Title: Evaluating the Combination of MK-3475 and Sterotactic Body Radiotherapy in Patients With Metastatic Melanoma or NSCLC

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TITLE: **A Phase I/II trial of Evaluating the Combination of MK-3475 and Stereotactic Body Radiotherapy in Patients with Metastatic Melanoma or NSCLC**

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Amendment 3	12-April-2016
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Amendment 6	09-Dec-2019

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1.0 TRIAL SUMMARY

Abbreviated Title	MK-3475 and SBRT in Metastatic Melanoma and NSCLC
Trial Phase	*Phase 1b / 2a*
Clinical Indication	Patients with metastatic melanoma or NSCLC, with at least 2 measurable lesions
Trial Type	This is a phase 1b dose escalation of SBRT, given in combination with MK-3475 at a constant dose of 200 mg every 3 weeks (+/- 7 days). There is then a phase 2a expansion with an NSCLC cohort
Route of administration	MK-3475 is intravenous, every 3 weeks (+/- 7 days)
Treatment Groups	Phase 1b: dose escalation cohorts based on anatomic site of the SBRT target (lung and non-lung). Phase 2a: expansion cohort of patients with NSCLC
Number of trial subjects	Maximum of 60 to complete SBRT
Estimated duration of trial	2 years
Estimated average length of treatment per patient	Approximately 1 year

2.0 TRIAL DESIGN

2.1 Trial Design

This is a 2-part prospective trial examining the ability of Stereotactic Body Radiation Therapy (SBRT) to induce a response to MK-3475, a humanized antibody to PD-1, in patients who progress on this antibody. Patients with metastatic melanoma and NSCLC will be enrolled after they have progressed on anti-PD-1 therapy. Patients with metastatic NSCLC (previously untreated with anti-PD-1 or anti-PD-L1 therapy) will be enrolled and treated with MK-3475 until they exhibit progression of disease (as defined in section 5.2.1). At this point (when patients have demonstrated progression of disease) a single target lesion will be selected and treated with SBRT, and then MK-3475 will be restarted and continued until there is further progression of disease. The first phase of the study is a radiation dose escalation with a constant dose of MK-3475. The second part of the study includes an expansion cohort of NSCLC patients.

The phase 1b portion of the trial is a radiation dose escalation study to determine the maximum tolerated dose (MTD) of SBRT when given to patients previously and subsequently exposed to anti-PD-1 therapy, including MK-3475. Because the class of PD-1 inhibitory antibodies conveys a risk of pneumonitis, there will be two parallel dose escalation arms- Arm A will include SBRT targets in the lung parenchyma, and Arm B will be limited to targets outside the lung parenchyma. Each arm will be separately escalated, and two MTDs will be determined. The starting dose will be 3000 cGy in 5 fractions; there will be one dose escalation cohort (3000 cGy in 3 fractions), and if necessary one dose de-escalation cohort (1000 cGy in a single fraction). If there is dose-limiting toxicity at the lowest cohort, that arm will be closed and SBRT to that site will be discontinued.

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The phase 2a portion of the study includes an expansion cohort for NSCLC, with SBRT delivered at the MTD. The primary endpoint of this phase of the study is the overall response rate to post-SBRT MK-3475. Secondary endpoints include determining the time to progression, overall survival, and exploratory biomarkers.

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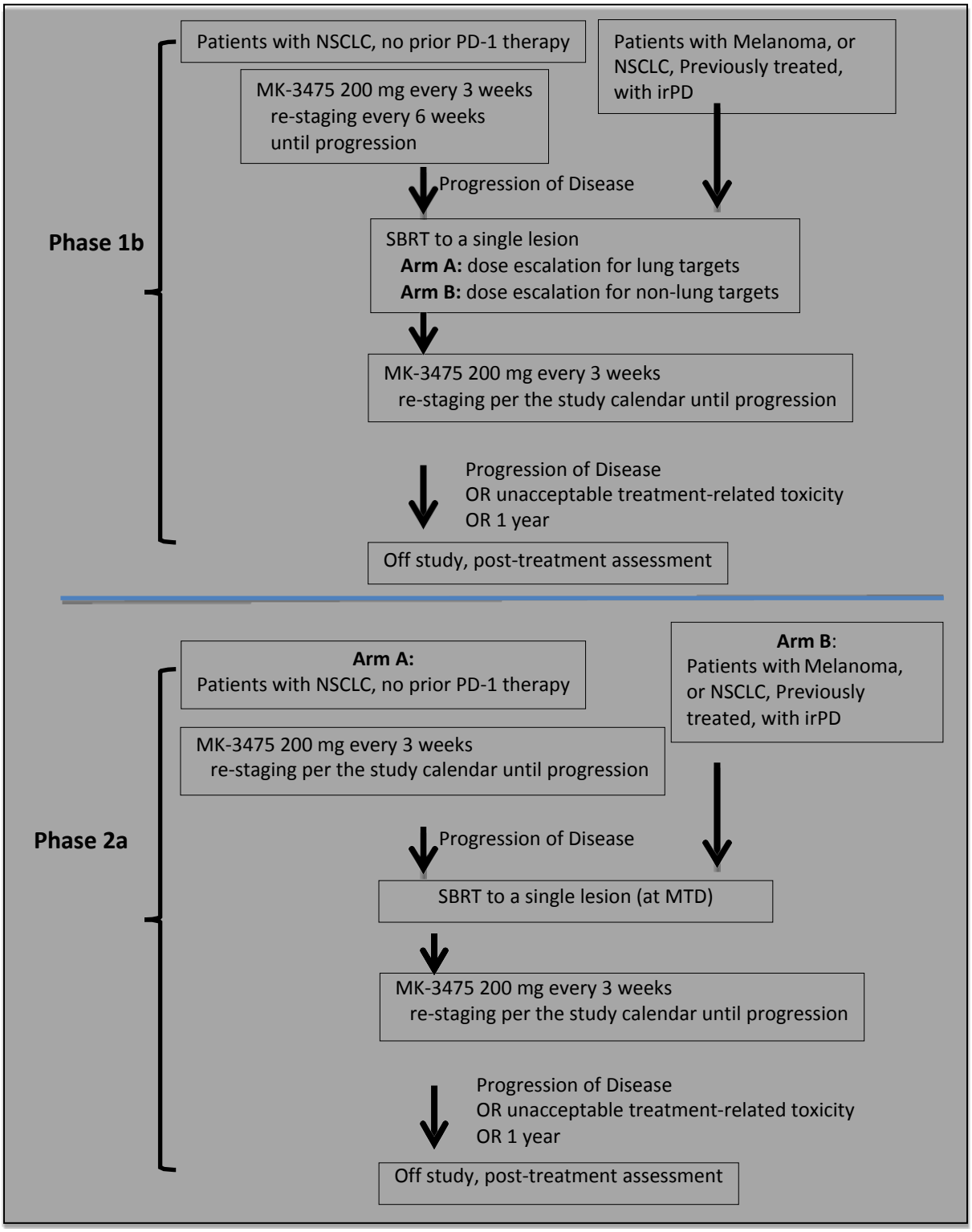
2.2 Trial Schema



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3.0 OBJECTIVE(S) & HYPOTHESIS(-ES)

The hypothesis is that SBRT might induce a systemic response to MK-3475 in patients who have previously progressed, by enhancing the host immune response. The overall objective of the phase 1b component is to determine a safe dose of SBRT in the lung and other organs, when given with MK-3475. In the phase 2a component, it is to determine whether SBRT can induce a response to MK-3475 in patients who have previously progressed on the antibody.

3.1 Primary Objectives

The primary objective of the phase 1b portion of the trial is to determine the MTD of SBRT to lung (Arm A) and non-lung (Arm B) targets in patients receiving MK-3475.

The primary objective of the phase 2a portion is to determine the overall response rate to post-radiation MK-3475, in patients whose disease had previously progressed on MK-3475 or another anti-PD-1 therapy.

3.2 Secondary Objectives

(1) To determine the local control of SBRT, when SBRT is given with MK-3475
(2) To determine the time to progression in patients receiving post-radiation MK-3475, in patients whose disease had previously progressed on MK-3475 or another anti-PD-1 therapy.
(3) To determine the progression-free and overall survival in patients receiving MK-3475, who receive SBRT
(4) To determine the safety and toxicity of the combination of SBRT and MK-3475
(5) To examine potential predictive biomarkers in tumor samples and peripheral blood in patients treated with MK-3475 and SBRT.

