COVER PAGE

Study Title: Phase 2B single-site, open-label, nonrandomized study evaluating the efficacy of neoadjuvant MK-3475 for unresectable Stage III and unresectable Stage IV melanoma

NCT02306850

Responsible Party: John Richart, MD

Documents: Study Protocol and Statistical Analysis Plan

Date of Study Protocol document: 1.8.19

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Saint Louis University

TITLE:
Phase 2B single-site, open-label, nonrandomized study evaluating the efficacy of neoadjuvant MK-3475 for unresectable Stage III and unresectable Stage IV melanoma

IND NUMBER: pending

EudraCT NUMBER:

1.0 TRIAL SUMMARY

Abbreviated Title	Neo MK-3475 for unresectable melanoma
Trial Phase	2B
Clinical Indication	Melanoma
Trial Type	single-site, open-label, nonrandomized
Type of control	n/a
Route of administration	intravenous
Trial Blinding	n/a
Treatment Groups	All subjects
Number of trial subjects	15
Estimated duration of trial	24-36 months after study start
Duration of Participation	20-24 months

2.0 TRIAL DESIGN

2.1 Trial Design

This is a Phase 2B single-site, open-label, nonrandomized 24-week study of the efficacy of neoadjuvant MK-3475 (200 mg every 3 weeks) in improving resectability rates in subjects with unresectable Stage III or unresectable Stage IV melanoma. Patients with unresectable Stage IV melanoma will be eligible for study entry if the investigators think that complete metastectomy would be possible if the anatomic site(s) of metastasis that are precluding curative resection at the time of study entry decreased in size by up to 50%.

A total of 15 subjects will be enrolled in the study.

At the Treatment Initiation Visit (Baseline/Day 1), eligible subjects will begin treatment with IV MK-3475 200 mg infusions every 3 weeks. Clinical assessments will be performed every 3 weeks during treatment. Imaging to assess initial response will be performed at Week 12 (after 4 cycles).

There are 5 types of response in this neoadjuvant trial:

- Complete Response (CR)
- Resectable Partial Response (rPR):
    - partial response amenable to curative resection in all affected sites
- Unresectable Partial Response (uPR):
    - partial response not yet amenable to curative resection
- Stable Disease (SD)
- Progressive disease (PD)

Patients with stable disease or any response at Week 12 will receive at least 24 weeks of treatment (8 cycles) and undergo repeat imaging at Week 24. Patients with no evidence of disease (CR or rPR after complete metastectomy) at Week 24 will be eligible to discontinue treatment (at Week 24 or Week 30 depending on time of response) enter the observation period with follow-up visits every 12 weeks for 1 year.

Complete responders at Week 12 will receive 4 additional cycles to complete 24 weeks of treatment (8 cycles). If CR is confirmed on Week 24 imaging, patients who achieved CR at Week 12 will discontinue treatment and enter the observation period. Patients who exhibit rPR at Week 12 assessment will undergo complete metastectomy and receive 4 additional cycles of MK-3475 to complete 24 weeks of treatment (8 cycles). If no evidence of disease is observed on Week 24 imaging, patients who achieved rPR at Week 12 will discontinue treatment and enter the observation period.

Subjects who display SD or uPR at Week 12 will continue MK-3475 for 12 additional weeks (4 cycles) with repeat imaging and resectability evaluation at Week 24.

If PD is noted on Week 12 imaging, repeat imaging will be performed 4 weeks later (Week 16). If PD is confirmed, the subject will exit the study. If stable disease or partial response is observed on Week 16 imaging, the patient will continue MK-3475 and be reassessed at Week 24 (after 8 cycles).

Patients who achieve CR at Week 24 (and who did not demonstrate CR at Week 12 assessment) will receive 2 additional cycles of MK-3475 (10 cycles total) before entering the observation period. At Week 24, complete metastectomy will be performed in patients with rPR; after surgery, these patients (rPR after complete metastectomy) will receive 2 additional cycles of therapy (10 cycles total) before entering the observation period.

Subjects who display SD or uPR at Week 24 will continue MK-3475 infusions every 3 weeks until disease progression or completion of 24 months of treatment.

If PD is observed on Week 24 imaging, repeat imaging will be performed 4 weeks later (Week 28). If PD is confirmed, the subject will discontinue MK-3475 treatment and exit the study. If stable disease or partial response is observed on Week 28 imaging, the patient will continue MK-3475 infusions every 3 weeks until disease progression or completion of 24 months of treatment.

The rationale for using 24-week treatment schedule for primary endpoint analysis (increase in 'resectability rate') is based on previous data from pilot studies. Data from a previous trial of 135 subjects with metastatic melanoma, demonstrated that 84.5% (44 of 52) of responders responded by 24 weeks. (Hamid et al 2013)

Tissue, blood and bone marrow aspirate specimens will be collected to further understand the immunomodulatory effects of MK-3475 and to identify any biomarkers of response. Histopathologic evaluation of affected and unaffected tissue will be performed during the study to characterize any differences in cellular profiles.

At the baseline visit, skin biopsy of melanoma tissue (if applicable), non-sun-exposed unaffected skin, and any nevi on non-sun-exposed skin will be performed. These specimens will be examined along with the metastatic specimen for pre-treatment immunohistochemical (IHC) evaluation.

