two absolute lymphocyte levels below.

1) ≥1 K/ul, (normal)

2) <1K/ul (below normal)

5.5 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.

5.5.1 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.

Patients are allowed to have further radiation to other clinical appropriate sites as per the discretion of their treating radiation oncologist.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and the active Treatment Phase 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
- Radiation to dose higher than those used for palliation, ie >45Gy.
- 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.

5.6 Radiation Treatment

5.6.1 Radiation Dosimetry

All patients will receive stereotactic body radiation therapy (SBRT) for a total dose of 50 Gy with 12.5 Gy/fraction in 4 fractions or conventional non-SBRT wide field radiation therapy (WFRT) to a total dose of 45 Gy in 15 fractions prescribed to the planning target volume (PTV) for all treatment groups. It is required that the prescribed isodose line should cover 100% of the internal gross tumor volume (IGTV) and more than 95% of the PTV. Per the discretion of the investigating physician a boost will be allowed to a total dose of 60 Gy to the GTV as a simultaneous integrated boost (SIB) while the PTV dose remains the same at 45Gy. Consideration will first be given to treatment with SBRT; however, if normal tissue dose is not within threshold (as defined in 5.6.5) or the patient exhibits a large primary tumor (>5cm), then patients will be treated in the arms utilizing WFRT pending judgment of the treating radiation oncologist. For central liver or thoracic lesion close to critical structures, compromised PTV coverage is allowed in order to meet normal tissue dose constraints, pending clinical judgments regarding optimal target coverage and normal tissues sparing by the treating physician.

There is no or little aperture margin recommended. The external border of the PTV will be covered by a lower isodose surface than usually used in conventional radiotherapy planning, which typically ranges from 70-95%. However, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. Heterogeneity correction should be applied for planning.

The lose dose radiation technique will be specifically addressed in section 5.6.6.

5.6.2 Radiation Technique and Simulation

Patients will undergo a planned radiation therapy simulation section approximately 1 week prior to initiation of radiation therapy. For patients treated in the Phase I portion and treated in Phase II Treatment Groups 1 and 3 this will occur during the pre-treatment evaluation. For patients treated in the Phase II Treatment Groups 2 and 4, simulation will occur as soon as PD is determined at the 3 month efficacy evaluation.

During simulation, patients will be evaluated for regularity of breathing, responsiveness to feedback guidance, breath-hold capability. Based on this evaluation, a treatment delivery technique will be selected among the following:

1. Breath-hold (with or without feedback guidance).

2. Gated treatment.

3. Free-breathing (with or without feedback guidance).

4. Abdominal compression.

5. A combination of the above techniques.

At simulation, a CT scan obtained using the same method of respiratory management as intended for treatment will be required for treatment planning purposes. This includes 4-dimensional CT (4DCT) for free-breathing, gated or abdominal compression techniques or repeated breath-hold CTs for breath hold techniques. Feedback guidance, including visual and/or audio techniques, will be used for all patients who would both benefit from and respond to training with such devices.

4DCT is a fast CT scan that capable of imaging tumor position during the entire breath cycle. A CT scan is obtained with the patient in each couch position for a whole breath cycle (usually lasting 5 to 6 seconds in each position) followed by repositioning to the next couch position. Following a scan, the computer resorts all images and reconstructs the tumor positions for an entire breath cycle, i.e., a movie file is created which captures organ movement throughout the breath cycle. Radiotherapy will be designed based on the path of organ motion captured by 4DCT.

5.6.3 Target Volumes

1. Gross Target Volume (GTV): Gross tumor as observed on a non-contrast CT should be delineated on thoracic and liver tumors from either 4DCT or repeated breath-hold CTs (see IGTV below).

2. Internal Gross Target Volume (IGTV): IGTV is the volume containing the GTV throughout its motion during respiration or positional variability during repeated breath holds. The motion during free breathing (with or without abdominal compression) will be determined from 4DCT, the variability of tumor location during breath hold will be determined by repeated breath hold CTs obtained on the same day. One method to combine the data from the multiple CT datasets is to create a maximal intensity projection (MIP) that is used as an aid to contour the IGTV. All CT datasets will be transferred to the treatment planning system for reference.