4.0 BACKGROUND & RATIONALE

4.1 Melanoma

The incidence of melanoma has been rising faster than that of any other cancer in the United States, and the mortality rate has also been rising. In 2010, the projected incidence was 68,130 and the death rate from the disease was projected to rise to 8,700[1]. This represents a sharp increase in recent years. For example, in 2006 the incidence was 62,190 and the death rate was 7,910, representing an increase of 10% in both incidence and death rate in a mere four years [2].

Therapeutic options are limited once melanoma metastasizes[3], although recent advances in development of novel therapies will likely expand the repertoire of active drugs for this disease. Older therapies, such as cytotoxic and cytokine agents, including dacarabazine, temozolomide, cisplatin, paclitaxel, interleukin-2 (IL-2), and interferon-alfa (IFNa), produce low objective responses in the range of 10-20%. None of these agents appear to have an impact on median survival, although responses can be associated with meaningful palliation of disease and 4-5% of patients treated with high-dose IL2 achieve long-term complete responses [4]. Various combinations of the active single-agents have been evaluated in phase II trials and in

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randomized phase III trials. Some of the regimens, such as cisplatin-vinblastine-dacarbazine (CVD), or CVD-IFNa-IL2 (biochemotherapy), produced high response rates exceeding 40% in single-arm trials. However, in prospective randomized studies, the combinations failed to demonstrate clinically meaningful improvements in median survival, and the toxicity was not negligible [5]. Until recently, dacarbazine has been the standard of care for treatment of metastatic melanoma, although median survival in patients treated with dacarbazine is less than 8 months [6-8]. For selected patients with good performance status and normal organ function, high-dose IL-2 remains a reasonable option, although treatment is associated with substantial acute toxicity and requires inpatient administration.

More recently, in a pivotal phase III study of ipilimumab, a monoclonal antibody against cytotoxic T lymphocyte associated antigen (CTLA-4), improved survival was observed[9]. This and other studies led to the FDA approval of ipilumumab for metastatic melanoma in March of 2011. Other recent clinical trials investigating targeted therapies in melanoma have shown promise. One novel agent, vemurafenib, an inhibitor of mutated B-raf, had a survival benefit when compared to dacarbazine[10]. Based on these studies, vemurafenib was recently FDA approved for metastatic melanoma.

The FDA granted accelerated approval to MK-3475 on September 4, 2014 for treatment of patients with advanced or unresectable melanoma. It is intended for use following treatment with Ipilimumab, and after Ipilimumab and a BRAF inhibitor in patients with BRAF V600E mutation.

4.2 Non-Small Cell Lung Cancer (NSCLC)

NSCLC is the leading cause of cancer-related death in the United States and worldwide, and results in over 160,000 deaths in the United States per year[1]. In patients with advanced or metastatic disease, platinum-based chemotherapy had been the mainstay of management with a response rate and median overall survival of approximately 30% and 12 months, respectively[11]. In patients who are able to tolerate treatment beyond first line, responses are even lower and median survival is only minimally improved with chemotherapy. Targeted therapies, including agents targeting the epidermal growth factor receptor pathway have been shown to be effective as first-line therapies for select patients with response rates up to 70% and progression-free survival of about 1 year. However, none of these treatments has been shown to be curative in patients with metastatic disease, and despite the development of new and effective therapies, the five-year survival rate for patients with advanced NSCLC remains less than 5%.

4.3 Pharmaceutical and Therapeutic Background of MK-3475

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades[12]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies[13-17]. 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.

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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)[18, 19]. The structure of murine PD-1 has been resolved[20]. 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[18, 21-23]. 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[24, 25]. 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[26, 27]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells[28]. 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[24, 29-31]. 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[24]. 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)[32]. 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.

For further preclinical and clinical trial data, refer to the investigator's brochure.

4.4 SBRT

Stereotactic body radiation therapy (SBRT) is a technique that has become increasingly used over the past decade. In contrast to conventionally fractionated radiation therapy, which uses daily fractions of 1.8 to 2 Gy per day over the course of 30 or more fractions, an SBRT

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treatment plan typically delivers 30 to 60 Gy over 3 to 8 fractions. This results in a much higher biologically effective dose than is possible with conventionally fractionated radiation, and requires a high degree of precision to avoid delivering the increased dose to the surrounding tissue. This necessitates the use of advanced simulation techniques that capture the internal motion of tumors, reliable patient immobilization, and modern radiation treatment devices with on-board imaging capability. SBRT conveys a markedly higher rate of local control and survival, and markedly lower toxicity, when compared to conventional radiotherapy. The majority of the prospective experience using this technology has been for the curative treatment of early-stage NSCLC in patients who are at high surgical risk. In this cohort, trials demonstrate that local control after SBRT is in excess of 90%, in comparison to external beam radiation where the expectation is 40 to 50%[33].

The use of SBRT in patients with metastatic disease has been evaluated in several prospective a retrospective studies, primarily directed at oligometastatic lesions in the lung and liver but also including targets in bone and soft tissue. A prospective study of SBRT in 38 patients with 1 to 3 pulmonary metastases reported 96% local control of the radiated metastases at 2 years, with low toxicity (8% grade 3, and no grade 4 or 5) using doses of 48 to 60 Gy in 3 fractions[34]. The risk of grade 3 pneumonitis in this study was 2.6%, particularly low considering the relatively high dose, and the use of SBRT to treat multiple targets simultaneously. This is consistent with a large body of retrospective data; a review compiling the data from more than 250 patients in more than a dozen series suggests that grade 3 or greater toxicity is between 0 and 14%, and grade 3 or greater pneumonitis is between 0 and 6% when patients are treated with SBRT to lung lesions, at doses in the range of 40 to 60 Gy[35].

The risk of radiation pneumonitis following SBRT is not only low but also predictable using accepted dose and volume metrics during treatment planning. In a group of 143 patients treated with SBRT to a median dose was 60 Gy in 3 fractions, the volume of lung receiving 20 Gy or greater (V20) was established to significantly predict the risk of pneumonitis. Radiation pneumonitis (Grade 2-4) occurred in 9.4% of all cases, but only 4.3% of patients with a V20 $\leq$ 4%. In our own institutional experience of 350 patients treated to 50 to 60 Gy, with more than one year of follow-up, the overall rate of acute Grade 3 or greater pneumonitis was 4.8%; V20 was predictive. The proposed doses in the present study are significantly lower, and based on standard regimens and following more conservative dose constraints.

4.5 Radiation and the Immune Response

For many years, there have been case reports of patients with metastatic disease who receive radiation to a target site, and subsequently have a partial or complete response of unirradiated metastatic sites. This so-called “abscopal effect” has been clinically observe in multiple tumor types, in patients who did not receive any systemic therapy[36, 37] and may be due to the activation of the activation of the host immune response to the tumor. This is supported by the observation that radiation induces a local inflammatory response, and that after radiation anti-tumor antibodies are observed in patient peripheral blood[38]. The abscopal effect has also been observed in patient receiving anti-CTLA4 antibody, in both NSCLC and melanoma[39, 40]. Beyond case reports, this interaction has not been documented in a prospective study, and the details of the mechanism are unclear.

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4.6 Rationale

Rationale for the Trial and Selected Subject Population

Immunotherapy is an area of active interest in both melanoma and NSCLC. Although clinical trials are ongoing in both diseases with MK-3475 and demonstrate promisingly long survival, the response is not uniform within the populations. In patients unselected for PD-L1 expression, approximately 40% of patients with melanoma and 20% of patients with NSCLC will respond to therapy. While PD-L1 expression appears to predict response in both populations, some PD-L1 positive patients will not respond and some PD-L1 negative patients will respond. A number of studies have shown that PD-L1 may be induced after drug treatment, and that expression is correlated to lymphocytic infiltrate in melanoma patients. The latter has been observed to increase after radiation therapy, suggesting a mechanism by which radiation might make some patients more responsive to PD-1 antibodies. We propose to treat patients with metastatic NSCLC or melanoma without regard to PD-L1 expression, to determine whether the use of radiation may sensitize otherwise non-responsive patients to therapy, and to determine whether these patients subsequently express PD-L1 on specimens obtained after radiation.

Rationale for Dose Selection/Regimen/Modification

Prospective and retrospective studies suggest that the use of SBRT for patients with oligometastatic disease is associated with a low risk of significant toxicities, at doses as high as 60 Gy in 3 fractions (A biologically effective dose (BED) of 180 Gy). Lower doses appear to result in similar local control in this population, with equivalent overall survival. Because the risk of significant radiation-related toxicity to organs at risk is relatively predictable using accepted radiation dose and volume limits, the use of a lower SBRT dose will minimize the expected risk of treatment while simultaneously allowing the inclusion of moderately larger tumors, as well as those in closer proximity to critical normal organs.