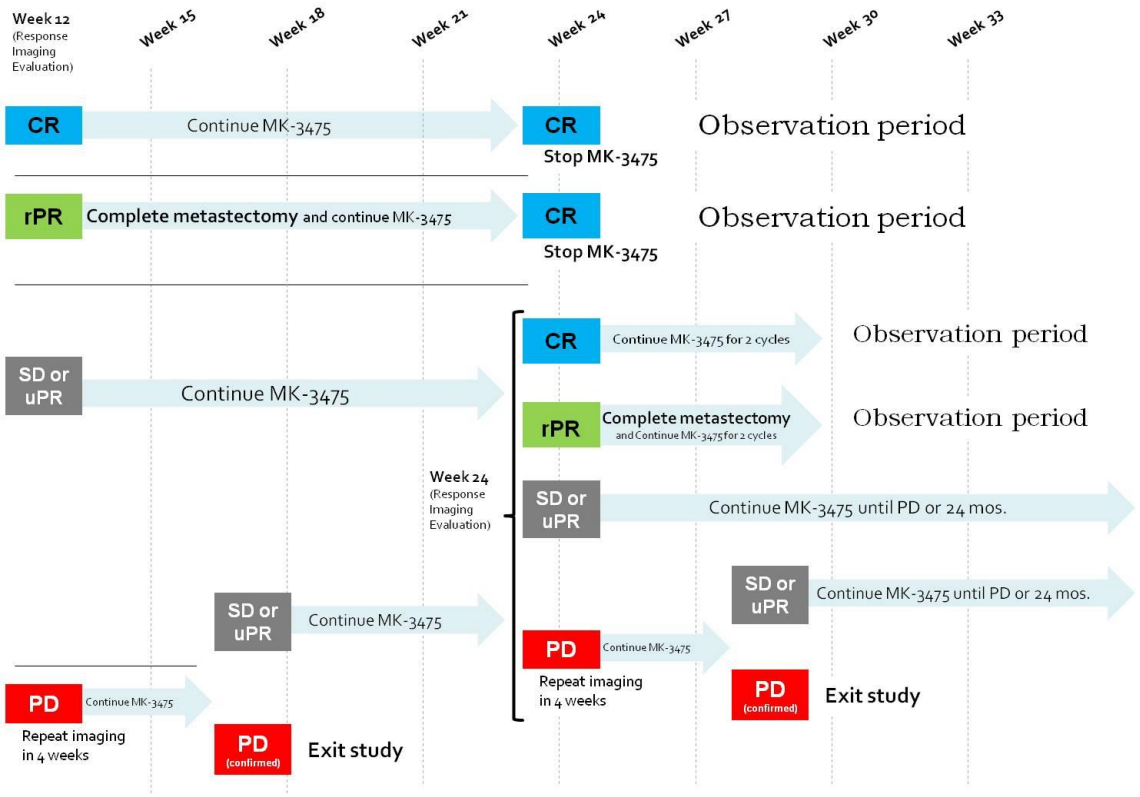
Histopathologic evaluation from unaffected skin and nevi in non-sun-exposed skin will be conducted at Week 12 and Week 24.

Post-treatment tissue histopathologic evaluation will be performed after curative resection on both responding and nonresponding tissue where possible. In complete responders, skin biopsies of non-sun-exposed unaffected skin and nevi will be performed.

In addition, flow cytometry of blood and bone marrow aspirates will be followed during the study to determine if MK-3475 induces any host immune response.

Safety assessments including adverse event (AE) monitoring will be performed at every visit and assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

2.2 Trial Diagram



Treatment Algorithm
All enrolled subjects will receive 4 cycles of IV MK-3475 infusions (200 mg) every 3 weeks. At Week 12, imaging to assess initial response will be performed. There are 5 types of response in this neoadjuvant trial:

1.) **Complete response (CR)**
2.) **Resectable partial response (rPR)**
3.) **Unresectable partial response (uPR)**
4.) **Stable disease (SD)**
5.) **Progressive disease (PD)**

Week 12:
Subjects that display CR, uPR, or SD at Week 12 will continue MK-3475 with reassessment at Week 24 (after 8 cycles). Patients with rPR at Week 12 will undergo complete metastectomy and continue MK-3475 with re-evaluation at Week 24. If PD is observed on Week 12 imaging, the subject will continue MK-3475 and repeat imaging will be performed in 4 weeks (Week 16). If PD is confirmed, the patient will stop MK-3475 and exit the study. If SD or uPR is seen on Week 16 imaging, the patient will continue MK-3475 for 4 additional cycles and imaging to reassess response will be performed at Week 24.

Week 24:
Subjects who, at Week 12, either attained CR or demonstrated rPR and underwent complete metastectomy, will discontinue MK-3475 after Week 24 (after 8 cycles) and enter the observation period if no evidence of disease is seen on Week 24 imaging. Patients that achieve CR at Week 24 (and did not exhibit CR at Week 12) or those that demonstrate rPR and undergo complete metastectomy at Week 24 will receive 2 additional cycles of MK-3475 (10 cycles total) before entering the observation period. Subjects who display SD or uPR at Week 24 will continue MK-3475 infusions every 3 weeks until disease progression or completion of 24 months of treatment. If PD is observed on Week 24 imaging, the subject will continue MK-3475 and repeat imaging will be performed in 4 weeks (Week 28). If PD is confirmed, the patient will stop MK-3475 and exit the study. If SD or uPR is seen on Week 28 imaging, the patient will continue MK-3475 infusions every 3 weeks until disease progression or completion of 24 months of treatment.