3. Clinical Target Volume (CTV) + Planning Target Volume (PTV): GTV plus 5-10 mm margin (based on physician discretion). Due to tight PTV margin, CTV margin is not recommended to be edited except when normal tissue toxicity is concerning based on treating physician's judgment. The prescribed dose of radiation (either 50 Gy or 45 Gy) will be dosed to the PTV, we recommend 95% coverage if possible.

5.6.4 Daily Treatment Setup

The appropriate immobilization will be chosen for each patient. Most patients will be immobilized with arms up using a commercially available vacuum immobilization bag that extends from the patient's head to their pelvis combined with a wing board.

On-board imaging: Daily on-board imaging such as CT on-rails, cone beam CT, or 4-D cone beam CT will be conducted prior to each radiation fraction. Position adjustment and target coverage confirmation will be performed daily based on imaging study. The setup uncertainty will be kept to less than a 3 mm (2 s) variation. This value is based on the uncertainties of the couch readouts added in quadrature with ½ the voxel size of the CT. Adjustment of patient position is needed if target coverage is judged by the treating physician to be inadequate and/or critical normal tissues toxicity is concerning. Repeated on-board CT after position adjustment is recommended if more than 5 mm shift is conducted.

5.6.5 Dose Volume Constraints

Maximum doses allowed in radiation planning are as outlined below. In the event that a treatment plan cannot reasonably meet dose constraints for 50 Gy in 4 fractions, then a separate plan will be generated for 45 Gy in 15 fractions. In the event that the subsequent treatment plan cannot reasonably meet dose constraints for 45 Gy in 15 fractions, then this patient is ineligible for this study, pending treating physician judgment.

50 Gy in 4 fractions dose constraints:

- Spinal Cord: 25 Gy ≤1 cc
- Lung: V20 ≤20%, V10<30%, V5<40%
- Esophagus: 40 Gy ≤1 cc, 36 Gy ≤10 cc
- Trachea: 40 Gy ≤1 cc, 36 Gy ≤10 cc
- Main bronchus and bronchial tree: 48 Gy ≤1 cc, 40 Gy ≤10 cc
- Heart: 48 Gy ≤1 cc, 40 Gy ≤10 cc
- Brachial plexus: 40 Gy ≤1 cc, 35 Gy ≤10 cc
- Major vessels: 48 Gy ≤1 cc, 40 Gy ≤10 cc
- Skin (defined as outer 0.5 cm of body surface): 40 Gy ≤1 cc, 35 Gy ≤10 cc

45 Gy in 15 fractions dose constraints:

- Spinal Cord: 36 Gy ≤1 cc
- Lung: V20 ≤30%, mean lung dose < 20Gy
- Heart: V30 ≤45%, V45 ≤30%

For patients who have received previous radiotherapy, the attending radiation oncologist is required to evaluate the previous treatment plan, particularly the dose delivered to critical structures and make a clinical judgment based on BED, previous radiation therapy, and current SBRT doses using above dose volume constrains as a guide.

5.6.6 Low Dose Radiation

Low dose radiation will consist of a dose range between 500-1000cGy delivered over the same number of fractions as the SBRT or WFRT. This can be done with various techniques such as 3D conformal 2D planning or even IMRT, protons would also be allowed. This can be delivered as a homogenous field to encompass the entire PTV at one low dose or could even

use a gradient of low doses as long as they are in the range described above. This could be achieved using part of the dose optimization for the primary treatment or as a separate isocenter.

5.7 Rescue Medications & Supportive Care

5.7.1 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:

- Dermatitis: Subjects should be monitored for radiation-induced dermatitis especially at the skin radiation entry and exit site. For mild (Grade 1-2) dermatitis, subjects will be treated with skin lotions including aquaphore for symptomatic relief. For moderate and severe (Grade 3-4) dermatitis, consideration will be made for application of mepilex or adhesive bandages.

- 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 5.7.1.1 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; Pruritus/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	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).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	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.**	
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		

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

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 per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

5.7.1.2 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 or radiation 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

5.8 Diet/Activity/Other Considerations

5.8.1 Diet

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

5.8.2 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 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.

5.8.3 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 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 Merck and followed as described above and in Section 7.2.2.

5.8.4 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.

5.9 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 7.1.4 – 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 32 cycles of MK-3475 treatment
- ☐ 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.