The proposed starting SBRT dose of 30 Gy in 5 fractions (BED = 48) is a widely used regimen in patients with melanoma first reported by this institution in 1976[41], and adopted in several prospective trials since then[42]. Our institutional experience is that this is associated with excellent local control and low toxicity when used in small to moderate sized melanoma metastases, in patients receiving concurrent anti-CTLA4 antibodies – in 12 melanoma patients treated with a BED of 48 Gy with concurrent ipilumimab, none had progression of disease at the treated site. The dose de-escalation cohort of 10 Gy in 1 fraction (BED = 20) is one of several standard palliative doses, associated with negligible toxicity when used as single agent in a wide variety of body sites, in patients with metastatic disease who have been heavily pre-treated[43]. This schedule was chosen because a single large fraction has been demonstrated to have the largest ablative and immunologic potential. The dose escalation cohort of 30 Gy in 3 fractions (BED = 60) is a common, conservative SBRT dose used in liver, lung, and spine treatment, and associated with a low risk of toxicity.

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Rationale for Biomarker Research

The phase I dose escalation studies of MK-3475 in patients with melanoma and NSCLC showed that response was not uniform, with response rates of 40% and 20%, respectively. In the melanoma cohorts the association between response and expression of PD-L1 was not entirely clear[44]. In NSCLC there appears to be an association between PD-L1 expression and response, although the numbers are small and the correlation is not perfect. Of the 22 patients with PD-L1 expression, six (27%) responded, while one of the 12 patients with expression below this threshold responded (8%). The association between PD-L1 expression and response to other PD-1 inhibitors is suggested by phase I trials in solid tumor patients, also with small numbers of patients[45, 46]. These studies need to be validated in additional patient cohorts. Moreover, not all patients with PD-L1 positive tumors responded to MK-3475. Some of the studies used whole tumor resections to determine PD-L1 expression, while others used cores from biopsies. In addition, a number of pre-clinical studies have now shown that PD-L1 expression is inducible with drugs such as interferon and vemurafenib[47]. The expression of PD-L1 has also been correlated with the extent of tumor lymphocytic infiltrate. The latter has been observed to be increased after radiation therapy, suggesting one possible mechanism for an improved systemic response after SBRT. We propose here to treat NSCLC and melanoma patients without regard to PD-L1 expression on biopsies done just prior to initiating protocol treatment. When feasible, tissue specimens will be obtained after MK-3475 treatment, and again after SBRT, and local and systemic response will be correlated to expression.

Other studies conducted by Dr. Lieping Chen's group, that characterized the PD-L1/PD-1 axis a number of years ago, suggest that presence of CD4 and CD8 positive cells in tumor deposits might also be important for response to PD-1 targeting therapies. [48] They found that the majority of PD-L1 positive tumors were associated with CD4 and CD8 tumor infiltrating lymphocytes (TILs), while the minority of the PD-L1 negative tumors had associated TILs. Moreover, the staining pattern of PD-L1 on melanocytes differed based on proximity to TILs. Interferon-γ, a primary inducer of B7-H1 expression, can be detected at the interface of PD-L1 positive melanocytes and TILs, possibly reflecting activation of PD-1 on the TILs. This interaction, therefore, might be predictive of antitumor response to PD-1 blockade. Additional mediators of this pathway that might be associated with anti-tumor response, and will be studied on pre-treatment specimens from patients enrolled in this trial. Expression of other members of the B7 super-family of ligands, including PD-L2 and B7-H4 on tumor cells, might be associated with activation of PD-1 on tumor cells [49, 50]. Galectin-9 (the ligand to TIM-3), has been proposed as a mediator of PD-1 related T-cell exhaustion [51].

A more sophisticated and accurate predictive biomarker model might be built by incorporating markers on T cells, in addition to quantification of T cell tumor infiltrate. Specifically, co-expression of TIM-3 and PD-1 might be associated with sensitivity to PD-1 blockade [51]. LAG-3 (lymphocyte-activation gene 3) synergizes with PD-1 to inhibit T cell activation. [52] Co-expression of PD-1 and CTLA-4 on T cells is thought to be co-inhibitory, and co-inhibition of these molecules is the basis of ongoing clinical trials. [53] The T-cell stimulatory role of PD-1H (PD-1 Homologue) on T cells was recently described by Dr. Chen's laboratory; its association with anti-tumor response in the setting of PD-1 blockade has yet to be determined. [54]

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An additional potential biomarker of tumor response is cell-free tumor-derived circulating DNA (ctDNA). The laboratory of Abhi Patel has developed an ultrasensitive assay for measuring small amounts of cell-free mutant DNA released into the blood from dying tumor cells. The assay covers a broad panel of mutations and uses novel error suppression techniques applied to next-generation sequencing data to enable identification of rare mutant DNA down to a fractional abundance of ~0.02%. Because such ctDNA is highly tumor-specific and is rapidly cleared from the bloodstream, it is showing excellent promise as a quantitative cancer biomarker. Indeed, we (and others) have observed decreases in ctDNA levels following treatment with surgery, radiation therapy, and systemic therapy (sometimes with an initial spike from tumor kill). Thus, we hypothesize that quantitative changes in ctDNA may provide information that is complementary to radiologic studies for tracking the efficacy of treatment with the PD-1 inhibitor MK3475 in patients with metastatic melanoma or non-small cell lung cancer.

5.0 METHODOLOGY

5.1 Entry Criteria

Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Have metastatic melanoma or NSCLC, or locally advanced NSCLC not suitable for curative-intent local therapy.
4. For melanoma patients and NSCLC patients treated with prior anti-PD-1 therapy, patients must have received prior PD-1 therapy and have progressed (irPD) by irRC.
5. Have 2 or more measurable sites of disease as defined by either RECIST 1.1, or cutaneous lesions at least 1 cm in greatest dimension
6. Have at least one site of disease that is considered potentially suitable for treatment with SBRT
7. Have provided tissue from an archival or newly obtained tissue sample of a tumor lesion, sufficient for analysis of PD-L1 and other biomarkers. Patients who have had PD-L1 analysis previously performed at Merck can substitute earlier analysis results and are not required to submit additional tissue for PD-L1 testing. Expression of PD-L1 is NOT required for study entry.
8. Have a performance status of 0, 1 or 2 on the ECOG Performance Scale.
9. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 28 days of protocol treatment.

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
Renal	

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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	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
[a]Creatinine clearance should be calculated per institutional standard.	

10. 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.
11. Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in section 5.6 – Contraception, for the course of the study through 120 days after the last dose of study medication.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

12. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in section 5.6 – Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

Subject Exclusion Criteria

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

1. Has had radiation therapy within 2 weeks of the first protocol treatment.
2. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 2 weeks of the first protocol treatment.
3. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 2 weeks of the first protocol treatment. The use of low-dose steroids for management of chronic conditions is allowed.
4. Non-small cell lung cancer patients enrolling to MK-3475 as first protocol therapy (no prior anti-PD-1 therapy): Has had a prior monoclonal antibody within 4 weeks prior to first protocol treatment or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
5. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks of the first protocol treatment or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

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- Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
- Note: Patients who have had prior treatments with Tyrosine Kinase Inhibitors (e.g. Tarceva) require only a 72-hour washout period prior to starting protocol treatment.

6. 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.
7. Has known active and untreated brain (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate.
8. 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 example of an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Those with a history of hypothyroidism who are now stable on hormone replacement will not be excluded. Those with Sjorgen's syndrome will not be excluded from the study.
9. Has a history of (non-infectious) pneumonitis that required steroids, current pneumonitis or evidence of interstitial lung disease.
10. Has an active infection requiring systemic therapy.
11. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
12. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
13. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
14. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
15. Has received a live vaccine within 30 days prior to the first protocol treatment.

5.2 Trial Treatment Plan

The treatment to be used in this trial is outlined below in **Table 2**

Table 2 Trial Treatment

Treatment	Dose	Frequency	Route	Use
MK-3475	200 mg*	Every 3 weeks (+/- 7 days)	IV infusion	Experimental
SBRT	30Gy **	One time over 1 to 5 fractions		Standard

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*MK-3475 may be modified as described in Section 5.2.1 **SBRT dose escalated/de-escalated as described in Section 5.2.2

5.2.1 Study Design

This is a two-part study, including both phase 1b and 2a portions.

The **phase 1b** is an SBRT dose escalation study, in which patients with both NSCLC and melanoma will be enrolled. NSCLC patients will be enrolled and treated with MK-3475 until they have progression of disease (irPD). Patients who have progression within 12 months of study entry will be evaluated for SBRT and re-initiation of MK-3475. Patients who do not have progression of disease within that timeframe may continue to receive MK-3475 for up to 18 months per protocol. These patients will not be evaluable for the study endpoints, although their response rates and overall survival will be reported.