3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objective & Hypothesis:

Resectability Rate

Objective:

To evaluate the efficacy of intravenous MK-3475 as a neoadjuvant therapy in unresectable Stage III and unresectable Stage IV melanoma

Hypothesis:
Our hypothesis is that treatment with MK-3475 will result in a 20% increase in "resectability rate" in the study cohort compared to 0% (baseline before treatment) in melanoma, defined as 20% of study subjects becoming eligible for curative resection after treatment with MK-3475

3.2 Secondary and Exploratory Objectives & Hypotheses:

(1) Response by RECIST criteria

Objective:

To evaluate intravenous MK-3475 for response by RECIST criteria

Hypothesis:

Our hypothesis is that subjects treated with MK-3475 in this study have similar rates of response as demonstrated in previous studies by Hamid et al 2013.

(2) **Immunomodulatory effects and biomarkers of response**

Objective:

To further understand the immunomodulatory effects of MK-3475 and to identify any biomarkers of response by evaluating uninvolved skin tissue and blood/bone marrow aspirates

Hypothesis:

Our hypothesis is that uninvolved skin and blood/bone marrow aspirate will demonstrate changes in T-cell expression that can serve as a biomarker(s) of response and help to explain the systemic immune response during MK-3475 treatment

(3) Cellular profiles of responding and nonresponding tissue

Objective:

To evaluate differences in cellular or immunohistochemical (IHC) profiles of responding and nonresponding tissue

Hypothesis:

Our hypothesis is that the density of infiltration with CD8 T-cells in tumor tissue will correspond to the magnitude of response (amount tumor decreases after treatment)

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Pharmaceutical and Therapeutic Background

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [7; 8]. The structure of murine PD-1 has been resolved [9]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade [7; 10; 11; 12]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [13; 14]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells [15; 16]. Expression has also been shown during thymic development on CD4-CD8-

(double negative) T-cells as well as subsets of macrophages and dendritic cells [17]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [18; 19; 20; 13]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [13]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL) [21]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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

4.1.2 Preclinical and Clinical Trial Data

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

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

When melanoma presents at an early stage (Stage I or II) as in the majority of patients, it is a highly curable cancer. When diagnosed at an advanced stage, melanoma has a poor prognosis with reported 10 year survival rates of 24-43% in Stage IIIB/C melanoma and 5 year survival rates of 10-15% in Stage IV melanoma [22]. Surgery is the treatment of choice or a part of standard management in nearly all cases of melanoma (for both Stage I and II and most Stage III cases) [23]. In contrast, traditionally, for melanoma that has metastasized to any distant site, whether it be soft tissue, visceral, or a distant lymph node, the prevailing orthodoxy has been that systemic therapy alone was the only option. Surgery and locoregional management were thought to be futile as the development of multiple distant metastases was considered inevitable in any patient with metastatic disease, even in those with a solitary metastasis or oligometastases [24].

Currently, the paradigm is shifting and metastectomy now has a more prominent role in the management of advanced melanoma as there is increasing data to suggest that surgical resection may help to prolong survival. Sub-group analysis of data from the First Multicenter Selective Lymphadenectomy Trial (MSLT-1) revealed that those who received surgical management of their Stage IV disease only (no systemic therapy) had the longest median

overall survival duration (22.0 months), while those who received systemic therapy before surgery had the next longest median overall survival duration (17.0 months). By comparison, patients who received systemic therapy alone (no surgery) had a median overall survival duration of 6.9 months [25].

Though not completely understood, there are several theoretical biologic mechanisms that may explain the therapeutic benefit of surgery in advanced melanoma. The most commonly held belief is that tumor resection is immediately advantageous because it decreases the effects of tumor-induced immunosuppression [24]. It has also been suggested that surgical resection may interrupt the metastatic cascade that leads to hematogenous seeding or trigger the augmentation of the patient's own immune system [25]. One practical explanation that may account for the favorable disease course seen in those who undergo curative resection is that since metastases themselves can metastasize, removal of a metastasis limits the potential growth of future systemic tumor burden by making it physically impossible for the metastasis to spread [26, 24].

Despite the potential benefit of curative resection, unfortunately, the majority (78.6%) of patients with Stage IV disease are ineligible for complete metastectomy at initial presentation due to anatomic location or size of the metastatic lesion(s) [27]. On the other hand, in Stage III disease, complete surgical resection and lymph node dissection is almost always achievable; in only a small minority of cases, is it not feasible due to size and location of the primary tumor or lymph nodes. For both groups – unresectable Stage III and unresectable Stage IV melanoma, it has been proposed that a "neoadjuvant" approach, using a systemic therapy to decrease tumor burden before curative resection would be beneficial.

Neoadjuvant treatment in melanoma has been studied for decades, initially with chemotherapy and biochemotherapy, but is underutilized and still not commonly employed in routine clinical practice [28]. Data available are from retrospective analyses where 'resectability rate' was not the primary endpoint [29].

Recently, neoadjuvant vemurafenib has been shown to lead to rapid impressive tumor bulk reduction, within a few weeks in some cases [30]. However, while vemurafenib was effective in maintaining local disease control, it did not decrease the risk of metastatic relapse [31]. Immunotherapies may be a better option for use as a neoadjuvant agent compared to chemotherapy or molecular targeted therapies, which target tumor cells only. In theory, immunotherapies provide not only the possibility of tumor size reduction and resection, but also offer the prospect of inducing a systemic immune response, which may delay or prevent future metastatic relapse. There have been some preliminary studies with ipilimumab as a neoadjuvant therapy, but further studies of immunotherapies with a neoadjuvant approach are still needed [32].