5.10 Subject Replacement Strategy

Additional subjects will be enrolled at an as needed basis for patients who are removed for reasons related to compliance. In the phase I component, if patients were removed prior to DLT evaluation additional subjects enrolled to achieve the needed population for MTD determination. For both phase I and II components, if patients were removed prior to their first

efficacy evaluation, additional patients will be enrolled to achieve 20 evaluated patients per cohort, pending judgment of the study investigators.

5.11 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 dates will have an allowance of +/- 3 days from the study calendar)

Trial Period:	**Screening Phase**		**Treatment Cycles**								**Post-Treatment**		
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	3	4	5	6	7	8-32	Safety Follow-up	Follow Up Visits	Survival Follow-Up
Scheduling Window (Days):	8 weeks prior to registration	28 days prior to registration	XRT[a]	± 3	± 3 (XRT[b])	± 3	± 3	± 3	± 3	± 3	30 days post discon	Every 12 weeks post discon	Every 12 weeks
Administrative Procedures													
Pre-screening Consent	X												
Informed Consent		X											
Medical History	X												
Concomitant Medication Review	X	X											
Trial Treatment Administration	X												
Survival Status											X	X[d]	X[d]
Clinical Procedures/Assessments													
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	X[d]	X[d]
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X[d]	X[d]
Vital Signs and Weight		X	X	X	X	X	X	X	X	X	X	X[d]	X[d]
ECOG Performance Status		X	X	X	X	X	X	X	X	X	X	X[d]	X[d]
Radiation Simulation		X[a]			X[b]								
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory													
Pregnancy Test – Urine or Serum □-HCG		X											
Routine Urinalysis		X											
PT/INR and aPTT		X											
CBC with Differential		X	X	X	X	X	X	X	X	X	X	X[d]	
Comprehensive Serum Chemistry Panel		X	X	X	X	X	X	X	X	X	X	X[d]	
T3, FT4 and TSH		X		X		X		X		X	X		

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Trial Period:	Screening Phase		Treatment Cycles								Post-Treatment		
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	3	4	5	6	7	8-32	Safety Follow-up	Follow Up Visits	Survival Follow-Up
Scheduling Window (Days):	8 weeks prior to registration	28 days prior to registration	XRT[a]	± 3	± 3 (XRT[b])	± 3	± 3	± 3	± 3	± 3	30 days post discon	Every 12 weeks post discon	Every 12 weeks
PFTs		X									X[e]		
Optional Serum Tests[e, f]		X		X		X				X		X	
Optional Biopsies[e]			X[g]		X[g]								
Efficacy Measurements													
Tumor Imaging (CT or PET scan)	X			X[c]			X[c]			X[c]	X	X[d]	X[d]

a. Patients will be simulated followed one week later by radiation therapy (XRT) administered as 4 consecutive days of SBRT in Phase I Group 1 and Phase II Group 1 and as 15 consecutive days of WFRT in Phase I Group 2 and Phase II Group 3. Optimally, patients will receive the first dose of MK-3475 on day 1 and radiation that day or the day after. However, radiation can be initiated anytime during the first week of treatment. No simulation or XRT will be administered during these time frames for Phase II Groups 2 and 4.

b. Patients enrolled in Phase II Groups 2 and 4 will be simulated followed one week later by XRT (either SBRT [Group 3] or WFRT [Group 4]) if progressive disease is noted at first imaging evaluation or later (5 weeks months, see below). Radiation treatment can be delayed up to 2 weeks to allow for treatment planning.

c. Patients enrolled in Phase II Groups 1, 3 and 5 will have imaging done prior to cycle 3 then repeat imaging will be done every 12 weeks +/- 7 days. Patients enrolled in Phase II Groups 2 and 4 who exhibit progressive disease at the first imaging evaluation will be treated with either SBRT (Group 3) or WFRT (Group 4) concurrent with the subsequent cycles of MK-3475. Imaging will be repeated every 6 weeks while patient is receiving MK-3475. For patients at all subsequent time points that have PD they will get XRT with their next dose of MK-3475. In the event that a tumor originally thought amenable to SBRT treatment progressed and can only now be treated safely with WFRT, patients will receive WFRT and will be analyzed as part of group 4. Patients treated with a PD-1 inhibitor not on this study can be enrolled directly into Phase II Groups 2, 4 or 5 and receive salvage radiation with concurrent MK-3475.