Melanoma and selected NSCLC patients will be enrolled after having progression of disease on prior PD-1 therapy (irPD). They will be immediately treated with SBRT, followed by re-initiation of MK-3475.

After progression of disease on an initial course of anti-PD-1 therapy (either prior to enrollment, or during trial therapy), a target for SBRT will be selected and patients will be assigned to one of two arms on the basis of the anatomic location of the target (Arm A: lung, Arm B: non-lung). The SBRT target will be chosen and ideally SBRT will be delivered as quickly as feasible after the last infusion of MK-3475. NSCLC patients who do not have a suitable SBRT target (as defined in section 5.2.3) on the imaging study that shows progression of disease may undergo interval re-imaging without further therapy, but if no suitable target has been identified for SBRT within 12 weeks of the last infusion of MK-3475, that patient will be removed from treatment and moved to survival follow up.

Patients may continue to receive MK-3475 post disease progression while radiation therapy with SBRT is scheduled. Patients who require continuing corticosteroid treatment, or who have adverse events (grade 3 or greater non-hematologic, or grade 2 pneumonitis) due to MK-3475 that do not resolve within 12 weeks of AE start date will not receive SBRT and will also be removed from study. Patients who develop grade 3 pneumonitis will be removed from the study, regardless of whether it resolves. SBRT will delivered in dose cohorts as described below in section 5.3.

Following SBRT, all patients will restart MK-3475 as soon as feasible. They will continue until they have further progression of disease, defined as irPD, or at the discretion of the treating physician if they are felt to receiving clinical benefit.

If MK-3475 is held at any point during a subject's participation in the trial for any reason, the subject will be followed as per standard of care until treatment with MK-3475 is resumed. When treatment with MK-3475 is resumed, the subject will continue with Day 1 procedures for the next planned cycle.

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The **phase 2a portion** is an expansion cohort with enrollment closing when 20 NSCLC patients have been enrolled (including those enrolled on phase I). Similar to the phase Ib portion, NSCLC patients who initiated trial therapy on MK-3475 will receive MK-3475 until there is progression of disease (irPD). Patients who do not have progression of disease within that timeframe may continue to receive MK-3475 for up to 18 months per protocol. These patients will not be evaluable for the study endpoints, although their response rates and overall survival will be reported. NSCLC patients will be enrolled after they have irPD on anti-PD-1 therapy received prior to study entry. After progression, an SBRT target will be selected and patients will be treated at the SBRT MTD as determined in the Phase Ib portion of the study, for lung and non-lung targets. The SBRT target will be chosen and ideally SBRT will be delivered as quickly as feasible after the last infusion of MK-3475. In the event of drug-related toxicity or other delay, SBRT may start up to 12 weeks after the last infusion as detailed below in section 5.2.3. Following SBRT, all patients will receive MK-3475 until they develop progression of disease (as defined by irPD), or until they are no longer receiving clinical benefit.

For each phase of the study, the first course of MK-3475 will start on day 1, and will be given every 3 weeks (+/- 7 days) (one cycle). Patients will undergo re-imaging CT of the chest, abdomen, and pelvis at the end of cycle 2, cycle 4, and every 4 cycles thereafter (i.e., at cycles 8, 12, etc.). After the SBRT, when MK-3475 is re-initiated, imaging will be done at the end of cycles 2, 4, and then every 4 cycles. Exceptions to the timing of re-imaging can be made by the treating investigator as necessary to determine course of treatment.

Following SBRT, MK-3475 will be re-started and administered in 3-week cycles as quickly as feasible. Dose modifications or delays may be made per section 5.2.2, based on prior toxicity from the first course of drug treatment. Treatment will continue until progression of disease, which **will be defined for this purpose as progression in comparison to the tumor imaging obtained immediately before or after SBRT (whichever is more recent).** At the discretion of the principal investigator, patients may continue to receive treatment if they are receiving clinical benefit. For the purpose of measuring response, the irradiated lesion will no longer qualify as measurable disease.

Progression of Disease (irPD) for this study will be defined using the Immune-Related Response Criteria (irRC), with the following qualification:

> Radiographic progression of disease by RECIST criteria (but not by irRC) where, in the opinion of the investigator, the patient would no longer benefit from continuing drug therapy, will be considered progression of disease.

During the **pre-SBRT** MK-3475, radiation to isolated sites of metastatic disease is not permitted.

During the **post-SBRT** MK-3475, local surgery and/or radiation therapy to isolated sites of metastatic disease is permitted and the patient can continue the MK-3475 provided there is evidence of continuing benefit from systemic treatment (i.e., stable disease or response in at least one other measurable lesion, or clinical improvement).

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5.2.2 MK-3475 Dose and Dose Modification

Drug Dose & Storage

Clinical Supplies will be provided by Merck & Co., Inc., as summarized in table 3 below.

Table 3. Product Description

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

MK-3475 will be administered at 200 mg, by IV infusion, every 3 weeks (+/- 7 days) on day 1 of each cycle.

Dose Modification (Escalation/Titration/Other)

MK-3475 will be withheld for drug-related Grade 4 hematologic or laboratory toxicities, non-hematological toxicity ≥ Grade 3, or severe or life-threatening AEs as per Table 4 below. If MK-3475 is held at any point during a subject's participation in the trial for any reason, the subject will be followed as per standard of care until treatment with MK-3475 is resumed. When treatment with MK-3475 is resumed, the subject will continue with Day 1 procedures for the next planned cycle.

Table 4: Dose modification guidelines for drug-related adverse events.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

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Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[b] 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; Refer to **Error! Reference source not found.** – Infusion Treatment Guidelines for further management details.

[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

In case toxicity does not resolve to Grade 0-1 within 12 weeks of AE start date, trial treatment should be discontinued after consultation with the sponsor. With sponsor and principal investigator agreement, subjects with a laboratory adverse events 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 5.5.

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.

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 7 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

MK-3475 will be administered as a 30 minute IV infusion. 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).

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5.2.3 Stereotactic Body Radiation Therapy (SBRT)

Target Selection

Target selection for SBRT will occur after the patient develops progression of disease on the pre-SBRT treatment with MK-3475. For the Phase Ib portion, patients will be allocated to Arm A (Lung target) if the SBRT target overlaps the lung parenchyma, otherwise patients will be allocated to Arm B (Non-Lung target). Targets suitable for SBRT for all phases of the study must meet all of the following requirements. Melanoma and NSCLC patients with prior treatment on anti-PD1 therapy will only be enrolled if there is a suitable target. In NSCLC patients initiating MK-3475 as first protocol treatment, if there are no suitable targets for SBRT after the pre-SBRT MK-3475, the patient may be observed and interval re-imaging may be obtained at the discretion of the investigators. Patients who cannot be treated with SBRT within 12 weeks of the most recent infusion of MK-3475 will be taken off treatment and moved to survival follow up. Exceptions to the 12 week window may be allowed for individual patients at the discretion of the Principal Investigator. MK-3475 may be administered after progression has been determined while SBRT is planned. Additionally, target lesions:

1. Must not be located in the liver, small or large bowel
2. Treatment must be accomplished without exceeding any normal tissue dose limit, as defined in the report of the American Association of Physicists in Medicine, Task Group 101 report[55].

SBRT Planning

Patients will undergo CT simulation and treatment planning per standard practice. Patient immobilization should be sufficient to ensure minimal intra- and inter-fraction set-up error, and is otherwise left to the discretion of the treating radiation oncologist. For lung targets, a technique for motion management is required, which may include tumor tracking, respiratory gating, or 4D-CT simulation. The treating physician will define a planning target volume (PTV) to which the dose will be described, and which will be used to define local control or local failure. At least 90% of the PTV should receive 90% or more the prescription dose. All organs at risk within 5 cm of the PTV will be contoured, and dose-volume histograms produced. For all organs at risk contoured, dose limits will be followed without exception[55].

SBRT Treatment Administration

The first fraction of SBRT should be delivered as soon as feasible after progression of disease. For the following events, SBRT should be delayed until they resolve (for toxicities, to grade 0 or 1), up to 12 weeks after the last infusion of MK-3475. If the listed events do not resolve within 12 weeks of the last infusion of MK-3475, the patient will be removed from the study and replaced.

1. Grade 2 or greater pneumonitis
2. Corticosteroid use within 2 weeks of SBRT, except in individual cases allowed by the Principal Investigator
3. Grade 3 or greater non-hematologic toxicity related to study therapy

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Patients who develop grade 3 or greater pneumonitis during the pre-SBRT MK-3475 will be taken off of the study, and will not be eligible for SBRT, or re-initiation of MK-3475.