MK-3475 is an intravenously administered programmed death (PD-1) receptor inhibitor which is pending FDA approval for metastatic melanoma that may be useful as a neoadjuvant therapy in melanoma [33].

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) is being conducted by Merck, Inc. to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the Merck MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

A novel primary endpoint, ”resectability rate”, was developed for this trial. Resectability rate is defined as the proportion of subjects in the trial that were unresectable at baseline who after treatment with MK-3475 are now eligible for curative resection with complete metastectomy.

Using resectability rate as the primary endpoint by definition makes those with resectable Stage III/IV disease ineligible for study entry. This decision was deliberate. Patients with resectable Stage III/IV disease were excluded; in non-responders delaying surgery may unnecessarily endanger the patient possibly allowing their melanoma to progress to an unresectable state which could potentially negatively affect their clinical outcome.

Ideally, the goal of any advanced melanoma treatment is to lead to complete response. For systemic therapies, it has been demonstrated that complete response is associated with increased overall survival [34]. In addition, it has been established that complete metastectomy in Stage IV melanoma improves survival for all M stages [25].

Thus, taken together, the goal of a neoadjuvant trial should be the ability of the treatment to lead to curative resection. This approach, should not only improve the duration of overall survival for patients, but also allows for the most tissue to be collected for histopathologic evaluation to further understand the mechanism of action and response of MK-3475.

The decision to use an increase in resectability rate as the endpoint was also based on our institutional experience and the inadequacy of current response criteria.

It is common practice at our institution (Saint Louis University) to perform curative resection when possible in Stage IV melanoma after systemic therapy. Though systemic therapy was not utilized initially to be a “neoadjuvant” therapy, we have found that performing curative resection after high-dose interleukin-2 (HD IL-2) has favorable results on both median duration of response and overall survival. Out of 55 evaluable patients with melanoma who underwent HD IL-2 at our institution, 8 achieved complete response (14.5%) and 6 achieved partial response, 3 of whom had “resectable partial response” and 3 of whom who had “unresectable partial response” [35].

In patients that were able to achieve "resectable partial response" or a decrease in tumor burden rendering a patient's disease amenable to complete metastectomy, a longer median duration of response (9.1 months) than reported rates (~6 months) for partial response to HD IL-2 was seen [36]. In addition, the overall survival of these patients was much longer than would have been expected by their M stage if they received systemic therapy alone based on data from MSLT-1 trial [25].

Patient	Sites of metastasis Prior to HD IL-2	Sites of metastasis After HD IL-2 (which were resected)	Progression-free duration (months)	Duration of survival (months)	Expected duration of survival if treated with systemic therapy alone**
1	Lung, bone, lymph nodes	LN	4.37	39.5	6.3
2	lung, LN, gallbladder	gallbladder	13.3	17.9	6.3
3	Multiple lung nodules	few lung nodules	9.1	19.0	9.1

** Survival estimates based on data from MSLT-1 trial (Howard et al 2012) from patients with same M stage treated with systemic therapy alone

The RECIST criteria, designed to evaluate the benefit of systemic therapies, which measure response by assessing the measurement of overall tumor burden, are not well suited for use as an endpoint or the deciding factor in whether to perform surgery in a neoadjuvant trial. [37]. Using partial response by RECIST criteria as the deciding factor at the very least may be incongruent with clinical reality and may possibly prohibit surgery where it is in the best interest of the patient.

There are situations where a minimal response to systemic therapy may permit curative resection, which theoretically should improve survival. In the example below, the retroperitoneal tumor is unresectable making curative resection unattainable, but this site is potentially resectable with a small decrease in size, which if it occurred would make the patient eligible for complete metastectomy.

	Size	Resectable or unresectable
Brain	0.7 cm	Resectable
Skin	1.9	Resectable
Retroperitoneal mass	6.0 cm	Unresectable due to proximity to vital structures (potentially resectable if decrease in size by 1.2 cm to 4.8cm)
Overall tumor burden	**8.6cm**	

If the retroperitoneal tumor did decrease in size to 4.8 cm and even if the other sites did not respond to treatment, the patient would be eligible for curative resection in this study. However, by RECIST criteria, which measures overall tumor burden, this patient would be considered stable disease and not eligible for complete metastectomy, since overall tumor burden has only decreased in size by 14%.

	Size (cm)	Size after MK-3475 treatment (cm)
Brain	0.7	0.7
Skin	1.9	1.9
Retroperitoneal mass	6.0	4.8
Overall tumor burden	**8.6cm**	**7.6 cm**

Stable disease by RECIST criteria, only 14% decrease in overall tumor burden, but patient would be eligible for curative resection

Even though partial response by RECIST criteria, which requires a decrease in the measurement of overall tumor burden by 30%, appears to be a higher standard for undergoing surgery, there are situations when achieving partial response by RECIST criteria may be an inaccurate determinant in resectability as detailed below. Even though in this example, the patient had remarkable response including resolution of brain metastasis, the patient's Stage IV disease is still unresectable.