d. Can be done over the phone, in the event that follow up can only be done over the phone, PE, vitals, labs, imaging and weight do not have to be obtained.

e. Optional, biopsy after radiation treatment

f. Optional serum biomarkers will be obtained pretreatment and on cycles 2, 4, 8, 12 of MK-3475 and up to 3 follow up visits after.

g. Optional biopsies can be obtained up to 3 weeks prior and up to 3 weeks after radiation is administered in patients who receive radiation

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 or treating physicians.

Furthermore, additional evaluations/testing may be deemed necessary by MD Anderson 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.

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 Assignment of Screening Number

All patients will be assigned a screening number prior to trial initiation during the main study screening visit.

7.1.1.6 Assignment of Randomization Number

All patients participating in the phase II portion of this study will be assigned a randomization number prior to therapy initiation during the pretreatment screening visit.

7.1.1.7 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 12.2). 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 12.1) 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 12 assessment of ECOG status will be performed during every 3 month follow up visit with the directed or full physical exam.

7.1.2.5 Tumor Imaging and Assessment of Disease

7.1.2.5.1 Correlative Studies Blood Sampling

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.

7.1.2.5.2 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.

SBRT/WFRT-treated index lesions: Defined as all index liver, thoracic or liver lesions treated by SBRT as part of this protocol.

Non-SBRT/WFRT-treated index lesions: Defined as all index lesions not treated by SBRT 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 SBRT PTV and outside the SBRT PTV

will also be assessed as follows:

1. **Global irRC:** irRC that factors all lesions including both index and non-index as outlined in 9.5.

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

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

7.1.2.5.3 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 and MRI. 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.

7.1.2.5.4 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[40]. "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 SBRT in this protocol) + SPD(new, measurable lesions inside the SBRT PTV)

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

7.1.3 Laboratory Procedures/Assessments

Laboratory procedures/assessments to be performed in this trial will be conducted as per standards at MD Anderson Cancer Center.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 9. 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 will be per standard at MD Anderson Cancer Center.

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Table 9 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free thyroxine (T4)
	(CO_2 or bicarbonate)	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		PK
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
‡ If considered standard of care in your region.

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Laboratory tests for screening or entry into the Second Course Phase should be performed within 28 days prior to study registration and up to the first dose of drug administration. 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.

7.1.4 Other Procedures

7.1.4.1 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 that 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 in Section 7.1.5.2.1. 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 7.1.5.4).

7.1.4.2 Blinding/Unblinding

The trial will be open label. There will be no treatment blinding.

7.1.5 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.

7.1.5.1 Screening

7.1.5.1.1 Screening Period

The following appropriate imaging studies for tumor assessment should be obtained within 8 weeks prior to study registration to provide diagnosis and measurement of target lesions.

- ☐ CT scans of the chest, abdomen and/or pelvis (contrast-enhanced preferred); or
- ☐ MRI of the abdomen or pelvis; or
- ☐ PET/CT scan (preferred)

The following imaging modalities are to be used in the event that above imaging modalities cannot be obtained.

- ☐ Ultrasound (US) (special circumstances only, as described below in 9.4); or
- ☐ Chest radiograph (least preferred)

The following studies should be obtained within 28 days prior to study registration up to the first dose of study drug. All abnormal and normal results must be noted in the case report

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forms (CRF).

- ☐ Medical history to include determination of tumor-related symptoms.
- ☐ CT simulation for purposes of SBRT or WBRT planning (as described in 5.6.2) for patients enrolled in the phase I arms and phase II arm receiving concurrent radiation and MK-3475.
- ☐ Full physical examination to include height, weight, vital signs, and performance status.
- ☐ CBC with differential and platelet count.
- ☐ Serum chemistry studies to include sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, magnesium, calcium, phosphorus, albumin, total protein, SGOT or SGPT, total bilirubin, alkaline phosphatase, cholesterol and uric acid.
- ☐ Routine urinalysis.
- ☐ Serum or urine pregnancy test for females of childbearing potential within 7 days of registration up to first dose of study drug.
- ☐ Initial optional serum biomarkers will be obtained under an IRB approved laboratory protocol.
- ☐ Thyroid functions tests including T3, fT4, and TSH