Patients will be treated on non-consecutive days whenever possible, with all fractions to be scheduled within 15 calendar days from first to last. Localization of the tumor target before each fraction is required, by either cone-beam CT scan, kilovoltage on –board imaging, or an internal fiducial.

SBRT Dose Modification and Supportive Care

SBRT will be discontinued if any grade 3 or greater adverse event occurs during radiation treatment that is probably or definitely attributable to radiation. This will be counted as a DLT if it occurs during the phase Ib portion of the study. These patients will be allowed to continue with trial therapy (the second course of MK-3475, but not the remainder of their SBRT) if the toxicity resolves to grade 0 or 1 with supportive measures within 12 weeks of AE start date.

SBRT will also be discontinued if the completion of all fractions is prolonged beyond 30 days for reasons unrelated to toxicity (i.e., intercurrent illness, or patient refusal). This will not be counted as a DLT, and these patients will be allowed to continue with trial therapy (the second course of MK-3475, but not the remainder of their SBRT) as long as the investigator believes that they will be compliant with the remainder of the trial therapy. In the phase Ib portion of the study, these patients will not be counted towards the minimum number of patient treated at that dose level as long as they have not experienced a DLT before treatment is abort, but instead will be replaced. If they have experienced a DLT during that period, then they will be counted toward that dose cohort.

No other SBRT dose modification for individual patients is permitted during the phase Ib portion of the study. During the phase 2a portion, at the discretion of the treating radiation oncologist and with the agreement of the principal investigator, the prescription dose for SBRT may be reduced in an effort to reduce the risk of toxicity. In this case, one of the 3 dose levels specified in the dose escalation section 5.3 will be used.

Adverse events that occur during or after SBRT should be managed per section 5.5, or with best supportive care.

5.3 SBRT Dose-Escalation or De-Escalation

In the Phase 1b (SBRT dose escalation/de-escalation) portion, patients will be allocated to Arm A (Lung) or Arm B (non-Lung) based on the anatomic site of the target chosen for SBRT. Dose escalation or de-escalation will be done separately for each arm, and the MTD determined separately for each arm. Once an MTD has been determined for lung and non-lung targets, future patients with those SBRT targets will be allocated to the Phase IIa portion of the trial.

In the Phase 2a (expansion) portion, patients will be treated at the SBRT MTD for lung or non-lung lesions, as appropriate.

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Dose-Escalation or De-Escalation

In the Phase Ib portion of the trial, the SBRT dose will be escalated or de-escalated in successive cohorts. The starting dose will be 3000 cGy in 5 fractions. A single de-escalation cohort (1000 cGy in a single fraction), and a single escalation cohort (3000 cGy in 3 fractions) will be allowed.

Because SBRT target selection and treatment will occur in a rolling fashion after a patient progresses on the pre-SBRT MK-3475, availability for enrollment on the dose escalation cohorts will be somewhat unpredictable. In an effort to maximize the number of available treatment slots, enrollment in the dose escalation arms will be done using a "Rolling Six" design, following the guidelines in Table 5, below[56]. A minimum of two patients will be enrolled at each dose level. After 2 patients have been enrolled, the treatment cohort will be determined by the number of patients enrolled, the number who have experienced a DLT, the number who have not, and the number who have not yet completed the DLT follow-up period. The rolling enrollment design allows more than three patients to be enrolled within a dose cohort before safety has been demonstrated, and reflects the fact that both MK-3475 and SBRT have demonstrated safety at higher doses than prescribed in this protocol, as single agents.

If the lowest dose cohort of 1000 cGy in a single fraction is not completed with acceptable toxicity, those targets (i.e., lung or non-lung) will be excluded from the remainder of the study. If neither arm is able to be completed at the lowest SBRT dose level, the study will be terminated. If the highest dose level of 3000 cGy is reached and successfully completed, that will be the MTD for the phase IIA portion of the study. A minimum of 6 patients will be treated at the MTD in the phase Ib portion of the study.

Table 5.

Enrolled	DLT	No DLT	In follow-up	Cohort to enroll
2	0, 1	Any	Any	Enroll at same dose level
2	2	Any	Any	Enroll at **lower** dose level
3	0	0, 1, 2	3, 2, 1	Enroll at same dose level
3	0	3	0	Enroll at **higher** dose level*
3	1	0, 1, 2	2, 1, 0	Enroll at same dose level
3	>= 2	Any	Any	Enroll at **lower** dose level
4	0	0, 1, 2, 3	4, 3, 2, 1	Enroll at same dose level
4	0	4	0	Enroll at **higher** dose level*
4	1	0, 1, 2, 3	3, 2, 1, 0	Enroll at same dose level

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4	>= 2	Any	Any	Enroll at **lower** dose level
5	0	0,1,2,3,4	5,4,3,2,1	Enroll at same dose level
5	0	5	0	Enroll at **higher** dose level*
5	1	0,1,2,3,4	4,3,2,1,0	Enroll at same dose level
5	>= 2	Any	Any	Enroll at **lower** dose level
6	0	0,1,2,3,4	6,5,4,3,2	SUSPEND enrollment
6	0	5, 6	1, 0	Enroll at **higher** dose level**
6	1	0,1,2,3,4	5,4,3,2,1	Suspend enrollment
6	1	5	0	Enroll at **higher** dose level**
6	>= 2	Any	Any	Enroll at **lower** dose level

*At the maximum dose level, continue current dose cohort
**At the maximum dose level, STOP, this is the MTD

Definition of Dose Limiting Toxicity

For the purpose of determining the MTD of SBRT, a DLT will be considered to be any of the following adverse events which are probably or definitely attributable to study treatment, and which occur between the first fraction of SBRT and within 60 days of the last fraction of SBRT.

1. Any non-hematologic, non-laboratory toxicity which is grade 3 or greater and does not resolve to grade 2 or lower with supportive care within 14 days.
2. Any non-hematologic, non-laboratory toxicity which is grade 4 or greater
3. For patients in Arm A (lung targets), the development of grade 3 or greater pneumonitis that is probably or definitely attributable to either SBRT or MK-3475 within the follow-up period will be considered a DLT, regardless of whether it resolves.

5.4 Concomitant Medications/Vaccinations (allowed & prohibited)

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.

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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 as defined in Section 7.2.

Prohibited Concomitant Medications

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

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

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of 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.

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

5.5 Rescue Medications & Supportive Care

Supportive Care Guidelines

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

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require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 5.2.1 for dose modification.

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

- Pneumonitis:
    - For Grade 2 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For Grade 3-4 events, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- Diarrhea/ Colitis: Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For Grade 2 diarrhea/ colitis, administer oral corticosteroids.
    - For Grade 3 or 4 diarrhea/ colitis, treat with intravenous steroids followed by high dose oral steroids. All subjects who experience diarrhea/ colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)
    - For T1DM or Grade 3-4 Hyperglycemia

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        - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.

        - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- Hypophysitis:

    - For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

    - For Grade 3-4 events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- Hyperthyroidism or Hypothyroidism:

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

    - Grade 2 hyperthyroidism events (and Grade 2-4 hypothyroidism):

        - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.

        - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.

    - Grade 3-4 hyperthyroidism

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

- Hepatic:

    - For Grade 2 events, monitor liver function tests more frequently until returned to baseline values (consider weekly).

        - Treat with IV or oral corticosteroids

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- For Grade 3-4 events, treat with intravenous corticosteroids for 24 to 48 hours.
- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- Renal Failure or Nephritis:
  - For Grade 2 events, treat with corticosteroids.
  - For Grade 3-4 events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
-

Management of Infusion Reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Table 6 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of MK-3475.

Table 6 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from**	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).

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NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	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		

5.6 Other Considerations

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.

For this study, male subjects will be considered of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to any underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

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OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence† from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- Cervical cap with spermicide (nulliparous women only)
- Contraceptive sponge (nulliparous women only)
- Male condom or female condom (cannot be used together)
- Hormonal contraceptive: oral contraceptive pill (estrogen / progestin pill or progrestin-only pill), contraceptive skin patch, vaginal contraceptive ring or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region

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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, subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study drug initiation (or 14 days prior to the initiation of study drug of oral contraception) throughout the study period up to 120 days after the last dose of study drug. 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.

Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with MK-3475, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 8.

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.

5.7 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 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.

A subject must be discontinued from treatment, or removed from the study for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Progression of disease during the second course of MK-3475 (as defined in section 5.2.1)
- Unacceptable adverse experiences as described in Section 5.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test

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- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 12 months of treatment with post-SBRT MK-3475
  Note: 12 months of study medication is calculated from the date of first dose of the second course. Subjects who stop MK-3475 after 12 months will be eligible for up to one year of additional study treatment if they progress after stopping study treatment
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Sections 6 and 7. 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 8). Subjects who discontinue treatment will be followed for survival until death, withdrawal of consent, or the end of the study, whichever occurs first. Survival follow up may be a phone call only.