	Baseline Size (cm)	Size after MK-3475 treatment (cm)
Brain	0.7	0
Skin	1.9	0
Retroperitoneal mass	6.0	6.0
Overall tumor burden	**8.6cm**	**6.0cm**

Partial response by RECIST criteria (30% decrease in overall tumor burden), but still unresectable.

For these reasons, an increase in resectability rate was selected as the most appropriate primary endpoint for this neoadjuvant trial.

4.2.3.2 Biomarker Research

Tissue (primary cutaneous melanoma and/or metastatic specimen), blood and bone marrow aspirate specimens will be collected before treatment and at Weeks 12 and 24 for T-cell subset analyses and functional assays to further understand the immunomodulatory effects of MK-3475.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

5.1.2 Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Have measurable disease based on RECIST 1.1.
4. Has a diagnosis of unresectable Stage III or Stage IV melanoma with anatomic site(s) of metastasis that could be amenable to curative resection if the site(s) decreased in size by up to 50% (at the investigators' discretion).
5. Have provided tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion.
6. Have a performance status of 0 or 1 on the ECOG Performance Scale.
7. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

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

	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

8. 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.

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

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

5.1.3 Subject Exclusion Criteria

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

1. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.

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

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

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

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

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

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

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

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

8. "Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.Has an active infection requiring systemic therapy.

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

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

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

12. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

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 dose of trial treatment.

16. Is currently being treated with ipilimumab (defined as ipilimumab treatment less than 6 weeks before first dose of MK-3475).

5.2 Trial Treatments

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

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
MK-3475	200mg	every 3 weeks	IV infusion	24 weeks to 24 months	regimen granted FDA's 'Breakthrough Therapy' designation – pending approval
The MK-3475 dosing interval may be increased due to toxicity as described in Section 5.2.1.2.					

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

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

5.2.1.2 Dose Modification

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

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

Toxicity	**Grade**	**Hold Treatment (Y/N)**	**Timing for restarting treatment**	**Dose/Schedule for restarting treatment**	**Discontinue Subject**
Hematological Toxicity	1, 2	No	N/A	N/A	N/A
	3* *Excluding Grade 3 neutropenia, anemia, and thrombocytopenia	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week	Toxicity does not resolve within 12 weeks of last infusion

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

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

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

5.2.2 Timing of Dose Administration

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

All trial treatments will be administered on an outpatient basis.

MK-3475 will be administered as a 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 5.2.1.2). Every effort will be made 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).

5.2.3 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

Not applicable. This is an open-label trial.

5.4 Stratification

Not applicable. This is an open-label trial.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required.

5.5.1 Acceptable Concomitant Medications

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

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications

administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.5.2 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
    - Note: Radiation therapy to symptomatic lesions or to the brain may be allowed.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed..
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved if the investigator deems it to be medically necessary..

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

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

- Diarrhea: Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.

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

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

- All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

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

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

- Immune-related adverse events: Please see Section 5.6.1.1 below and Appendix 12.4 regarding diagnosis and management of adverse experiences of a potential immunologic etiology.

- Management of Infusion Reactions: Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

- Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.

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

Table 5 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of MK-3475 with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated.	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	Subject is permanently discontinued from further trial treatment administration.	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

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

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

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

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

Table 6 General Approach to Handling irAEs

irAE	Withhold/Discontinue MK-3475?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold MK-3475	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3 and Grade 4	Withhold MK-3475 Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

5.6.1.2 Supportive Care Guidelines for Pneumonitis

Subjects with symptomatic pneumonitis should immediately stop receiving MK-3475 and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule

out other causes such as infection. If the subject is determined to have study drug associated pneumonitis, the suggested treatment plan is detailed in Table 7.

Table 7 Recommended Approach to Handling Pneumonitis

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

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

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

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

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

start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

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

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

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with MK-3475, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to 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 record the condition of the fetus or newborn. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Investigator's IRB and to Merck and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

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

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of treatment with MK-3475

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop MK-3475 after 24 months
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.4 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.9 Subject Replacement Strategy

5.10 Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug

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

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**									**Observation**
Treatment Cycle/Title:	Screening Visit	1	2	3	4	5	6	7	8	Week 24	(up to 4 visits)
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	Every 12 weeks
Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Demographics and Medical History	X										
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X
Trial Treatment Administration		X	X	X	X	X	X	X	X	(X)	
Clinical Procedures/Assessments											
Review Adverse Events		X	X	X	X	X	X	X	X	X	X
Full Physical Examination	X	X	X	X	X	X	X	X	X	X	X
Bone marrow aspirate (9 subjects)		X				X				X	
Surgical Assessment	X					X				X	
Cutaneous evaluation and skin biopsy		X				X				X	
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X										
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory											
Pregnancy Test – Urine or Serum β-HCG	X	X	X	X	X	X	X	X		X	X
CBC with Differential	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel and LDH	X	X	X	X	X	X	X	X	X	X	X
T3, FT4 and TSH	X				X				X		
Efficacy Measurements											
Tumor Imaging and Resectability Evaluation	X					X				X	X

Product: MK-3475
Protocol/Amendment No.: 2

Trial Period:	Screening Phase	Treatment Cycles[a]									Observation
Treatment Cycle/Title:	Screening Visit	1	2	3	4	5	6	7	8	Week 24	(up to 4 visits)
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	Every 12 weeks
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood											
Archival or Newly Obtained Tissue Collection		X				X				X	
Correlative Studies Blood and Bone Marrow Aspirate Collection (9 subjects)		X				X				X	

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to Investigator's IRB/ERC requirements, applicable laws and regulations.