7.1.5.2 Treatment Period

The following studies should be obtained at the end of every treatment cycle/immediately prior to the next cycle during MK-3475 treatment:

- ☐ Physical examination to include height, weight and vital signs.
- ☐ Interim history pertaining to any change from baseline, current medications and treatment-related toxicities. Adverse events will be monitored using the NCI CTCAE Version 4.0.
- ☐ Serum chemistry studies to include sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, magnesium, calcium, phosphorus, albumin, total protein, SGOT (AST) or SGPT (AGT), total bilirubin, alkaline phosphatase, cholesterol and uric acid.
- ☐ Thyroid functions tests including T3, fT4, and TSH will be conducted every other MK-3475 cycle.
- ☐ Laboratory testing CBC with differential/platelets

The follow study will be obtained during the 2^{nd}, 4^{th}, 8^{th}, and 12^{th} MK-3475 cycles

- ☐ Follow-up optional serum biomarkers under an IRB approved laboratory protocol.

The following studies should be obtained during the 5^{th} week of treatment MK-3475 cycle (corresponds to day 35). If progressive or stable disease is noted at this time point, patients will receive salvage radiation therapy (described in section 7.1.5.2.1). Aside from this early imaging time-point, imaging studies will generally be conducted every 3 months during MK-3475 treatment:

- ☐ Imaging studies: Response assessment during and post treatment should be performed using the same modality as the pretreatment assessment whenever feasible, and all lesions

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assessed pretreatment must be included in the post-treatment evaluation:
- ☐ CT scans of the chest, abdomen and/or pelvis (preferred); or
- ☐ MRI of abdomen and pelvis; or
- ☐ PET/CT (preferred)

7.1.5.2.1 Salvage Radiation Therapy (Phase II Treatment Groups 2 and 4 only)

Patients randomized to Phase II Treatment Groups 2 and 4 will be given salvage radiation therapy if during early evaluation progressive disease is noted (at 5 weeks). Patients will be scheduled for simulation at the next available date and receive radiation therapy as soon as a treatment plan is completed (approximately 1 week time). To allow adequate time for treatment planning, radiation can be delayed up to 2 weeks in patients receiving salvage radiation therapy. Radiation therapy will be conducted concomitant with the remaining cycles of MK-3475. Radiation therapy will consist of SBRT 50 Gy in 4 fractions (Group 2) and 45 Gy in 15 fractions (Group 4). In the event that lesion progression precludes safe administration of SBRT, patients will receive WFRT and analyzed as part of Group 4.

Patients who are receiving a PD-1 inhibitor (Pembrolizumab, Nivolumab, etc.) not on this study and are exhibiting progressive disease can be enrolled directly into Phase II, Groups 2 and 4 if they exhibit a lesion amenable to radiation (either SBRT or WFRT) and meet the other study requirements. Patients who access the study in this manner will initiate radiation and concurrent MK-3475 at this study MTD for a total of 32 cycles (counting prior cycles of PD-1 inhibitor).

7.1.5.3 Post-Treatment Visits

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.

The following studies should be obtained within this visit. All abnormal and normal results must be noted in the case report forms (CRF).

- ☐ Medical history to include determination of tumor-related symptoms.
- ☐ Full physical examination to include height, weight, vital signs, and performance status.
- ☐ CBC with differential and platelet count.
- ☐ Serum chemistry studies to include sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, magnesium, calcium, phosphorus, albumin, total protein, SGOT or SGPT, total bilirubin, alkaline phosphatase, cholesterol and uric acid.
- ☐ Thyroid functions tests including T3, fT4, and TSH

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- ☐ Imaging studies: Response assessment during and post treatment should be performed using the same modality as the pretreatment assessment whenever feasible, and all lesions assessed pretreatment must be included in the post-treatment evaluation:
  - ☐ CT scans of the chest, abdomen and/or pelvis (preferred); or
  - ☐ MRI of abdomen and pelvis; or
  - ☐ PET/CT (preferred)

7.1.5.4 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 (84 ± 7 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, or death. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

The following studies should be obtained every follow up visit:

- ☐ Physical examination to include height, weight and vital signs.
- ☐ Physical examination, interim history pertaining to any change from baseline, current medications and treatment-related toxicities. Adverse events will be monitored using the NCI CTCAE Version 4.0.
- ☐ Laboratory testing CBC with differential/platelets
- ☐ Serum chemistry studies to include sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, magnesium, calcium, phosphorus, albumin, total protein, SGOT (AST) or SGPT (AGT), total bilirubin, alkaline phosphatase, cholesterol and uric acid.
- ☐ Imaging studies: Response assessment during and post treatment should be performed using the same modality as the pretreatment assessment whenever feasible, and all lesions assessed pretreatment must be included in the post-treatment evaluation:
  - ☐ CT scans of the chest, abdomen and/or pelvis (preferred); or
  - ☐ MRI of abdomen and pelvis; or
  - ☐ PET/CT (preferred)

7.1.5.4.1 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.

7.1.5.4.2 Correlative Studies relating to immunologic response:

Optional tumor tissue and blood samples will be collected on the separate IRB approved laboratory protocol for immune monitoring under the supervision of the Immunotherapy Platform. In tumor tissues, immunohistochemical studies will be performed to evaluate CD4

and CD8 T cells. In peripheral blood, we will also evaluate T cell populations including CD4 and CD8 cells in pre and post therapy samples.

7.1.5.4.3 Tumor tissues

Optional tumor tissue collected before & after radiation and will be banked under an IRB-approved laboratory protocol. Biopsies can be conducted up to 3 weeks prior and 3 weeks after radiation administration. No new procedures will be required while on protocol.

7.1.5.4.4 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:

- At screening
- 2^{nd}, 4^{th}, 8^{th}, and 12^{th} MK-3475 cycles
- Every 4 weeks for a total of 3 visits after the last dose of drug

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

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.

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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 MD Anderson 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

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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

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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 (Appendix 12.4).

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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 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

General descriptive statistics will be computed to compare toxicity and preliminary signs of efficacy among different phase II treatment groups. Rates of complete and partial response will be compared utilizing multivariate logistic regression, which will include treatment sequencing (concurrent MK-3475 and RT v. MK-3475 alone), (concurrent MK-3475 and concurrent MK-3475 with low dose XRT) and radiation therapy technique (SBRT v. WFRT).

8.2 Statistical Analysis Plan

8.2.1 Descriptive Statistical Analysis

Descriptive statistics will be computed for all relevant outcomes, including tumor response, occurrence of adverse events, and biomarker changes. Descriptive analysis will include a global assessment of patient outcomes among all cohorts. Cohort analysis will be conducted between cohorts (see table below). All patients receiving at least 1 treatment with MK-3475 at the MTD will be included in the analysis.

Demographics, safety, and treatment efficacy will be described/compared in the following separate analyses:

1. Among different radiation treatments: Treatment Groups 1 and 2 (SBRT) v. 3 and 4 (WFRT) and groups 1 and 3 vs. 5.
2. Among different treatment schemes: Treatment Groups 1 and 3 (MK-3475 and concurrent radiation) v. 2 and 4 (MK-3475 alone)
3. Described for patients in Treatments Groups 2 and 4 who exhibited stable or progressive disease and received salvage radiation therapy.

8.2.2 Exploratory Efficacy analysis

The primary efficacy endpoint will be progression free survival defined as time between enrollment and progression as defined by irRC criteria (PD as defined by irRC). Kaplan Meier curves and log rank analysis will be used to compare progression free survival between strata and between patients who received or did not receive salvage radiation. With two equally sized groups of 40 patients we will have 80% power to detect a 30% difference in progression free survival (55% v. 25%). To increase statistical power, we will also combine the patients into a single dataset and fit a single logistic regression model with progression free response as the

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outcome and radiation modality (SBRT v. WFRT), (with or without low dose XRT) and therapy sequencing (concurrent MK-3475 and radiation vs. MK-3475 alone) among other factors (including but not limited to: number of metastatic disease sites, absolute lymphocyte count, number of prior treatments, primary cancer histology, age, pre-treatment KPS and Royal Marsden Score) as the predictors.