5.8 Subject Replacement Strategy

In both phases of the study, patients will be replaced if

1. They do not complete at least one fraction of SBRT.
2. They do not complete their entire course of SBRT as prescribed due to reasons other than toxicity (e.g., patient refusal, or intercurrent illness).

5.9 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.

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6.0 STUDY CALENDAR – NSCLC PATIENTS WITHOUT PRIOR ANTI-PD-1 THERAPY

Trial Period:		**Treatment**										**End of Treatment**	**Follow Up**	
Treatment Cycle/Title:	Screening	1	2	3+	4+	At Progression[10]	SBRT	1	2	3+	4+	At Progression, Discontinuation	Safety Follow-Up Visit	Survival Follow-up
Scheduling Window (Days):	-28 to -1	± 7	± 7	± 7	± 7	± 7		± 7	± 7	± 7	± 7	± 7	30 Days post End of Treatment (± 7)	Every 12 weeks (± 7)
Informed Consent	X													
Medical History	X													
Full Physical Exam, VS & weight	X													
Height	X													
Medication Review	X	X	X	X	X	X		X	X	X	X	X		
CT chest/abdomen/pelvis[1]	X		X		X				X		X			
Directed Physical Exam, VS & weight		X	X	X	X	X		X	X	X	X	X		
ECOG Performance Status	X	X	X	X	X	X		X	X	X	X	X		
Adverse Event Assessment	X	X	X	X	X	X	X[3]	X	X	X	X	X	X[14]	
Pregnancy Test – Urine or Serum β-HCG	X[11]													
Archival or Fresh Tumor Collection[4]	X[2]													
CBC with Differential	X	X	X	X	X			X	X	X	X			
CMP, LDH	X	X	X	X	X			X	X	X	X			
TSH & Free T4 [15]	X		X		X				X		X			
Selection of SBRT target[7]						X								
Blood for correlative studies	X[5, 12]	X[5, 12]	X[5]	X[5]	X[5]	X[5]	X[5, 12]	X[5, 12]	X[5]	X[5]	X[5]	X[5]		
Survival follow-up														X
Administer study drug, MK-3475[9]		X[11]	X	X	X[6, 13]			X[8]	X	X	X[16]			

[1] During week 3 every 2 cycles (during the last week of cycles 2 and 4), and then every 4 cycles (at the end of cycles 8, 12, etc.). See Section 8.5 for exceptions.

[2] Includes PD-L1 testing
[3] Study visit the last day of SBRT
[4] When feasible, if a biopsy is done for clinical purposes as per standard of care at any point during a subject's participation on trial, tissue may be collected at the time of the biopsy
[5] Blood for correlative studies will be drawn at cycles 2 through 4 for both pre- and post-SBRT, then every even-numbered cycle thereafter (e.g. 6, 8, 10, etc.). If MK-3475 is held for any reason when blood for correlative samples is to be drawn, the blood may be drawn at the discretion of the Principal Investigator. When MK-3475 is resumed, blood for correlative samples will be taken as per the calendar above.
[6] May be administered for up to 18 months if no disease progression. If no disease progression and > 12 months on study drug, patient cannot receive SBRT on trial
[7] Must be determined within 12 weeks of last dose of MK-3475 or patient will be removed from study and replaced. Exceptions to timing may be made by the Principal Investigator
[8] Will be restarted following SBRT as soon as possible
[9] Given every 3 weeks on Day 1 of each cycle (+/- 7 days) until progression
[10] Patients who have progression within 12 months of study entry will be evaluable for SBRT and re-initiation of MK-3475. First SBRT fraction should be administered as soon as feasible after disease progression, following resolution of toxicities listed in section 5.2.3, and at least 1 week post last MK-3475 infusion
[11] Pregnancy test within 72 hours of first dose of study medication for WOCBP
[12] First pre-treatment correlative lab draw for lung patients can be drawn either during screening and/or prior to first MK-3475 administration and post-SBRT and/or prior to cycle 1 dose of MK-3475 following SBRT. Both are not required, but can be collected.
[13] Following disease progression, MK-3475 may continue to be administered while subjects wait for radiation therapy with SBRT to begin at the discretion of the treating investigator.
[14] Required 30 days (+/- 7 days) from the End of Treatment visit, unless there were no toxicities > Grade 1 probably, or definitely related to protocol treatment at the End of Treatment visit. In this case, the End of Treatment visit will suffice as the safety follow up visit.
[15] After the screening period, TSH and Free T4 to be done every other cycle starting with week 2
[16] Drug may be administered for up to 12 months from the first dose of the second course. Subjects who stop drug after 12 months will be eligible for up to 1 year of additional treatment if they progress after study drug is stopped.

STUDY CALENDAR – MELANOMA PATIENTS AND NSCLC PATIENTS WITH PRIOR ANTI-PD-1 THERAPY

		Treatment					End of Treatment	Follow-Up	
Treatment Cycle/Title:	Screening	SBRT	1	2	3+	4+	At Progression, Discontinuation	Safety Follow-Up Visit	Survival Follow-Up

Scheduling Window (Days):	-28 to -1		± 7	± 7	± 7	± 7	± 7	30 Days post End of Treatment (± 7)	Every 12 weeks (± 7 days)
Informed Consent	X								
Medical History	X								
Full Physical Exam, VS & weight	X								
Height	X								
Medication Review	X		X	X	X	X	X		
CT chest/abdomen/pelvis[1]	X			X		X			
Directed Physical Exam, VS & weight			X	X	X	X	X		
ECOG Performance Status	X		X	X	X	X	X		
Adverse Event Assessment	X	X[3]	X	X	X	X	X	X[9]	
Pregnancy Test – Urine or Serum β-HCG	X[7]								
Archival or Fresh Tumor Collection[4]	X[2]								
CBC with Differential	X		X	X	X	X			
CMP, LDH	X		X	X	X	X			
TSH & Free T4 [10]	X			X		X			
Selection of SBRT target									
Blood for correlative studies	X [8]	X [8]	X[8]	X[5]	X[5]	X[5]	X		
Survival Follow-up									X
Administer study drug, MK-3475 [6]			X[7]	X	X	X			

[1] During week 3 every 2 cycles (during the last week of cycles 2 and 4), and then every 4 cycles (at the end of cycles 8, 12, etc.)
[2] Includes PD-L1 testing
[3] Study visit the last day of SBRT
[4] When feasible, if a biopsy is done for clinical purposes as per standard of care at any point during a subject's participation on trial, tissue may be collected at the time of the biopsy
[5] Blood for correlative studies will be drawn at cycles 2 through 4 for both pre- and post-SBRT, then every even-numbered cycle thereafter (e.g. 6, 8, 10, etc.). If MK-3475 is held for any reason when blood for correlative samples is to be drawn, the blood may be drawn at the discretion of the Principal Investigator. When MK-3475 is resumed, blood for correlative samples will be taken as per the calendar above.
[6] Will be started following SBRT as soon as possible every 3 weeks on Day 1 of each cycle (+/- 7 days) until progression. Drug may be administered for up to 12 months from the first dose of the second course. Subjects who stop drug after 12 months will be eligible for up to 1 year of additional treatment if they progress after study drug is stopped.
[7] Pregnancy test within 72 hours of first dose of study medication for WOCBP
[8] Correlative lab draw can be taken either post-SBRT and/ or prior to cycle 1 dose of MK-3475 following SBRT. Both are not required, but can be collected.

[9]Required 30 days (+/- 7 days) from the End of Treatment visit, unless there were no toxicities > Grade 1 probably, or definitely related to protocol treatment at the End of Treatment visit. In this case, the End of Treatment visit will suffice as the safety follow up visit.
[10] After the screening period, TSH and Free T4 to be done every other cycle starting with week 2

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

Furthermore, additional evaluations/testing may be deemed necessary by the investigators 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.