7.1.1.2 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.

7.1.1.3 Medical History

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

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

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

7.1.1.4.2 Concomitant Medications

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

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

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

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

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

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

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

7.1.2.2 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,

7.1.2.3 Vital Signs

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

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart. After Cycle 8 assessment of ECOG status will be performed every other cycle in conjunction with the directed or full physical exam.

7.1.2.5 Tumor Imaging and Assessment of Disease

The investigators will review imaging at screening to confirm that the subject meets criteria for study entry. The investigators will assess response after Cycle 4 and Cycle 8 for primary endpoint analysis (increase in 'resectability rate'). Depending on the subject's response after Cycle 8, the subjects may receive additional cycles of MK-3475. After Cycle 8, repeat response assessment will be performed every 12 weeks.

7.1.2.6 Tumor Tissue Collection and Correlative Studies Blood Sampling

Tumor tissue and blood and bone marrow aspirate sampling will be obtained at baseline, Week 12, Week 24. Tumor tissue will be collected if accessible via skin, subcutaneous, or lymph node biopsy.

7.1.2.7 Laboratory Safety Evaluations (Hematology, Chemistry)

Laboratory tests for hematology, chemistry, and others are specified in Table 9. Laboratory tests for screening should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

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Table 9 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Urine pregnancy test †	Total thriiodothyronine (T3)
Hemoglobin	Alkaline phosphatase		Free thyroxine (T4)
Platelet count	Alanine aminotransferase (ALT)		Thyroid stimulating hormone (TSH)
WBC (total and differential)	Aspartate aminotransferase (AST)		
Red Blood Cell Count	Lactate dehydrogenase (LDH)		
Absolute Neutrophil Count	Carbon Dioxide ‡		
	(CO_2 or bicarbonate)		
	Uric Acid		
	Calcium		
	Chloride		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

7.1.3 Other Procedures

7.1.3.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. All subjects may receive up to 24 months of therapy during the course of the study.

Subjects who meet all of the following criteria may discontinue treatment prior to completing 24 months of therapy:

1. CR or rPR with complete metastectomy has been confirmed.
2. Patient has received at least 24 weeks (8 cycles) of MK-3475 therapy.
3. Patient has received at least 2 cycles of MK-3475 after CR or rPR with complete metastectomy is documented.

After discontinuing treatment following assessment of CR or rPR with complete metastectomy, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.4.5.4) and then proceed to the Observation Period (aka Follow-Up Period) of the study (described in Section 7.1.4.6).

7.1.4 Visit Requirements

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

7.1.4.1 Screening

Subjects will be screened prior to the first dose of MK-3475 (Baseline/Day 1) to confirm that they meet the entrance criteria for the study. The Screening visit may occur up to 4 weeks prior to initiation of study drug.

The study investigator or qualified designee will discuss the following with each subject the nature of the study, its requirements, and its restrictions. Written informed consent must be obtained prior to performance of any protocol-specific procedures.

The following procedures will be performed at the Screening visit

- Confirmation that subject meets all inclusion criteria and exclusion criteria, excluding evaluation of whether tumor burden is potentially amenable to curative resection.
- Recording of medical history. (Medical history is defined as a disease or syndrome that is ongoing at or stopped before Informed Consent.)

- Recording of current medications and all other drugs (including non-prescription drugs, vitamins, and dietary supplements) taken within 4 weeks prior to Screening.
- Complete physical examination
- Physical examination includes: general appearance, skin, HEENT (head, eyes, ears, nose and throat), heart (auscultation), lungs (auscultation), abdomen (palpation and auscultation), lower extremities (peripheral edema),
- Vital signs [blood pressure (BP); heart or pulse rate; and oral, tympanic, or temporal temperature], height and weight.
- Urine pregnancy test only for women who are of childbearing potential.
- Review of imaging to assess baseline metastatic tumor burden

7.1.4.2 Screening Period

7.1.4.2.1 Pre-treatment Surgical Assessment Visit

The following procedures will be performed at the Pre-Treatment Surgical Assessment visit:

- Review of medical history and concomitant medications
- Physical examination
  - Physical examination includes: general appearance, skin, HEENT (head, eyes, ears, nose and throat), heart (auscultation), lungs (auscultation), abdomen (palpation and auscultation), lower extremities (peripheral edema),
- Vital signs [blood pressure (BP); heart or pulse rate; and oral, tympanic, or temporal temperature], weight.
- Review of imaging to assess baseline metastatic tumor burden

7.1.4.2.2 Pre-treatment Resectability Evaluation

As part of the screening process, evaluation of the patient's tumor burden to verify that it meets criteria to be potentially amenable to curative resection (defined below) will be performed.

7.1.4.2.2.1 Tumor burden potentially amenable to curative resection:
Anatomic site(s) of metastasis that could be amenable to curative resection if the site(s) decreased in size by up to 50%.

If it is determined that the patient's tumor burden is potentially amenable to curative resection and the patient meets all other study criteria, the subject will enter the study.

7.1.4.2.3 Pre-treatment Cutaneous Evaluation

The Pre-treatment Cutaneous Evaluation will be performed after it has been determined that patient meets the requirements for study entry.