Time-to-event analyses will be conducted via Kaplan-Meier analysis, with comparisons via the log-rank test made with regards progression free survival, with analysis beginning at trial enrollment until evidence of progressive disease receipt of the first MK-3475 dose. At the discretion of the investigators, multivariate Cox regression will be done to adjust for (among other factors): number of metastatic disease sites, number of prior treatments, primary cancer histology, age, pre-treatment KPS and Royal Marsden Score.

Phase II Treatment Groups

		Patient Lung Lesion Size and Location	
		Lesion treatable with SBRT (n=80)	**Lesion treatable with WFRT (n=40)**
Randomization	**MK-3475 and concurrent radiation**	Treatment Group 1 (n=20): SBRT+MK-3475	Treatment Group 3 (n=20): WFRT+MK-3475
	MK-3475 alone (radiation if PD at 3 mo. evaluation)	Treatment Group 2 (n=20): MK-3475 alone (if PD then SBRT+MK-3475)	Treatment Group 4 (n=20): MK-3475 alone (if PD then WFRT+MK-3475)
	MK-3475 and concurrent high and low dose radiation	Treatment Group 5 (**n=40**): SBRT or WFRT + MK-3475 + low dose XRT	

8.3 Safety Monitoring Plan

The MD Anderson Data Safety Monitoring Board (DSMB) will be providing study-wide oversight in regards to the endpoints described in this protocol.

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8.4 Phase II Protocol Monitoring Mechanism

We will monitor toxicity separately in the five groups. The three typical ways to do this are: (1) frequent teleconferences between PI and sponsor discussing aggregate safety data; (2) a simple rule for each cohort such as stopping accrual if after the first 3 patients have been treated the aggregate DLT rate at any time exceeds 33%; or (3) a set of stopping boundaries based on Bayesian probability rules (e.g., Pr(p > 0.33|data) > 0.95 where p is the aggregate DLT rate).

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 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

9.2 Packaging and Labeling Information

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

9.3 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.

9.4 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.

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

9.5 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.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 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.

10.2 Compliance with Financial Disclosure Requirements

N/A

10.3 Compliance with Law, Audit and Debarment

N/A

10.4 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.

10.5 Data Confidentiality Procedures

This study is a prospective Phase I/II trial to evaluate patients' safety and toxicity from MK-3475 and SBRT for non-small cell lung cancer. Imaging data, disease progression, and overall survival will be tracked in this Phase I/II clinical trial. Baseline patient characteristics such as age, gender,

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and tumor stage are other standard variables that will be recorded. The risk related to data confidentiality will not involve more than minimal risk (i.e. risk of accidental release of personal and or confidential information) to the subjects because the patient history and treatment details will be gathered from the hospital records. Strict patient confidentiality will be maintained. Patient confidentiality will be respected at all times. Patient's name and medical record number will be removed from any stored data. Data will be stored on a password and firewall protected computer. Only the study team will have access to patient information, and only information relevant to this protocol will be examined.

All protected health information will be de-identified prior to releasing outcomes of the study. There will be no paper records of data with personal identifiers. Patient identifiers will be destroyed within 5 years of study completion. Until then, the database will be password protected on a limited access computer. Information will be destroyed within 5 years after study publication.

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12.0 APPENDICES

12.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.

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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.	

12.2 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)

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

Immune related RECIST criteria (irRC)* will be used in this study for assessment of tumor response. CT, PET/CT or MRI may be utilized.

* As published in Clinical Cancer Research:

Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, Maio M, Binder M, Bohnsack O, Nichol G, Humphrey R, Hodi FS: Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 15:7412-20, 2009

Further details regarding lesion monitoring are detailed in section 7.1.2.6.4.

12.4 Events of Clinical Interest

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PEMBROLIZUMAB PROGRAM

(MK-3475)

EVENT OF CLINICAL INTEREST

GUIDANCE DOCUMENT

Version 3.0

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Pembrolizumab Event of Clinical Interest Guidance Document

Pembrolizumab Event of Clinical Interest Guidance Document

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.

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			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:

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			- 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:

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			- 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.

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Pembrolizumab Event of Clinical Interest Guidance Document

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Pembrolizumab Event of Clinical Interest Guidance Document

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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.

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Table 2: 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

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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
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.	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
	Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.	
<u>Grades 3 or 4</u> Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	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		

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.

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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

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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? _____

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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?

_____