7.2 Screening Period

Prior to initiation of study therapy, the patient will require a screening visit(s). Scans, evaluations, and laboratory studies should be done as close to the initiation of therapy as feasible, and no more than 28 days prior. The following should be addressed during the screening period:

1. Informed Consent
2. Medical History
3. Complete physical examination, vital signs, and measurement of height and weight (pre-recorded height may be used from medical record)
4. Review of prior and concomitant medications
5. CT scan of chest, abdomen and pelvis (a PET/CT scan will be deemed sufficient)
6. Performance status evaluation
7. Determination of baseline adverse event status
8. Pregnancy test for women of childbearing potential, and counseling that sexually active women of childbearing potential must use an effective form of birth control during the entire study period
9. Determination of sufficient tumor specimen for evaluation of PD-L1 status
10. Laboratory studies: CBC with differential, serum chemistries, liver function tests, LDH, TSH and Free T4
11. Submission of blood for correlative studies (see footnote 5 above in the non-small cell lung cancer calendar and footnote 9 above in the melanoma calendar)

7.3 On-Study Visits

On-study visits will occur on day 1 of each cycle of MK-3475, and will include the following at <u>every</u> visit for melanoma and non-small cell lung cancer patients:

1. Directed physical examination, vital signs, and measurement of weight
2. Review of concomitant medications
3. Performance status evaluation
4. Determination adverse events

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5. Laboratory studies: CBC with differential, CMP, LDH
6. TSH and Free T4 will be done every other cycle starting with Cycle 2
7. CT scans of chest, abdomen and pelvis (a PET/CT scan will be deemed sufficient) will be done during week 3 every 2 cycles (at the end of cycles 2 and 4) and then every 4 cycles thereafter (at the end of cycle 8, 12, etc.)

A study visit will occur after clinically evident progression of disease on the first course of MK-3475 for non-small cell lung cancer patients, prior to SBRT treatment, and the following will be done prior to the initiation of SBRT:

1. Directed physical examination, vital signs, and measurement of weight
2. Review of concomitant medications
3. Performance status evaluation
4. Determination adverse events
5. Selection of SBRT target, and determination of lung versus non-lung arm

After clinically evident progression on the second course of MK-3475, the patient will be seen for a study visit, at which the following will be addressed:

1. Directed physical examination, vital signs, and measurement of weight
2. Review of concomitant medications
3. Performance status evaluation
4. Determination adverse events

During selected on-study visits, blood for correlative studies will be submitted per the study flow chart. Fresh tumor specimens will be obtained if feasible during therapy if the patient undergoes resection or biopsy for a standard-of-care clinical purpose per the study flow chart footnotes.

7.4 Post-Study Visits

Safety Follow-Up Visit

A follow-up will be conducted approximately 30 days (+/- 7 days) after the End of Treatment visit, or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs should be recorded. Subjects with an AE of Grade > 1 probably or definitely related to protocol treatment 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. However, if at the End of Treatment visit there are no toxicities Grade > 1 probably or definitely related to protocol treatment, the End of Treatment visit may be used as the safety follow up visit. 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.

Survival Follow-up

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Once a subject withdraws from study treatment, or discontinues trial therapy, the subject moves into a survival follow-up phase. They should be assessed for survival every 12 weeks, which may include being contacted by telephone. This should continue until patient death, until the patient withdraws consent for further follow-up, or until the study closes.

7.5 Tumor Imaging

CT scan of the chest, abdomen, and pelvis will be obtained at baseline. Then for each course of MK-3475 it will be obtained during the 3rd week of cycles 2 and 4, and then every 4 cycles thereafter (e.g., cycles 8, 12, etc). Additional re-imaging may be obtained at the discretion of the investigator. A PET/CT may be substituted for CT of the chest, abdomen, and pelvis if clinically appropriate. In the event the patient's insurance denies part of the scan (e.g only CT of the chest is approved), the Principal Investigator or patient's treating physician may waive part of the imaging requirement, or adjust the timing of imaging as medically necessary.

7.6 Study Assessments

Informed Consent

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

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

Medical History

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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.

Prior and Concomitant Medications Review

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.

Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

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.

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, or taken from the subject's medical record.

Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.4) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart. After Cycle 8 assessment of ECOG status will be performed every other cycle in conjunction with the directed or full physical exam.

Tumor Tissue Collection and Correlative Studies Blood Sampling

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Before and during trial therapy, if an irradiated or unirradiated lesion is biopsied or resected for clinical purposes, a sample will be retained for protocol-related correlative studies. After tissue is obtained, it will be subjected to flash freezing in liquid nitrogen and SNAP frozen tissue will be stored for further studies. If a patient has had a previous biopsy, the pre-treatment sample may be taken from paraffin-embedded tissue.

Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Procedures Manual.

Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

Study-Related Biopsies and Tissue Collection

Tissue from fresh or archival tissue (see below) is required at study entry. When a biopsy is being done for standard-of-care clinical purposes, tissue will be obtained from this procedure, if available.

Tumor tissue will be obtained prior to initiation of study therapy from any primary or metastatic site and processed according to the specifications of the lab manual. At the discretion of the principal investigator, archival tissue may be used in place of a fresh biopsy.

8.0 ADVERSE EVENT REPORTING

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.

8.1 Definitions

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-

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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 trial therapy, 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. All adverse events that after the consent form is signed but before treatment allocation must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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 fresh tumor biopsy, the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

Serious Adverse Events

A serious adverse event is any of the following:

- Death
- Any adverse event which is life threatening;
- Any adverse event leading to persistent or significant disability/incapacity;
- Any adverse event which results in or prolongs an existing inpatient hospitalization;
- A congenital anomaly/birth defect as a result of trial therapy;
- Any other important medical event
- Pregnancy

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. [21CFR312.32(a)]. Hospitalization related to convenience (e.g., transportation issues, etc.) will not be considered a SAE.

Progression of the cancer under study is not considered an adverse event.

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"Serious" Versus "Severe" Adverse Events: There is a distinction between serious and severe AEs. Assessment of seriousness will be made solely by the serious criteria listed above. Severity of AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events v4.0. Therefore, serious events will not be automatically considered severe. For example, a stroke that results in only a limited degree of disability may be considered a mild (not severe) stroke, but it would still meet serious criteria and thus, be captured as an SAE. Similarly, severe events may not always be serious. An example would be an episode of severe, transient nausea which persists for several hours. This would be classified as a "severe" episode of nausea, but if it did not require treatment, intervention, or somehow meet other serious criteria, it would not be considered an SAE.

Duration of Reporting of SAEs: From the administration of first treatment until 30 days (unless otherwise specified) subsequent to last treatment or withdrawal of subject, new onset adverse events will be captured. Follow-up and reporting of these events will follow the same procedure as for AEs observed during the study period. In addition, any unexpected Serious Adverse Event that occurs more than 90 days after drug administration but is possibly, probably or definitely attributed to drug administration will be recorded and reported.

Life-threatening Adverse Drug Experience: Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e. it does not include a reaction that, had it occurred in a more severe form, might have caused death. [21CFR312.32(a)]

Unexpected Adverse Drug Experience: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan. "Unexpected" as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.[21CFR312.32(a)]

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-Investigator and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor-Investigator and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new

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anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor-Investigator and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

- an overdose of Merck product. For the 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.
- 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.

Laboratory test abnormalities: Laboratory abnormalities that constitute an Adverse Event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. Please note that a dose hold or medication for a lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

Definition of an Overdose for This Protocol and Reporting of Overdose

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.

8.2 Attribution

Assessment of attribution is made by consideration of all clinically relevant data prior to, during, and after occurrence of the event, including diagnostic tests to assess the cause of the event. Clinically relevant data include, but are not limited to; underlying disease, past and present medical history (all concurrent non-malignant disease), concurrent medications, and timing between event and drug administration. The mechanism of action and prior toxicology of the study drug should be considered.

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An adverse event is *associated with the use of the drug* when there is a reasonable possibility that the experience may have been caused by the drug. [21CFR312.32(a)]

Attribution Standards per NCI – CTEP:

Unrelated	The Adverse Event is **clearly not** related to the investigational agent (s)
Unlikely	The Adverse Event is **doubtfully** related to the investigational agent(s)
Possible	The Adverse Event **may be** related to the investigational agent(s)
Probable	The Adverse Event **is likely** related to the investigational agent(s)
Definite	The Adverse Event **is clearly** related to the investigational agent(s)

8.3 Reporting to Merck

The Principal Investigator will report to Merck in an expedited manner all SAEs meeting the criteria of "serious", "unexpected" and "related to study treatment".

For the time period beginning when the consent form is signed until treatment allocation/ randomization, 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 must be reported within 24 hours to the Sponsor-Investigator and within two (2) working days to Merck Global Safety (GS) if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/ randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anti-cancer therapy, whichever is earlier, 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 whether or not related to Merck product, must be reported within 24 hours to the Sponsor-Investigator and within 2 working days to Merck GS.

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 following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Investigator-Sponsor and to Merck GS.

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

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

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Reporting of Overdose

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.