The following procedures will be performed at the Pre-Treatment Cutaneous Evaluation visit.

- Review of medical history and concomitant medications
- Skin examination and photography
- Skin biopsy of melanoma tissue (if applicable), non-sun-exposed unaffected skin, and any nevi on non-sun-exposed skin

7.1.4.3 Treatment Period

7.1.4.3.1 Treatment Initiation Visit

The objective of this visit is to ensure that subjects who will enter the study continue to meet all inclusion and exclusion criteria. The Treatment Initiation visit should take place within 4 weeks of Screening visit.

The following procedures will be performed at Treatment Initiation Visit (Baseline/Day 1) after confirmation that the subject has met all inclusion criteria and has no exclusion criteria present:

- Assessment of any changes (deletions, additions, or dose modifications) to medications.
- Adverse Event (AE) Monitoring.
- Physical examination
- Vital signs (BP; heart or pulse rate; and oral, tympanic, or temporal temperature), weight.
- Urine pregnancy test (β-hCG) for women who are of childbearing potential.
- Administration of MK-3475 (200 mg infusion)

7.1.4.4 Interval Visits

The objective of the interval visits is to monitor subject safety while ensuring continued compliance with study procedures. The Interval Visits will be performed every 3 weeks. Every attempt should be made to have individual subject assessments performed by the same physician (investigator or equally qualified physician listed on FDA form 1572).

The following procedures will be performed at all visits during treatment:

- Assessment of any changes (deletions, additions, or dose modifications) to medications.
- Adverse Event (AE) Monitoring.
- Physical examination
- Vital signs (BP; heart or pulse rate; and oral, tympanic, or temporal temperature), weight.
- Urine pregnancy test (β-hCG) for women who are of childbearing potential.
- Administration of MK-3475 (200 mg infusion)

After 4 cycles of MK-3475 (Week 12), the subject will undergo imaging to assess response to MK-3475. The subject will also undergo repeat Surgical Assessment and Cutaneous Evaluation at Week 12 (see below).

At Week 12, blood and bone marrow specimens will be collected for T-cell subset analysis and functional assay testing.

7.1.4.4.1 Week 12 - Surgical Assessment Visit

The following procedures will be performed at the Week 12 - Surgical Assessment visit after 4 cycles of MK-3475.

- Review of medical history and concomitant medications
- Physical examination
    - Physical examination includes: general appearance, skin, HEENT (head, eyes, ears, nose and throat), heart (auscultation), lungs (auscultation), abdomen (palpation and auscultation), lower extremities (peripheral edema),
- Vital signs [blood pressure (BP); heart or pulse rate; and oral, tympanic, or temporal temperature], weight.
- Review of imaging to assess metastatic tumor burden

7.1.4.4.2 Week 12 - Cutaneous Evaluation

The following procedures will be performed at the Week 12 - Cutaneous Evaluation after 4 cycles of MK-3475.

- Review of medical history and concomitant medications
- Skin examination and photography
- Skin biopsy of melanoma tissue (if applicable), non-sun-exposed unaffected skin, and any nevi on non-sun-exposed skin

7.1.4.4.3 Week 12 - Resectability Evaluation

Initial imaging will be performed at Week 12 (after 4 cycles) to assess whether tumor burden is amenable to curative resection.

Complete responders at Week 12 will continue MK-3475 for 12 additional weeks with repeat imaging to confirm CR at Week 24. Patients who exhibit rPR at Week 12 assessment will undergo complete metastectomy and continue MK-3475 for 12 additional weeks with repeat imaging at Week 24.

Subjects who display SD or uPR at Week 12 will continue MK-3475 for 12 additional weeks (4 cycles) with repeat imaging and resectability evaluation at Week 24.

If PD is noted on Week 12 imaging, repeat imaging will be performed 4 weeks later (Week 16). If PD is confirmed, the subject will exit the study. If stable disease or partial response is observed on Week 16 imaging, the patient will continue MK-3475 and be reassessed at Week 24 (after 8 cycles).

7.1.4.5 Week 24 Visits

At Week 24, assessments will be performed in a similar manner as those performed at Week 12 (e.g. Resectability Evaluation, Surgical Assessment, and Cutaneous Evaluation).

7.1.4.5.1 Week 24 - Surgical Assessment Visit

The following procedures will be performed at the Week 24 - Surgical Assessment visit after 8 cycles of MK-3475.

- Review of medical history and concomitant medications
- Physical examination
    - Physical examination includes: general appearance, skin, HEENT (head, eyes, ears, nose and throat), heart (auscultation), lungs (auscultation), abdomen (palpation and auscultation), lower extremities (peripheral edema),

- Vital signs [blood pressure (BP); heart or pulse rate; and oral, tympanic, or temporal temperature], weight.
- Resectability evaluation

7.1.4.5.2 Week 24 - Cutaneous Evaluation

The following procedures will be performed at the Cutaneous Evaluation visit after 8 cycles of MK-3475.

- Review of medical history and concomitant medications
- Skin examination and photography
- Skin biopsy of melanoma tissue (if applicable), non-sun-exposed unaffected skin, and any nevi on non-sun-exposed skin

7.1.4.5.3 Week 24 - Resectability Evaluation

Imaging to assess response will be performed at Week 24 (after 8 cycles).

In a similar manner as was performed at week 12, imaging will be performed at Week 24 (after 8 cycles) to assess whether tumor burden is amenable to curative resection.