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)

Reporting of Pregnancy and Lactation

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 that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure/

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported to the investigator. All reported pregnancies 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)

8.4 Reporting to the Food and Drug Administration

At the discretion of the Principal Investigator, SAEs may be reported to the FDA. Written safety reports will use a MedWatch Form 3500 for voluntary reporting of adverse events, product problems and product use errors. 8.5 Reporting to Yale Human Investigation Committee

Expedited Reporting of Unexpected SAEs

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All SAEs meeting the criteria for expedited reporting will be reported to the Yale University Human Investigation Committee (HIC) using HIC Form 6A within 48 hours of discovery.

The Yale University Human Investigation Committee expedited reporting criteria are either:

a. Serious AND unanticipated AND possibly, probably or definitely related events;
b. Anticipated Adverse Events occurring with a greater frequency than expected.

8.6 Yale Safety Reporting and Monitoring (DSMP)

The PIs will monitor the clinical trial for safety. The PIs will assess all expedited adverse events and will periodically review all adverse events observed on the trial. Yale Cancer Center standard operating procedures (SOPs) for assessment and reporting of adverse events are followed which are in compliance with 21 CFR 312.32 and 312.22.

The clinical trial data consisting of all required observations, AEs, and laboratory data are entered into a computerized database in a timely manner. The accuracy and completeness of the database, timely submission of SAEs and compliance with the protocol, is assured by periodic auditing conducted by the Yale Cancer Center Data and Safety Monitoring Committee (YCC DSMC). Safety data will be submitted at least once yearly or more often as required by the YCC DSMC. On a regular interval basis, status reports of all laboratory parameters, AEs and SAEs are reviewed by the PI to view composite data across subjects. Regular meetings are held to discuss ongoing patient treatment and adverse events.

Expedited SAE reports submitted by the Investigator to FDA are also copied to the HIC and other relevant institutional safety committees within the timeframes required by Yale. These are also copied to Merck. The Principal Investigator will distribute manufacturer-provided safety reports and updated Toxicity Lists to the institution's HIC and all relevant personnel involved in the conduct of the study. The Toxicity List, in addition to the Investigator's Brochure, will be used as a reference for reporting any new SAE.

Possible actions taken by the PIs or the YCC DSMC if a new unexpected toxicity is identified from the above safety review, or if the periodic review of all adverse events and laboratory data indicates a pattern of incidence or severity of toxicity that raises a safety concern, can be to:

1. Revise consent form
2. Amend the protocol
3. Suspend the protocol

9.0 STATISTICAL ANALYSIS PLAN

In the phase 1b portion of the trial, patients will be enrolled in parallel dose escalation cohorts using the "Rolling Six" method, as described in Section 5.

The primary endpoint of the phase 2a portion of the study is the response rate to post-SBRT MK-3475, separately determined for a NSCLC cohort. A total of 12 patients will be treated at the MTD in the first phase of the study (6 each of lung and non-lung SBRT

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targets), and we project that this will include an approximately equal number of NSCLC and melanoma patients. In the second phase of the study, an expansion cohort will be enrolled until a total of 20 NSCLC patients eligible to undergo SBRT is reached (including NSCLC patients treated in the phase I and II portions of the study). We project that approximately 30% of patients (unselected for PD-L1 expression) will respond to the initial MK-3475 for 12 months or more and be replaced. Of those who go on to progress and being SBRT, we estimate that 30% will drop out, or otherwise be ineligible for assessment of response to post-SBRT MK-3475.

There is no published data to suggest a historical control for response to re-treatment with MK-3475, in patients who have been previously treated with MK-3475 and have prior documented progression of disease. In melanoma patients treated with anti-CTLA4 antibody, there is a documented response rate for re-treatment of patients who previously responded and subsequently progressed. In a series of 31 patients who initially had a partial or complete response, and then had progression of disease, re-induction with antibody resulted in a response in 13% of patients. It should be noted, however, that treatment beyond standard RECIST criteria was not permitted in the initial treatment course for these patients, so some may have had pseudoprogression. It is therefore presumed that the expected ORR without SBRT in this population, allowing for treatment beyond RECIST in their initial therapy with MK-3475 is less than 5%. If 4 of 20 patients (20%) in in the NSCLC expansion cohort develop a partial or complete response to post-SBRT MK-3475, this strategy will be deemed worth of further investigation. The 95% confidence interval will be (0.05, 0.49) by using one-sample proportion test with continuity correction.

The primary endpoint of this trial will be response rate and the secondary endpoint will be progression-free survival. We will use descriptive statistics to calculate frequency and proportion for the response rate to post-SBRT MK-3475. 95% confidence interval will also be provided. Exact binomial test will be used to compare the observed response rate versus historical control. For the secondary endpoint, we will use Kaplan-Meier estimator to present the progression-free survival.

10.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

10.1 Investigational Product

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

Clinical Supplies will be provided by Merck as summarized in Table 9.

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Table 9. Product Descriptions

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

10.2 Packaging and Labeling Information

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

10.3 Clinical Supplies Disclosure

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

10.4 Storage and Handling Requirements

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

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

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

10.5 Returns and Reconciliation

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

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

11.0 LABORATORY CORRELATIVE/SPECIAL STUDIES

11.1 Handling of Tissue

Before initiation of systemic therapy, local surgical therapy may be performed to obtain fresh tumor tissue. After tissue is obtained, it will be subjected to flash freezing in liquid nitrogen

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and SNAP frozen tissue will be stored for further studies. If a patient has a previously obtained paraffin-embedded tissue that is available, a portion may be used to conduct the studies mentioned below.

The SNAP frozen tissue specimens will be analyzed at Yale University. FFPE specimens will be analyzed for PD-L1.

11.2 Correlative Studies

Correlative studies will be conducted tissue specimens obtained before and during trial therapy. PD-L1 positivity will be determined on FFPE tissue. A number of additional biomarkers will be studied for their potential predictive value. These exploratory studies include (but are not limited to):

1) Markers to be studied on tumor cells: B7H1, PDL2, B7H4, Galactin-9.
2) Percent of tumor sample that constitutes CD4 and CD8 cells
3) Antigen-specific markers on T cells

Patients who undergo surgical procedures while on systemic treatment will also be asked to provide a research specimen to determine changes in the above markers in the context of response or resistance to therapy.

Immune monitoring will be performed as a part of this study. Peripheral blood lymphocytes (PBLs) and plasma will be collected before and during treatment, and when patients come off of study. Peripheral blood mononuclear cells will be separated and cryopreserved for T and B cell studies. Samples will be stored for future immunophenotyping studies and serological profiling, as well as cytokine profiling at the Yale Immune Monitoring Core Facility.

12.0 MEASUREMENT OF RESPONSE

Response will be evaluated by imaging studies as described in the study calendar. If symptoms develop or clinical deterioration occurs, patients may be imaged prior to the pre-specified time points for imaging.

Response of all systemic metastases will be evaluated in this study using two methods: the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee v1.1, and the Immune-Related Response Criteria (irRC). The irRC will be used to make protocol-related decisions regarding treatment response. Response by RECIST will be recorded for later analysis. RECIST version 1.1 stipulates that the number of lesions required to assess tumor burden for response determination has been reduced to a maximum of five total lesions (two lesions maximum per organ).

Briefly, measurable lesions must have a minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm) in at least one dimension. Lesions with a longest diameter of <10 mm are considered non-measurable lesions and will be tracked as non-target disease. Tumor lesions in a previously irradiated area, or in an area subject to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion. Following SBRT, response will be measured in comparison to the most immediate pre-

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SBRT imaging study, or imaging immediately following SBRT, whichever is most recent. For this purpose, the metastatic target chosen for SBRT will not qualify as a measurable lesion. For complete definitions of measurable and non-measurable disease, please refer to the RECIST v1.1 criteria.

12.1 Evaluation of Best Overall Response

The Best Overall Response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). For purpose of the primary endpoint of the study, the overall response will be measured during the post-SBRT MK-3475, in comparison to the most immediate pre-SBRT imaging.

12.2 Progression-Free and Overall Survival

For the purpose of the secondary endpoints of this study, PFS is defined as the time from initiation of study drug post-SBRT, until the first documented, confirmed progression of disease as described in Section 5. PFS will also be measured and report from the initiation of study drug, pre-SBRT. OS will be measure from the initiation of study therapy.

12.3 Local Control

The target lesion selected for SBRT will be followed for local control. For the purpose of the study, local control will be defined as a complete response, partial response, or stable disease within the planning target volume. The duration of local control will be measured from the final SBRT treatment fraction.

13.0 ADMINISTRATIVE AND REGULATORY DETAILS

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 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.

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15.0 APPENDICES

15.1 ECOG Performance Status

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

15.2 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)

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

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

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

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

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