Subjects who achieved CR at Week 12 will discontinue treatment after Week 24 (after 8 cycles) and enter the observation period if CR is confirmed on Week 24 imaging. Subjects who exhibited rPR at Week 12 and subsequently underwent complete metastectomy will discontinue treatment after Week 24 (after 8 cycles) and enter the observation period if no evidence of disease is observed on Week 24 imaging.

Patients who achieve CR at Week 24 (and who did not demonstrate CR at Week 12 assessment) will receive 2 additional cycles of MK-3475 (10 cycles total) before entering the observation period. At Week 24, complete metastectomy will be performed in patients with rPR; after surgery, these patients (rPR after complete metastectomy) will receive 2 additional cycles of therapy (10 cycles total) before entering the observation period.

Subjects who display SD or uPR at Week 24 will continue MK-3475 infusions every 3 weeks until disease progression or completion of 24 months of treatment.

If PD is observed on Week 24 imaging, repeat imaging will be performed 4 weeks later (Week 28). If PD is confirmed, the subject will discontinue MK-3475 treatment and exit the study. If stable disease or partial response is observed on Week 28 imaging, the patient will continue MK-3475 infusions every 3 weeks until disease progression or completion of 24 months of treatment.

7.1.4.5.4 Safety Follow-Up Visit

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

7.1.4.6 Observation Period

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Observation Period (aka Follow-Up Phase) and should be assessed every 12 weeks (84 ± 7 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

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

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

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

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

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

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

All reports of overdose with and without an adverse event must be reported within 3 working days to the Investigator's IRB per institutional guidelines and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.2 Reporting of Pregnancy and Lactation to the Investigator's IRB and to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death,

miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 7 working days to the Investigator's IRB per institutional guidelines and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.3 Immediate Reporting of Adverse Events to the Investigator's IRB and to Merck

7.2.3.1 Serious Adverse Events

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

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

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

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

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 3 working days to the Investigator's IRB per institutional guidelines and within 2 working days to Merck Global Safety.

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

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

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

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

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

7.2.3.2 Events of Clinical Interest

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

Events of clinical interest for this trial include:

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

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

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

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

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

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

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

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

7.2.4 Evaluating Adverse Events

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

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

Table 10 Evaluating Adverse Events

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

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

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

7.2.5 Investigator Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

It was decided that if half of partial responders to MK-3475 could be amenable to curative resection after treatment, that this would be an acceptable rate to use as a benchmark for comparison. Based on available data from Hamid et al, the overall response rate was 44% and the partial response rate was 33.3 % [33]. If half of the responders from available data were amenable to curative resection, the benchmark would be 16.7%.

By definition all subjects enrolled in the trial have unresectable disease or 0% resectability rate at baseline.

Therefore, a 20-percentage point increase from the expected rate of 0% resectability rate exceeds the benchmark of 16.7 % and was deemed appropriate for use in the estimation of sample size requirements.

A sample size of 15 would provide 95% power to detect a statistically significant improvement of 20%-points over the expected resectability rate of 0%. This sample size estimation is based on an alpha 0.025 employing customary calculations for the normal approximation of the binomial distribution.

Descriptive statistics will be reported for all other measures collected as part of the study protocol.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

Clinical data will be collected at the time of enrollment from the patient's medical record.

Data will be entered into the study electronic database. The Study Coordinator will also use hard copy forms as worksheets. The paper worksheets will be retained at the Hematology and Oncology Clinic in a locked file cabinet within a locked office until the study is complete and all study analyses and publications have been accomplished. These paper worksheets will be subject to site safety monitoring reviews.

When the subject is enrolled in the study, a study number will be automatically provided. The research team will recode the dates of enrollment and birth to calculate the subject's age, in days, and the resulting analytical database fulfills the definition of a de-identified database according to HIPAA definitions.

10.2 Compliance with Financial Disclosure Requirements

In accordance with institutional, state and federal regulations, all investigators will disclose their participation in this trial.

10.3 Compliance with Law, Audit and Debarment

The investigator and other members of the research team will adhere to state and federal regulatory requirements during the course of the trial

10.4 Compliance with Trial Registration and Results Posting Requirements

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

10.5 Quality Management System

Quality assurance activities undertaken during this study include monitoring and source data validation by the study team.

10.6 Data Management

Data will be collected on hard-copy paper forms and electronically and will be stored and secured as detailed below.

Hard-Copy Data Forms

The investigators have a dedicated, locked research room within the Hematology and Oncology offices, and the building has 24 hour on-site security guards. Data forms will be kept in research binders in a locked cabinet.

Electronic Data

User authentication is maintained with user/group domain-level security, centralized to desktop computers that are password-protected. There will be no transfer of data over public networks.

The de-identified electronic database, which contains raw research data will also be pass-word protected and maintained on the Saint Louis University Hematology and Oncology department's secured server. Once the data is ready for analyses, it will be coded and locked. Analytical files will contain no identifiers and will contain accumulated data for report of findings.

Confidentiality Security Plan

The investigators and research staff are fully committed to the security and confidentiality of all data collected this study. All personnel involved in this study have signed confidentiality agreements concerning all data encountered in the study clinic. All personnel involved with this study have completed Human Subjects Protection and HIPAA education.

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12.0 APPENDICES

12.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

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

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

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

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.

12.4 MK-3475 Event of Clinical Interest Guidance Document

Separate attachment